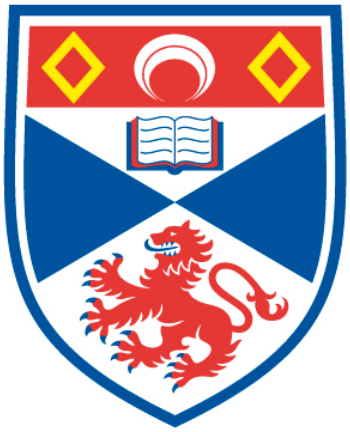
Au(I)- and Pd(II)-NHC catalysis: novel approaches towards the synthesis of fluoroarenes/alkenes and ketone derivatives

Alberto Gómez Herrera

A thesis submitted for the degree of PhD
at the
University of St Andrews



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I, Alberto Gómez Herrera, hereby certify that this thesis, which is approximately 62600 words in length, has been written by me, and that it is the record of work carried out by me, or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for a higher degree.

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AUTHOR CONTRIBUTIONS

Some of the work reported in this thesis has been published in peer-reviewed journal articles as described below. Unless stated otherwise, the work reported is all my own work and I was the primary researcher on all projects.

Chapter 2

This chapter presents up-to-date results of ongoing research work.
The workers have contributed as follows:
- Alberto Gómez-Herrera: optimisation of reaction conditions, characterisation of the isolated products, writing of the experimental session.
- Dr. Fady Nahra: conceived idea, discussion about experimental work.
- Dr C. S. J. Cazin: supervision.

Chapter 3

The chapter was rewritten based on data reported in the following publication:

"Sequential functionalization of alkynes and alkenes catalyzed by Au(I)- and Pd(II)-NHC complexes" Alberto Gómez-Herrera, Fady Nahra, Marcel Brill, Steven P. Nolan and Catherine S. J. Cazin, *ChemCatChem*, 2016, *Accepted*. DOI: 10.1002/cctc.201600868. Copyright© 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

The authors contributed as follows:
- A. Gómez-Herrera: optimisation of reaction conditions, scope of the reaction, characterisation of the isolated products, writing of the experimental session, writing of the article.
- Dr Fady Nahra: conceived idea, discussion about experimental work, correction of the final manuscript.
- Dr Marcel Brill: Correction of the final manuscript.
- Prof. Steven P. Nolan: supervision, article editing.
- Dr C. S. J. Cazin: supervision, article editing.

Chapter 4

The chapter was rewritten based on data reported in the following publications:

"Sequential functionalization of alkynes and alkenes catalyzed by Au(I)- and Pd(II)-NHC complexes" Alberto Gómez-Herrera, Fady Nahra, Marcel Brill, Steven P. Nolan and Catherine S. J. Cazin, *ChemCatChem*, 2016, *Accepted*. DOI: 10.1002/cctc.201600868. Copyright© 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

"*Au(NHC)-catalysed hydration of 1-iodoalkynes to α-iodomethyl ketones"*, Alberto Gómez-Herrera, Fady Nahra and Catherine S. J. Cazin, *manuscript in preparation*.

The authors contributed as follows:

i. "Sequential functionalization of alkynes and alkenes catalyzed by Au(I)- and Pd(II)-NHC complexes"

The contributions of this section have been described in detail in Chapter 3.

ii. "Au(NHC)-catalysed hydration of 1-iodoalkynes to α-iodomethyl ketones"

- A. Gómez-Herrera: conceived idea, optimisation of the reaction conditions, scope of the reaction, characterisation of the isolated products, writing of the experimental session, writing of the article.

- Dr Fady Nahra: discussion about experimental work.

- Dr C. S. J. Cazin: supervision, article editing.

Chapter 5

The chapter was rewritten based on data reported in the following publications:

"Sequential functionalization of alkynes and alkenes catalyzed by Au(I)- and Pd(II)-NHC complexes" Alberto Gómez-Herrera, Fady Nahra, Marcel Brill, Steven P. Nolan and Catherine S. J. Cazin, *ChemCatChem*, 2016, *Accepted*. DOI: 10.1002/cctc.201600868. Copyright© 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

" *Synthesis of diarylalkynes via palladium-catalysed decarboxylative coupling and C-H activation "*, Alberto Gómez-Herrera, Fady Nahra, Marcel Brill, J. Wu, Catherine S. J. Cazin and Steven P. Nolan, *manuscript in preparation*.

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- A. Gómez-Herrera: optimisation of the reaction conditions, scope of reaction, characterisation of the isolated products, writing of the article.
- Dr Fady Nahra: conceived idea, writing of the article.
- Dr. Marcel Brill: conceived idea, writing of the article
- Jiufeng Wu: optimisation of the reaction conditions, scope of the reaction, characterisation of the isolated products.
- Dr C. S. J. Cazin: supervision, article editing.
- Prof. Steven P. Nolan: supervision, article editing.

iii. "Au(NHC)-catalysed hydration of 1-iodoalkynes to α-iodomethyl ketones"

The contributions of this section have been described in detail in Chapter 4.

Several articles were published during the course of my PhD as a result of collaborative efforts, but have not been included in this thesis:

"Selective NaOH-catalysed hydration of aromatic nitriles to amides" Thibault E. Schmid, Alberto Gómez-Herrera, Olivier Songis, Deborah Sneddon, Antoine Révolte, Fady Nahra and Catherine S. J. Cazin, *Catal. Sci. Technol.* 2015, **5**, 2865. Copyright© 2015 Royal Society of Chemistry.

"Transition metal bifluorides" F. Nahra, M. Brill, A. Gómez-Herrera, C. S. J. Cazin and S. P. Nolan, *Coord. Chem. Rev.* 2016, **307**, 65. Copyright© 2016 Elsevier B. V.

Several articles are being written at the moment of the submission of this thesis as a result of collaborative efforts, but have not been included in this thesis:

"Gold-NHC complexes of mineral acids: the curious case of digold sulfate" F. Nahra, M. Brill, A. Gómez-Herrera, C. S. J. Cazin and S. P. Nolan, *manuscript in preparation*.

"Cu(I)-NHC complexes as NHC transfer reagents" F. Nahra, M. Brill, A. Gómez-Herrera, C. S. J. Cazin and S. P. Nolan, *manuscript in preparation.*

ACKNOWLEDGEMENTS

I would first like to acknowledge my supervisor, Dr Catherine S. J. Cazin, for making it possible for me to do a PhD in her research group in St Andrews. Your guidance, patience and experience have been key to get through four years of good and bad times, pushing my professional limits even beyond I could ever imagine. I've gained new perspectives about how to work professionally and efficiently thanks to your advice, and everything I've learnt will most certainly help me reaching higher goals as a professional. That is something invaluable, and I thank you for that. I would also like to thank Prof. Steven P. Nolan, who gave me the opportunity to work with his postdoctoral researchers, and provided an excellent support with scientific publications.

Thank you, Dr Fady Nahra. When things were stuck, you decided to be my guidance and provided me with very challenging projects that have put my skills and patience (and yours!) to the test. Everything has been finally wrapped up, after a long struggle, and you are probably the only one knowing how much this has costed. Definitely, the contents of my thesis would not have been here if it wasn't for you. Thanks for these two years of joint work. It has been a real pleasure, and I offer you my deepest gratitude.

Thank you to my mother Clarisa and my father Alberto, and to my younger brother Eduardo. They are that part of my life that never changed during these last years, despite the many situations I've been through during my thesis. Distance has not kept you from giving me hope, strength and everything you had. As a son, as a brother, as a human. You were constant support and inspiration, and you all have made it possible for me to be here today, achieving another one of my dreams. No words can precise how happy I am to be part of this family. Also to three out of my four grandparents, who could not hold my hand tightly enough during my PhD and could not see how that dream is now true, I dedicate this work to you. Thank you.

A special mention goes to the ones that have been there for me during my PhD, sharing good and bad moments and making my walk through these four years a much more pleasant one. My special thanks go to Paola, Michael and Anetta, who will always be part of me for their constant support, funny times and giving the very best of them to make every day a good one. Many others can be thanked, and I would like to mention Jester, Fran, Iris, Orlando, Brunello, Ramprasad and Rachel, among others.

To the former and current members of the Cazin group, who have made this professionally more bearable and socially less stressful, my deepest thanks and my very best wishes for your future careers in chemistry. I hope our paths can cross again at some stage, maybe as professors, maybe as group leaders, maybe as friends...Looking forward to that time. Good luck.

Thanks to all the doctors, professors and staff members of the University of St Andrews whom I have had the opportunity to meet. My special thanks to Prof. Andrew D. Smith, who temporarily accepted me in his research group in the beginning of my PhD. A very special mention goes to Mrs Melanja Smith, from the Spectroscopy Department in the School of Chemistry. With a very amicable personality and a great professionality, which definitely defines what should be part of the excellence in a research environment, you have been there with a smile and a friendly word every single day since I arrived to St Andrews, and there is nothing I could have appreciated more. You are a thousand times more valuable than a ^{13}C NMR spectrum with 3000 scans in Hector with a 30-mg sample, and you know what that means. Thank you, Melanja, I will truly miss you.

Thanks to all *lassies* and *ladies* who have welcomed me in Scotland. You made me feel like at home in a foreign country, you shared your culture and you made me part of the stories of your life, as well as you are now part of mine. I will always remember this part of the world and thank you for that.

Laura deserves a very special spot in these acknowledgements. The last months of my PhD have been very challenging, and she has been there every single day making it easier. Fun and laughter, movies and nice chats kept my mind clear for the last thesis writing steps and to deal with other issues, and without her this would have been a much more painful time. Thank you, I owe you a lot.

To everyone who has not been mentioned before, but you know you have fueled this thesis in diferent ways, thank you. These acknowledgments will never be enough to appreciate your individual contribution, and I will make sure to let you know about that.

Thank you all. This whole thesis is dedicated to you.

"The only place success comes before work is in the dictionary"

Vince Lombardi

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TABLE OF ABBREVIATIONS

$\%V_{Bur}$	Percent Buried Volume
Conv	Conversion
CPME	Cyclopentyl methyl ether
d	Doublet
DCE	1,2-dichloroethane
dd	Doublet of doublets
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDG	Electron-Donating Group
EWG	Electron-Withdrawing Group
EtOH	Ethanol
Equiv	Equivalent
F-TEDA-PF_6	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate)
KO*t*Bu	Potassium *tert*-butoxide
GC	Gas Chromatography
IMes	*N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	*N,N'*-bis[(2,6-di-*iso*propyl)phenyl]imidazol-2-ylidene
IPr^{Cl}	*N,N'*-bis[(2,6-di-*iso*propyl)phenyl]-4,5-dichloroimidazol -2-ylidene
IPr^{Me}	*N,N'*-bis-[2,6-(di-*iso*-propyl)phenyl]-4,5-dimethylimidazol-2-ylidene
IPr*	*N,N'*-bis-[2,6-bis-(diphenylmethyl)-4-methylphenyl]imidazol-2-ylidene.
^{i}PrOH	Isopropanol
MCPBA	*Meta*-chloroperbenzoic acid
MeOH	Methanol
$MgSO_4$	Magnesium sufate
NaO*t*Bu	Sodium *tert*-butoxide
NBS	*N*-bromosuccinimide
***n*-BuLi**	*N*-butyllithium
***n*-BuOH**	*n*-Butanol
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	N-Heterocyclic Carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
q	quadruplet
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
s	Singlet

sept	Septet
SIMes	*N,N'*-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPr	*N,N'*-bis[(2,6-di-*iso*propyl)phenyl]imidazolidin-2-ylidene
***t*-AmOH**	*Tert*-amyl alcohol
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TEMPO	(2, 2, 6, 6-tetramethyl-piperidin-1-yl)oxyl
TEP	Tolman electronic parameter
t	Triplet
TLC	Thin Layer Chromatography
TM	Transition metal
THF	Tetrahydrofuran
TREAT-HF	Triethylamine trihydrofluoride
2-Me-THF	2-Methyl tetrahydrofuran

ABSTRACT

The preparation of organic molecules utilising synthetically simple and economical strategies is nowadays a big field of study in chemistry. As part of this exciting area of study, this thesis presents a group of new methodologies involving the transformation of simple organic compounds into valuable fluorinated molecules (fluoroarenes and fluoroalkenes) or ketone derivatives. These competitive alternatives to traditional methods exploit the use of transition metal-NHC catalysts (NHC = N-heterocyclic carbene), with particular interest in Au(I) complexes.

The exploration of the use of arylsulfonic acids as substrates for the preparation of fluoroarenes was investigated for the first time. Our studies have obtained the first experimental proof of the fluorination of such substrates through either C-S or C-H activation. Preliminary optimisation and mechanistic studies for these reactions have been conducted, obtaining important information that is currenly being used by our research group to further unravel the synthetic value of arylsulfonic acids for aromatic C(sp^2)-F bond formation.

The use of terminal alkynes as substrates for the synthesis of complex organic molecules has also been exploited. Five new reactions and six sequential methods have been optimised. First, a new Au-catalysed protocol for the iodination of terminal alkynes was reported. This was followed by the individual study on two addition reactions (hydrofluorination and hydration), leading to new synthetic approaches to iodinated fluoroalkenes and ketones, respectively. Finally, these derivatives were further functionalised using coupling chemistry promoted by Pd(II)-NHC catalysts, accessing trisubstituted fluoroalkenes and functionalised ketones. All these reactions were compatible with sequential applications after minor changes, providing fast and easy functionalisation techniques that avoid the isolation of any intermediate, and maintain high performance and selectivity. These methods emphasise the highly convenient use of TM-NHC catalysts as versatile tools for organic synthesis.

CHAPTER 1

General Introduction

1.1 Introduction

Stable carbenes (also known as *persistent carbenes*)[1] are chemical entities consisting of a neutral carbon atom with two substituents and two unshared electrons, and with a particularly stable nature when compared to traditional carbenes. This longer lifespan allows persistent carbenes to actively participate in chemical reactions as non-innocent species, and their reactivity modulation has become very attractive for the chemistry community. Their extraordinary and unique properties benefiting organic synthesis have allowed this type of carbenes to be strongly present in the scientific literature.

N-Heterocyclic carbenes (NHCs) are considered one of the most representative families of persistent carbenes, having found very extensive applications as organocatalysts and ligands for metal complexes. These carbenes are contained within a nitrogen-based ring, and their steric and electronic features are generally unmatched by any other chemical species. Excellent reviews regarding the history of NHCs, their structures, reactivity and other distinguishing features, are available for a more in-depth understanding of their importance.[2] The interest in preparing, testing and implementing new NHC-based systems in synthesis is evident in scientific discussions, innovative projects and competitive objectives among the research community.

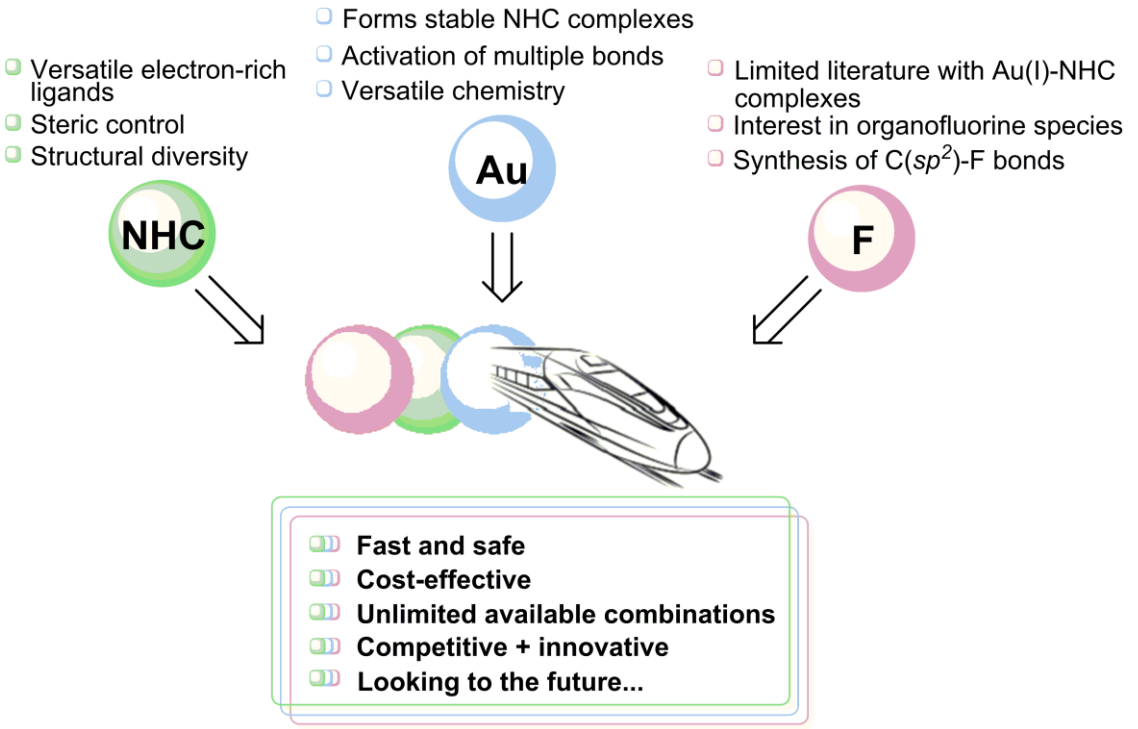


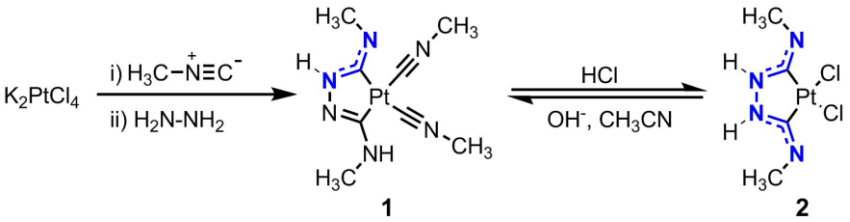
Figure 1.1. Interest in the integration of NHCs and Au chemistry in fluorination reactions.

In this chapter, a brief introduction to NHCs will be presented, covering the basic features of these molecules, their synthesis and a general overview of their applications in chemistry. An introduction to the synthesis of Au(I)-NHC complexes and their application in catalysis, will follow. Some historical overview, a comparative analysis of the different synthetic methodologies, together with the analysis of some of the most common families of Au(I)-NHC complexes, will provide a solid background to understand the interest in these complexes. Lastly, special attention will be paid to discussing the use of gold chemistry for fluorination purposes, and in particular for the formation of C(sp^2)-F bonds. This discussion is essential to a good comprehension of the projects presented in this thesis, and will allow a better assessment of the value of the presented synthetic chemistry (Figure 1.1).

1.2 N-Heterocyclic carbenes (NHCs)

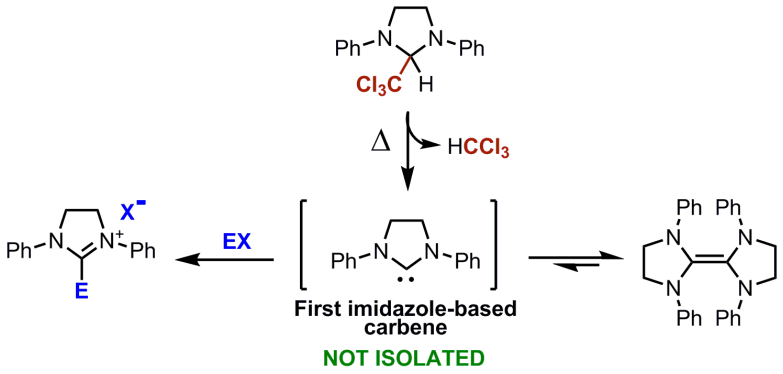
1.2.1 Historical overview

The first sign of NHC chemistry dates back to 1914, when Tschugajeff and co-workers reported a Pt compound obtained by reacting, in a two-step procedure, a tetrachloroplatinate alkaline salt with methyl isocyanide and hydrazine (Scheme 1.1).[3]



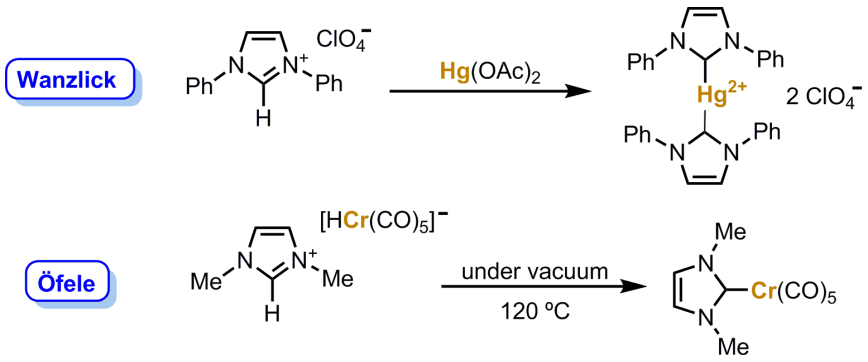
Scheme 1.1. Preparation of Tschugajeff's ``red salt´´ (**1**) and ``yellow salt´´ (**2**), the first reported examples of metal-diaminocarbene complexes.[3]

As spectroscopic and inert techniques evolved in the following decades, further information about these species was unraveled. The work of Wanzlick led to the most important discoveries in this area. His novel postulation of an imidazole-based free carbene obtained after pyrolysis of 2-trichloromethyldihydro-imidazole,[4] followed by later studies on the stability of such species,[5] were key to a broader understanding of the nature of carbenes and their reactivity (Scheme 1.2). On the other hand, the free carbene species could not be isolated at that time.



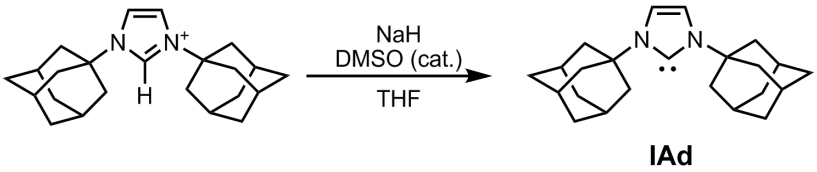
Scheme 1.2. Studies on imidazole-based carbene intermediates and their reactivity.[4,5]

A variety of other studies followed these contributions, detailing further characteristics of NHCs.[6] These efforts culminated with the first isolated and well-defined metal-NHC complexes in 1968, with the independent work from Wanzlick[7] and Öfele (Scheme 1.3).[8]



Scheme 1.3. First isolated metal-NHC species.[7,8]

Despite these advances, much remained unknown about carbenes until the work from Bertrand in 1988 and by Arduengo in 1991. The earlier reported the synthesis of a phosphinocarbene from a suitable α-diazophosphine, although its carbene character was doubted at that time due to strong similarities in reactivity with phosphaacetylenes.[9a] Due to this, the pioneering work from Arduengo is widely considered the first clear example of a fully characterised crystalline stable carbene.[9b] This compound, *N,N'*-diadamantyl-imidazol-2-ylidene (**IAd**, Scheme 1.4), was isolated as a white crystalline solid (Scheme 1.4), and was stable for prolonged periods of time when stored at low temperatures in the absence of air and moisture.



Scheme 1.4. Synthesis of **IAd**, the first persistent carbene.[9b]

With all this information on hand about the relative stability of NHCs and their incorporation as ligands in metal complexes, researchers established the pillars of NHC chemistry, a research field that has experienced one of the fastest growths of the last century.

1.2.2 NHC structures

Since the discovery of Arduengo's carbene, a wide range of new NHCs have been isolated and characterised, with a very broad structural variety going beyond acyclic diaminocarbenes and imidazole derivatives. However, 5-membered ring derivatives are the most common carbene-containing motifs, and therefore will be used to exemplify some of their important properties.

The diversity of heterocyclic carbenes is based on different structural aspects:

- ***Carbene position:*** the lone electron pair can be located in different carbon atoms in the heterocyclic ring, as shown in Figure 1.2. A major number of carbenes belong to the "normal carbene" type (**A**), with the unshared electron pair contained in a carbon between two heteroatoms (in the case of imidazole-based compounds, between two nitrogens). Despite this dominance of normal carbenes, abnormal (**B**) and remote carbenes (**C**) are increasingly finding their way on the chemist's bench as the knowledge about these NHCs increases and reveals a considerably different and versatile reactivity.[10]

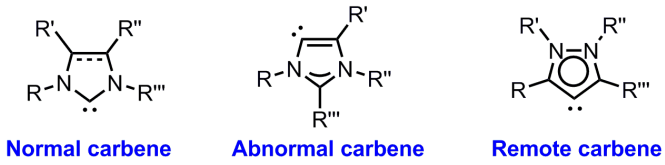


Figure 1.2. Generic structure of NHCs based on the carbene position: normal (**left**), abnormal (**centre**), and remote (**right**) (R, R', R"'= alkyl, aryl).

- ***Nature of the heterocycle:*** different atoms and bond types can be contained within the heterocyclic ring structure bearing the carbene (Figure 1.3). Imidazolidinylidene and imidazolylidene rings are the most widespread motifs, due to their low π–acceptor capability (caused by back-donation from the adjacent *N* atoms to the carbene centre), with the subsequent stronger effects on carbene stability and reactivity when compared to other nitrogen-containing cycles.

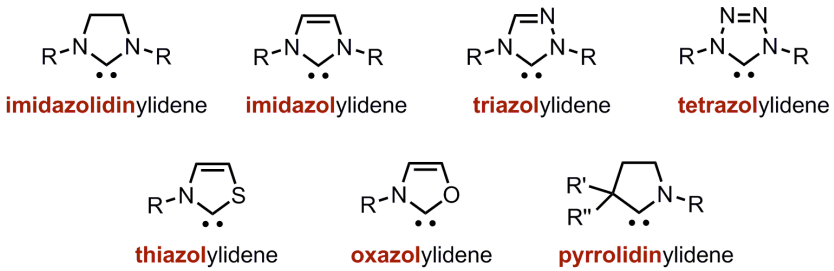


Figure 1.3. Some common heterocyclic structures bearing a carbene moiety (R, R', R"= alkyl, aryl).

- ***Nature of N-substituents:*** the substitution on the nitrogen atoms is probably the most important variable in the structure of an NHC, with a wide range of substituents being accessible. The synthetic versatility to access the imidazolium core from different substrates is still nowadays a clear opportunity to develop new carbenes with novel

structural features, and it has been indeed widely exploited. Some of the most commonly used NHCs are shown in Figure 1.4.

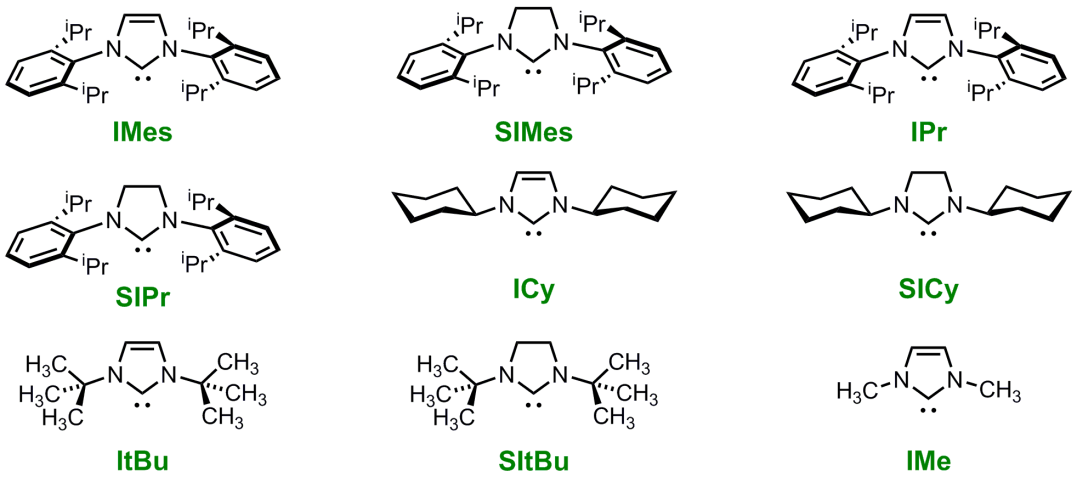


Figure 1.4. Commonly used NHCs, displaying different *N*-substituents, and their respective acronyms.

1.2.3 Properties of NHCs

1.2.3.1 Electronic properties

NHCs are neutral two-electron donor compounds[11] with two possible states: a *singlet state* (both electrons located in the σ orbital, or direct bonding orbital) or a *triplet state* (one of these electrons is instead located in the p_π orbital, or empty non-bonding orbital). The stability of either one or the other depends on electronic and steric parameters within NHCs, with the singlet state generally being the most stable species.

N-Heterocyclic carbenes also possess a σ-basic/π*-acidic electronic character. The high energy σ orbital of the carbene contains a lone pair of electrons which is responsible of the basicity of these molecules (Figure 1.5, **A**).[12] When electron-deficient metals are used, another donating electronic component can be observed, as a result of electron donation from the NHC to the metal through a combination of filled and empty π orbitals (Figure 1.5**, B**).[13] Upon coordination to metal centres, the presence of a low energy empty π* orbital allows for back-donation from the *d* orbitals in metals (Figure 1.5, **C**), further increasing the interaction between the metal centre and the NHC ligand.[14]

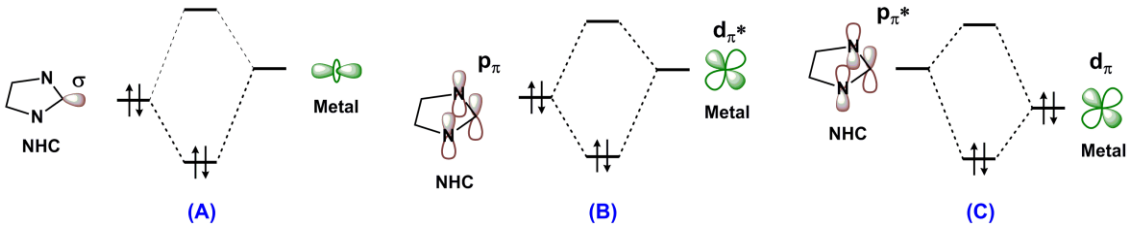
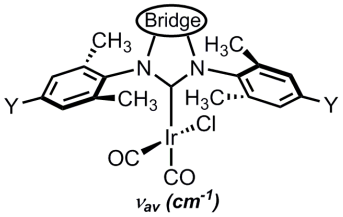


Figure 1.5. Orbital diagrams for the electronic interactions between NHCs and metal centres.

In essence, the strong σ-donation in combination with the back-donation properties translates into a very strong metal-NHC bond, a very practical feature for the synthesis of stable transition metal complexes. Their use as ancillary ligands competes with that of other traditional ligands (such as phosphines), relying on their higher resistance to moisture, air, extreme temperature and other external conditions when ligated to metal centers, making them a highly robust choice for catalysis.[15]

The strength of the metal-NHC bond depends mainly on the nature of the carbene. For that reason, a quantification tool was designed to measure the effect of the carbene in the metal-carbene bond. It was based on the value of the stretching frequency of CO in $[IrCl(CO)_2(NHC)]$ complexes (ν_{av}). This parameter indirectly accounts for the electron enrichment of the metal centre by measuring the strength of the metal-carbonyl bond using the CO stretching value. This tool has been of great use to determine general trends in electron donation of NHC ligands, allowing the differentiation of several contributions based on the structural parameters of NHCs (the presented ν_{av} values are reproduced from a reported literature review):[2f]

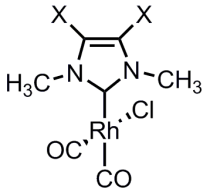


ν_{av} (cm^{-1})

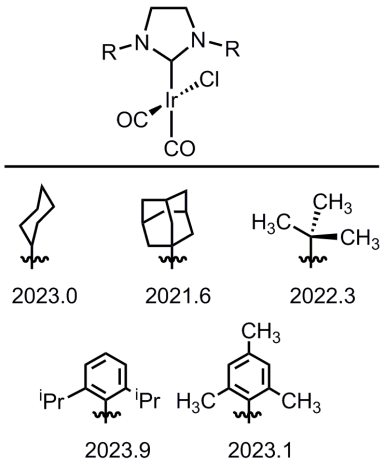
	Y = NEt_2	Y = Me	Y = SO_2-(*p*-tolyl)
Saturated bridge	2022	2025	2030
Unsaturated bridge	2021	2023	2029

1) While the stretching frequency analysis of saturated and unsaturated NHCs has revealed a slightly more donating capability of unsaturated backbones as opposed to the saturated counterparts, the real effect in metal complexes is generally negligible.

2) The substitution pattern in the backbone has a significant influence in the carbonyl frequencies. Strong electron-donating or electron-withdrawing groups can affect the electron density in the NHC core from higher to lower values, matching with the observed trends in stretching frequency variations.

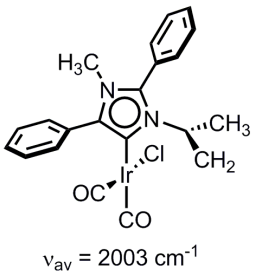


X	ν_{av} (cm^{-1})
H	2046
Cl	2051
NO_2	2053
CN	2058



3) Small differences between aromatic and aliphatic *N*-substituents to the stretching contribution can also be observed. The subtle differences can sometimes account for the various observed behaviors, but in general, as in the case of the NHC backbone, other parameters must be taken into account to explain such observations.

4) The evaluation with respect to standard values for normal carbenes (approx. 2020-2035 cm^{-1}) clearly shows a great enrichment of the five-membered rings when abnormal carbenes are used (approx. 2000-2020).



A direct comparison between electronics of carbene and phosphine complexes can be done by translating the obtained values of ν_{av} into the known values of stretching frequencies of CO for phosphine complexes. These values, also known as the *Tolman Electronic Parameter* (TEP), are tabulated using [Ni(CO)$_3$L) complexes. Plotting both values for phosphine and carbene complexes has verified the different electronic behavior of both families of ligands (Figure 1.6). The higher electron-density of metal centres when NHCs are used as ligands directly showcases their unique role in catalytic systems requiring such electron-rich metals, further supporting the use of these entities in synthesis.

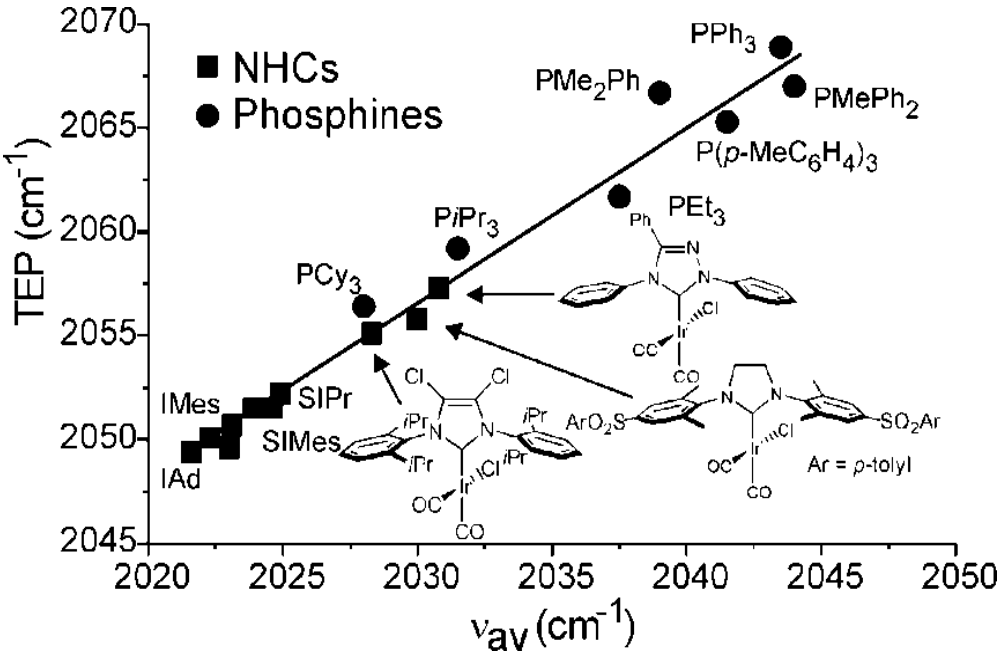


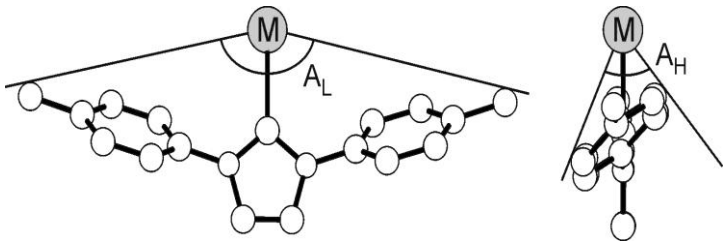
Figure 1.6. Plot of average CO stretching frequencies (ν_{av}) *vs* the Tolman Electronic Parameter (TEP) for some common NHCs and phosphines. Reproduced from reported literature.[2f]

The pioneering work that investigated the electronic parameters in carbenes was highly important for the understanding of NHCs and their effect on metal catalysis, and it is still considered as a very useful tool for mechanistic discussions and prediction of reactivity trends.

1.2.3.2 Steric properties

The steric effects derived from the use of carbenes are not only related to the geometry of the carbene site (C atom with a sp^2 hybridization and a *bent* geometry),[1] but also to the whole environment of the molecule, and its magnitude is quite important for the better understanding of NHCs.

Table 1.1. Graphic diagram of the *fence model*, with carbene length (A_L) and height (A_H) for some selected Ru-NHC complexes.[17] Image reproduced from reported literature.[2f]



Complex	A_L	A_H	Ru-C bond length (Å)
[RuCl(Cp*)(ICy)]	126.7	31.8	2.070
[RuCl(Cp*)(IAd)]	149.0	41.4	2.153
[RuCl(Cp*)(IMes)]	150.7	70.4	2.105
[RuCl(Cp*)($IMes^{Cl}$)]	152.0	69.9	2.074
[RuCl(Cp*)(ITol)]	155.2	30.8	2.068

The substituents located in different positions on the heterocycle modify, in different degrees, the accessibility to the carbene, thus tuning its reactivity. This property cannot be analysed using the Tolman cone angle (the standard method used for phosphine ligands)[16] due to the different spatial symmetry presented by both types of compounds. The first model adjusted for NHC analysis was the so-called *fence model.*[17a] This analysis considers the NHC as a "fence", with a given "length" and "height" which can be evaluated by angular measurements in crystallographic data (see Table 1.1 for some selected examples). The fence model is a simplistic yet useful analysis for the discussion of steric effect trends in NHC chemistry, and has provided very useful rationales for the comparison of sterics on NHCs.

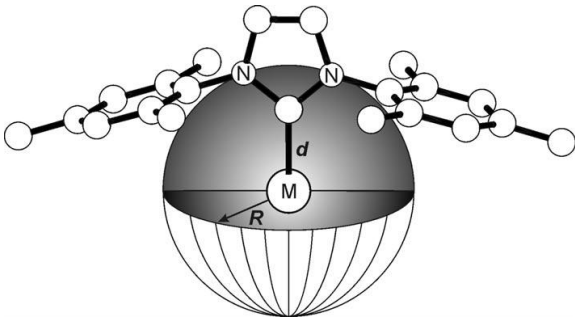
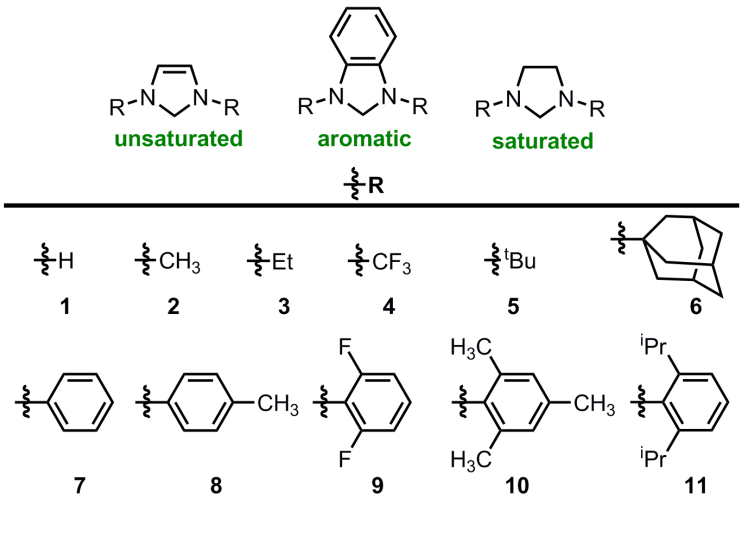


Figure 1.7. First coordination sphere on a metal-NHC complex. Reproduced from literature.[17b]

However, this model presented some inconsistencies with certain NHCs, which led to a re-evaluation of the method. As a result of the derived discussions, a new parameter was proposed. The *percent buried volume* ($\%V_{Bur}$)[18] is a quantitative parameter to evaluate

the fraction of the volume of the first coordination sphere around a given metal being occupied by a ligand (Figure 1.7). The interpretation of the quantified values is straightforward, with a higher percentage representing a more sterically congested metal centre. Trends in steric effects have been accurately analysed with this method (some selected examples are presented in Figure 1.8).



Percent of buried volume %V_{Bur}

NHC	Uns.	Arom.	Sat.
1	18.8	18.9	19.0
2	24.9	25.1	25.4
3	26.0	26.4	25.9
4	31.1	30.4	31.8
5	35.5	38.9	36.2
6	36.1	40.8	36.6
7	30.5	30.2	31.6
8	30.5	30.2	32.4
9	31.3	30.9	32.3
10	31.6	31.2	32.7
11	33.6	31.9	35.7
PPh_3	30.5		
PCy_3	35.3		

Figure 1.8. Some tabulated %V_{Bur} values for standard NHCs.[2f]

Due to its efficiency and consistency, the use of the %V_{Bur} remains the standard method of steric analysis in NHCs. Taking advantage of that, Cavallo and co-workers developed a user-friendly computational interface, named *SambVca*, which has rendered the steric studies of metal-NHC complexes accessible, thanks to a simple 3D mapping depicting the ligand topology and allowing algorithmic calculations to obtain %V_{Bur}.[19] This software can be found online for free, and is considered a highly important tool for NHC research activities. Recently, an updated version of this system, the *SambVca 2.0*, was released, providing advanced features and a more consistent interface for the analysis of catalytic pockets in metal centres.[20] An example of the obtained analysis for a selected Ru-NHC species is shown in Figure 1.9.

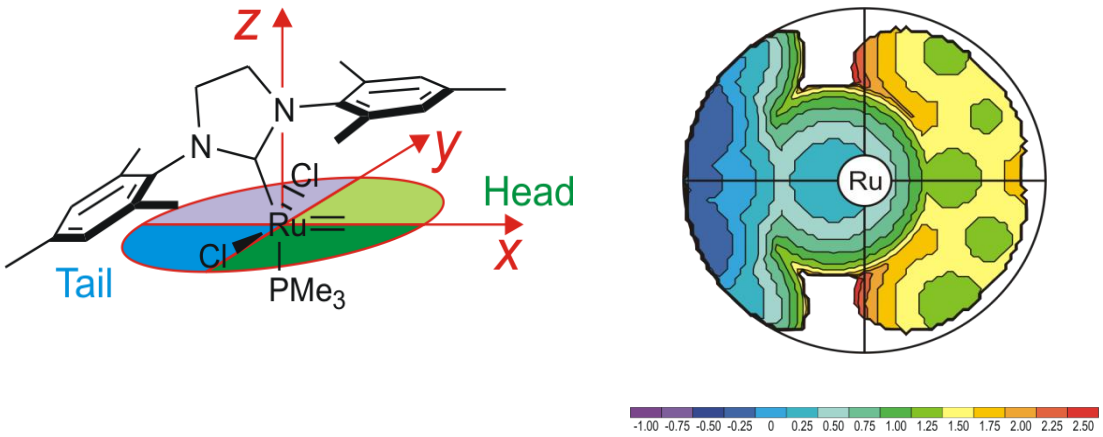
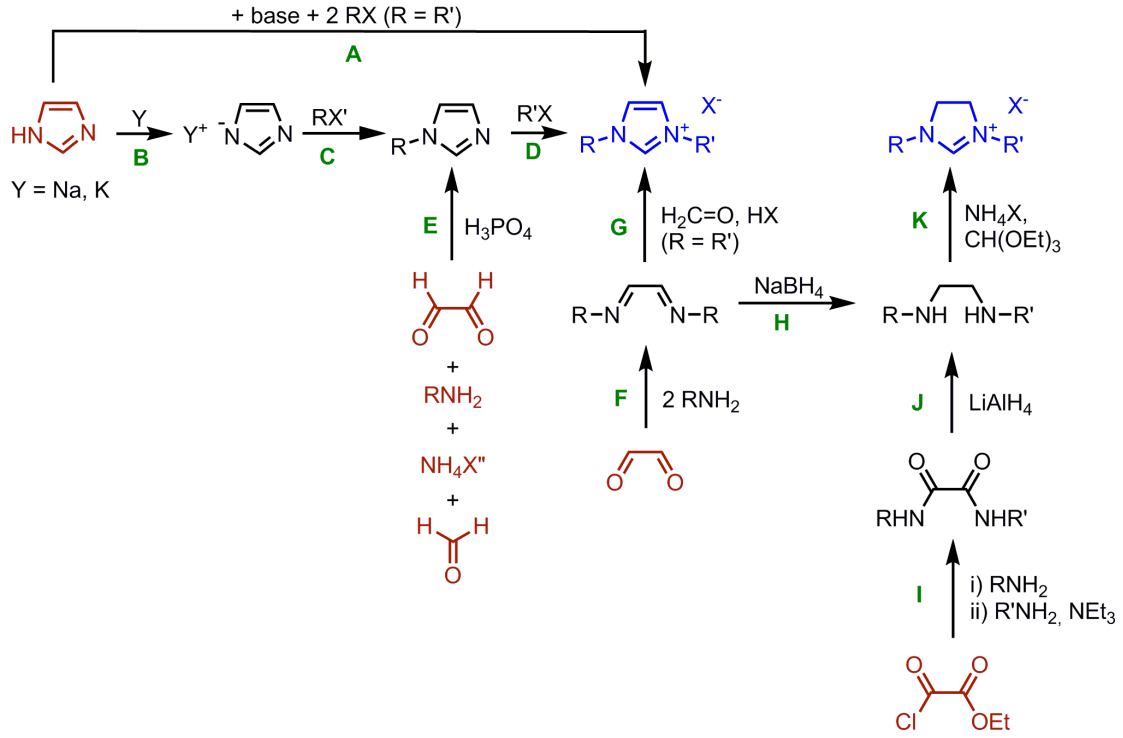


Figure 1.9. Selected example of a Ru-NHC (left) and the Samb*V*ca plot obtained for its structure (right). A topology legend is depicted below for further clarification. Reproduced from reported literature.[21]

1.2.4 Synthetic methods

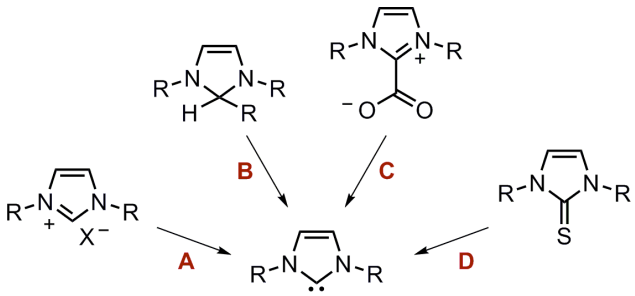
Due to the broad structural diversity of NHCs, a variety of synthetic methods have been used for their synthesis. The imidazolium salt motif (see Figure 1.3) will be used as a representative member of five-membered ring carbenes to discuss some general synthetic approaches.

The simplest route towards imidazole-based carbenes relies on the direct reaction of imidazole with alkyl or aryl halides in the presence of base, obtaining both symmetrical (Scheme 1.5, **A**) and unsymmetrical molecules (Scheme 1.5, **B-D**). The delicate stoichiometry control required, as well as the unsuitability of a range of organic halides for efficient addition to imidazole, has led to the investigation of alternative synthetic methods. While symmetric NHCs can be obtained by cyclization of glyoxal and paraformaldehyde in the presence of amines (Scheme 1.5, **E-D** and **F-G**), unsymmetrical NHCs are accessible by reducing unsymmetrical 1,2-diimines (Scheme 1.5, **H**) (obtained from controlled addition of amines to glyoxal, or also *via* reaction of amines with 1,2-dicarbonylic compounds; Scheme 1.5, **I-J**) to the corresponding 1,2-diamines and further cyclisation (Scheme 1.5, **K**).



Scheme 1.5. Common synthetic approaches towards symmetrical and unsymmetrical imidazolium salts.

The obtained imidazolium salts can be then further reacted with a base to obtain the corresponding free carbenes (Scheme 1.6, **A**). This methodology has been widely used for the preparation of imidazole-based carbenes due to its relative simplicity. However, base-free systems are sometimes necessary, thus other methodologies are required. Among these, the thermal extrusion of functional groups in the C_2 position has shown some versatility for the *in situ* generation of free carbenes. Some common examples of extrusion reactivity are the elimination of hydrocarbons (Scheme 1.6, **B**) or CO_2 (Scheme 1.6, **C**). Less practiced is the reductive desulfurization of imidazolthiones (Scheme 1.6, **D**), although also being a suitable approach towards the release of free carbenes.



Scheme 1.6. Common synthetic approaches for the synthesis of free carbenes from imidazolium salts.

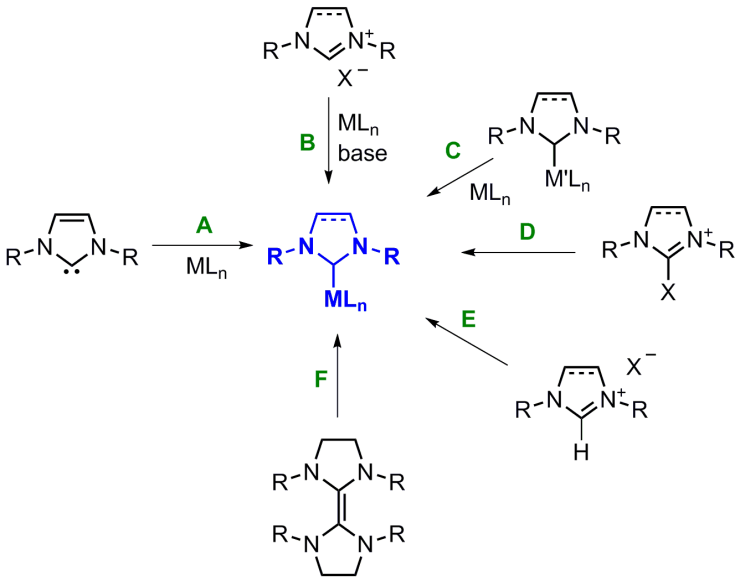
1.2.5 Applications of NHCs: organocatalysts and metal-NHC complexes

Aware of the extraordinary σ–donor capability of NHCs, the research community has used these molecules in a variety of processes involving nucleophilic activation of organic molecules. This role as organocatalysts has been extensively explored, and their mediation of carbonyl *umpolung* chemistry is an extended practise.[22] The role of free carbenes as generators of enolate,[23,24] homoenolate[25] or acyl anion equivalents[26] from suitable precursors has boosted the interest for their uses in organic synthesis. Transformations such as the benzoin condensation[27,28] or the Stetter reaction,[29,30] among many others,[31] have immensely benefited from their performance, and as a result, NHC organocatalysis has become a major synthetic tool for both simple reaction steps and more complex pathways, including total synthesis.[32]

Despite the extensive application of NHCs in organocatalysis, their use as ligands in organometallic chemistry has quickly grown since the first reports of Wanzlick and Öfele,[7,8] due to their great utility in metal-catalysed transformations.[33] Stabilising metals in high oxidation states[34] or their great performance under challenging reaction conditions (for example, organic reactions in aqueous media)[35] are only a few of the characteristics of NHCs that have proved beneficial in catalysis. The possibility to be combined with other ligands, such as mixed NHC/phosphine catalysts, has further increased the interest of their use.[36] The central role of NHCs in metal catalysis nowadays is therefore not extensively questioned, with catalytic applications ranging from C-H activation,[37] C-C[38] and C-N coupling,[38i] to hydrogenation[39] or polymerization chemistry,[40] among others.[41] Finally, their role in catalysis is also complemented with the utility of a modest number of species in other aspects, such as their exploitation as anticarcinogenic substances[42] or fluorescent chemosensors.[43]

The traditional preparation of these complexes is based on the reaction between a free carbene with a metal source (such as metal oxides or halides) (Scheme 1.7, **A**). However, in order to avoid the precautions ascribed to the handling of sensitive free carbenes, other pathways have been unveiled. Among the possible alternatives, the *in situ* generation of the carbene species using the corresponding imidazolium salt in the presence of a base, followed by complexation with a metal source, has a remarkable presence in the literature (Scheme 1.7, **B**). The synthesis of intermediate metal-NHC species and subsequent transmetallation also represents a very efficient way to obtain certain metal species that could otherwise not be accessible (Scheme 1.7, **C**). Less

common alternatives include oxidative addition of C-X (Scheme 1.7, **D**) or C-H bonds (Scheme 1.7, **E**), or the use of dimeric NHCs through C=C bond cleavage under thermal conditions (Scheme 1.7, **F**).



Scheme 1.7. Common approaches to the synthesis of transition metal-NHC complexes.

Complete summaries of these and other synthetic methods, as well as applications of transition metal-NHC complexes, are available in the literature,[44] generating an extensive library of knowledge that has been widely used by scientists. The great expansion of homogeneous catalysis based on NHC complexes is a reality that has brought this chemistry to a very competitive stage, and that continues providing new interesting applications in synthesis.

1.3 Au(I)-NHC complexes

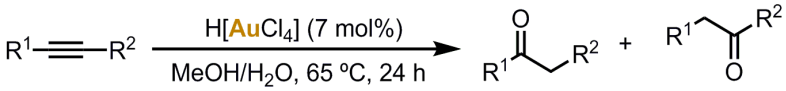
1.3.1 History of gold in chemistry

Gold is a transition metal from Group 11 that has found a very special place in catalysis, and its compounds are nowadays among the most versatile groups of catalysts for organic synthesis, with a copious amount of work available in the literature.[45]

Thinking retrospectively about gold in chemistry, it is surprising to acknowledge the success of this noble metal considering the early-stage assumptions of its inactivity towards the formation of any chemical bond. For that reason, ancient cultures used gold to prepare ceremonial masks for important members of their community, emphasising

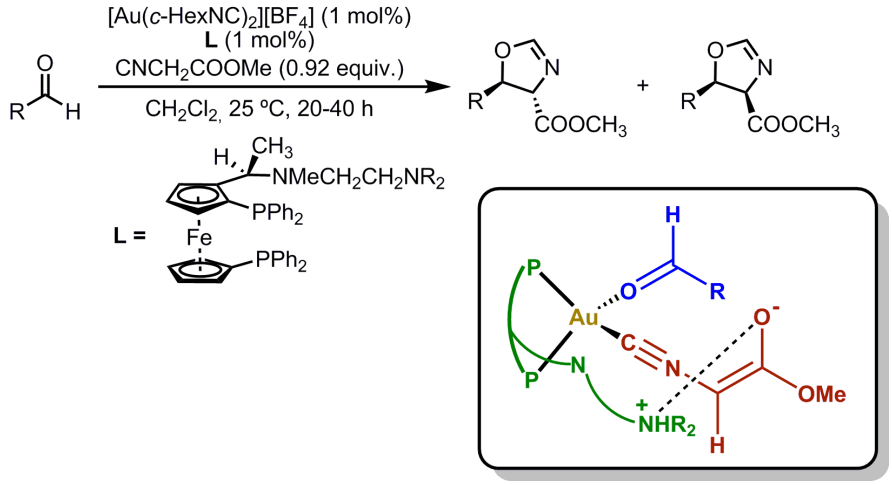
the concepts of inertness and precious value. However, the scientific facts behind such affirmations have been slowly demystified, and the studies performed in the last centuries have revealed a very rich chemistry. While the use of gold, especially important in the field of homogeneous catalysis, is not usually considered an interesting industrial approach, it is a much more common tool in academic research. The uses of Au range from the straightforward functionalisation of alkynes[46] to cross-coupling chemistry,[47] among many others;[48] the analysis of this broad applicability leaves little doubt about the interest of gold in research, with the so-called "Gold Rush" having overwhelmed the catalysis field in the last twenty years.

The earliest known report of homogeneous catalysis using gold dates back to 1976, when Thomas reacted alkynes with tetrachloroauric acid in aqueous MeOH, obtaining mixtures of ketones as reaction products (Scheme 1.8).[49]



Scheme 1.8. First homogeneous gold-catalysed reaction: hydration of alkynes.[49]

This piece of work inspired further studies into the integration of gold in synthesis by means of homogeneously catalysed systems, with very successful reports in the following years. One of the most interesting reactions was the asymmetric aldol reaction of aldehydes and isocyanoacetates using a ligand-stabilised Au(I) complex, published by Ito and Hayashi in 1986 (Scheme 1.9).[50]



Scheme 1.9. First asymmetric gold-catalysed reaction: aldol reaction with 2-cyanoacetates, and mechanistic participation of a Au-phosphine in chiral recognition.[50]

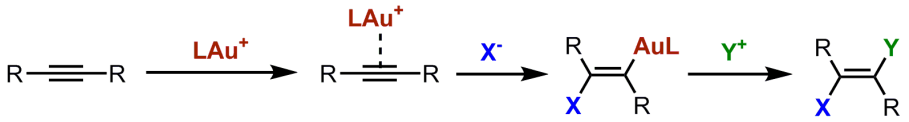
The decoordination of the cyclohexylisocyanate units in the gold precursor, followed by coordination of both the enolate of methyl isocyanoacetate and the aldehyde, was proposed as a consistent explanation of the good selectivity of this system (Scheme 1.9). These results were again surprising to the scientific community, as Au(I) complexes were considered poor enantioselective promoters due to their linear geometry. Another key feature for the high performance of this system was the strong affinity between gold and phosphorus; in view of these results, Hayashi's work supposed the beginning of the era of enantioselective catalysis using gold.[51]

These preliminary reports marked the start of prolific years for gold catalysis, with a special attention to Au(I)-phosphine species, which dominated homogeneous gold-catalysis for many years. A significant amount of work was developed during the 90's to unravel deeper features of gold chemistry, and the explosive growth of this field in the early beginning of the 21st century has been outstanding.[52]

1.3.2 Properties of gold

The reactivity of gold is dominated by the great influence of relativistic effects in the metal (in fact, the highest ones within the transition metal family),[53] whose nature is fully described by quantum physics.[54] A brief mention about its consequences in the application of gold in synthesis[55] is summarised below:

1) ***Strong π-acidity*****:** the cationic forms of gold (especially Au(I) species) can be categorised as soft Lewis acids, according to the HSAB theory ("Hard and Soft Acid and Base") introduced by Pearson in 1963.[56] The easily polarisable electrons in its valence shell result in a poor back-donation of gold to attached organic moieties, generating a lower LUMO for chemical interaction than that observed for other transition metals. This translates into cationic Au being a favourable species for the formation of π-based interactions, which is especially interesting for its interaction with soft nucleophiles, such as alkynes (in fact, one of the major fields of study in gold chemistry) (Scheme 1.10).[57]



Scheme 1.10. Activation of alkynes *via* π-acidic cationic gold species and prototypical functionalisation sequence of Au-alkyne adducts with nucleophiles and electrophiles.

2) ***Atomic radius:*** the contraction of the *s* orbitals in gold results in a significant reduction in its atomic radius (135 pm) when compared to the transition metals in group 11 of the periodic table (145 ppm for Cu, 165 ppm for Ag) (Figure 1.10).[54,55,58a] The high influence of the nuclear effects, that is, a greater electronic pull effect, essentially represents a higher Lewis acidity of Au than that expected for an element with its chemical properties.

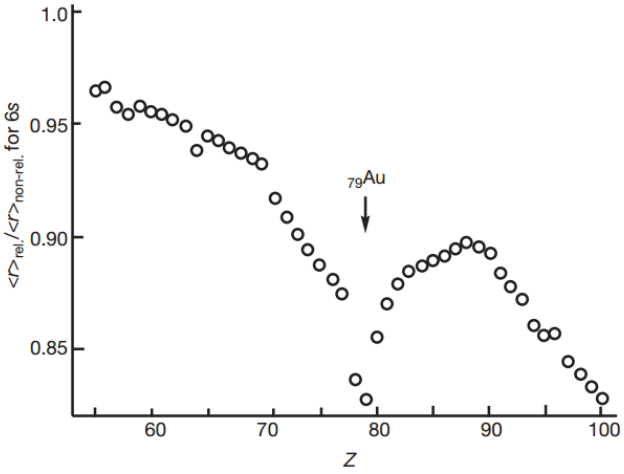


Figure 1.10. Calculated contraction of the *6s* orbital in gold by considering relativistic effects. Reproduced from reported literature.[58b]

3) ***Aurophilicity:*** the feasibility for the formation of weak Au-Au interactions with Au(I) species has led to the detection (and in some cases, isolation) of a variety of complex multinuclear Au aggregates (Figure 1.11).[59] This species can sometimes be active in catalysis, and have led to some interesting optimised results in reactions where mononuclear species were either inactive or displayed low reactivity.

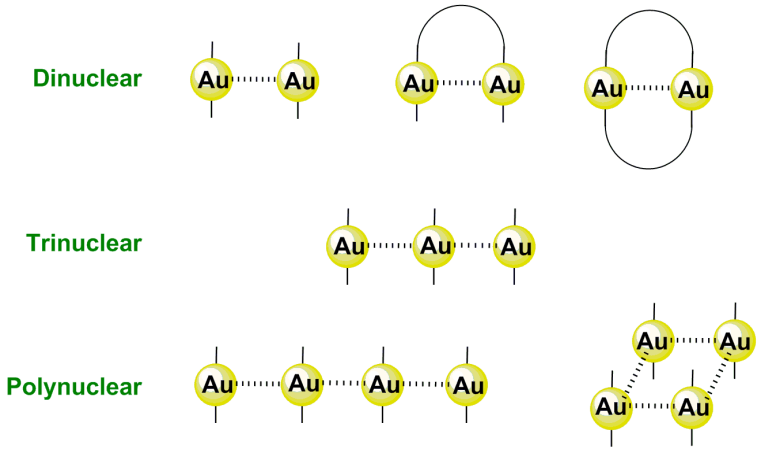


Figure 1.11. Some schematic polynuclear Au structures available in the literature.

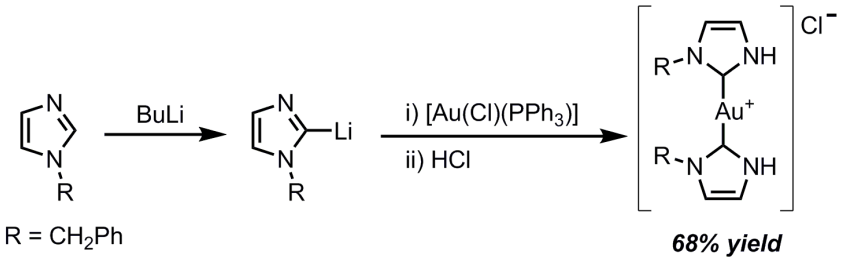
4) Active high-oxidation-state species: Au(0), Au(I) and Au(III) are the most common oxidation states for gold. While the first ionisation of the contracted 6*s* orbital is more challenging, the second and third ionization potentials are significantly lower due to more accessible *5d* orbitals being involved. Of special importance are the Au(I) species, allowing both oxidative and reductive chemistry. However, non-stabilised Au(I) species disproportionate to Au(0) and Au(III) in aqueous solutions, and the avoidance of moisture has been a major difficulty to overcome with these systems. The use of ancillary ligands has successfully addressed this stabilisation issue for Au(I). These have allowed moving from simple salts like AuCl to more complex species such as Au-phosphine adducts (for example, complexes with the formula $[Au(Cl)(PR_3)]$, where R = alkyl or aryl)[60] and also Au(I)-NHC complexes. On the other hand, the square-planar Au(III) complexes have also found catalytic applications, although being harder Lewis acids translates into a lower carbophilic character when compared to Au(I) species.[52,61]

Gold also possesses other advantages among transition metals, such as a generally low toxicity of its related compounds or high reactivity under very mild conditions, which is highly desirable for an industrial perspective[62] and provides further evidence of the useful place of gold in chemistry.

1.3.3 History of Au-NHC species in chemistry

In 1998, Teles remarked that cationic gold could be the most likely active species in gold catalysis, and that highly electron-donating ligands would be beneficial for Au-based catalysts.[46a] In response to this claim, the use of NHCs was indeed contemplated as suitable for more stable Au(I) species to be prepared, leading to almost two decades of very active work and hundreds of reports in catalysis[63] and other fields, such as biomedicine.[64]

The first isolated gold-NHC complex was reported in 1989 by Burini and co-workers. This cationic Au(I) bis-NHC species was prepared through lithiation of *N*-monosubstituted imidazole with BuLi, followed by reaction with $[Au(Cl)(PPh_3)]$ and HCl, yielding the corresponding chloride complex (Scheme 1.11).[65]



Scheme 1.11. First isolated Au(I)-NHC complex.[65]

These cationic species were, at those times, certainly difficult to isolate, and despite the copious work in the field, such as the studies from Baker[66] or Gagosz,[67] decomposition to Au(0) was commonly observed. The understanding of Au(I)-NHC species has broadened quite significantly over the years when the important stabilising role of ligands was consistently used for catalyst formulation. An interesting discussion about this occurred in 2006, when a stable cationic complex based on Au(I) and containing a solvent molecule (CH_3CN) as a stabilising moiety, was prepared.[68] The isolated complex, with the formula $[Au(IPr)(NCCH_3)][PF_6]$ (Figure 1.12, left), was also proven catalytically active in the cycloisomerisation of enynes.[69] Inspired by this "stabilised intermediate" approach, further work revealed a vast range of possibilities to obtain similar Au(I)-NHC species with catalytic activity. The work of Nolan[70] and more recently of Bertrand[71] was decisive in this field by expanding the available stabilising ligands (Figure 1.12, right), demystifying the inaccessibility of cationic Au(I)-NHC species and thus opening a new area of study that has certainly grown over the years.

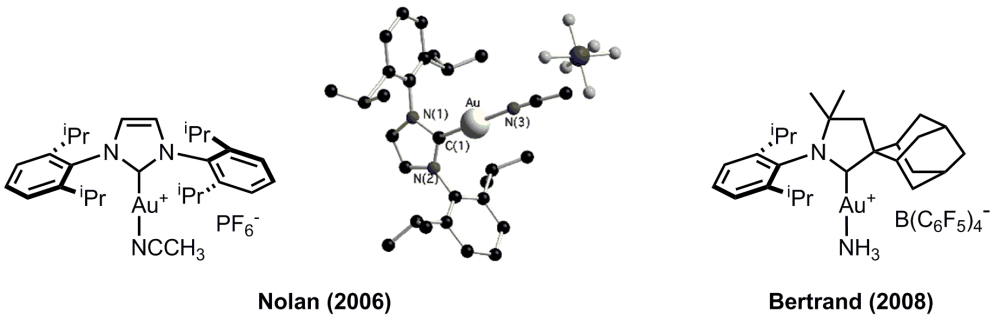


Figure 1.12. Selected early examples of stabilised Au(I)-NHC cationic complexes.[68,71] Crystal structure reproduced from reported literature.[68]

1.3.4 Au(I)-NHC complexes

The presented theoretical background about Au(I)-NHC species will serve as a base for the discussion of the current catalytic systems available in the literature and

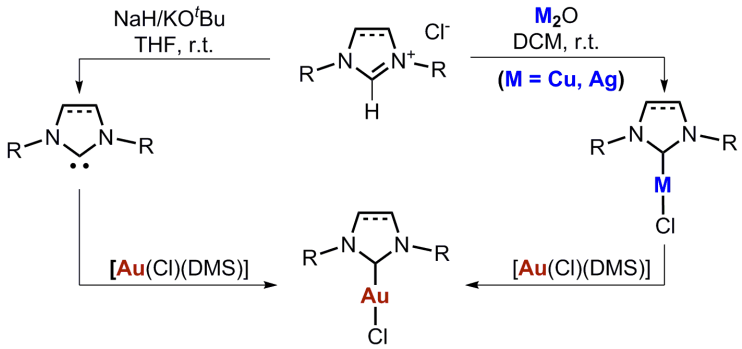
also present throughout this thesis. Before analysing their application to the particular synthetic needs of our projects, some fundamental facts about the main families of Au(I)-NHC complexes will be summarised, with special interest in synthetic methods, reactivity patterns and some applications in catalysis.

1.3.4.1 [Au(Cl)(NHC)] complexes

Despite the intense study on the synthesis of cationic Au(I) complexes, the field of Au(I)-NHC chemistry is mainly represented by the family of neutral Au(I)-NHC halides with the general formula [Au(X)(NHC)]. Among these species, chloride complexes with the formula [Au(Cl)(NHC)] constitute the largest category of Au(I)-NHC compounds.[44b] Their stability to moisture and air, their ease of preparation and an unmatched role as precursors for other Au(I)-NHC species, have led them to be highly desirable benchmark compounds in gold-focused research labs.

The preparation of [Au(Cl)(NHC)] complexes[72] mainly uses two approaches:

1) Free carbene route: this route involves the use of a preformed gold(I) chloride complex with a weakly coordinated ligand that could be substituted by simple exchange in the presence of a free carbene (generated from the corresponding imidazolium salt in the presence of a base, as discussed in Chapter 1.2) (Scheme 1.12, left). Acceptable yields are usually obtained through this methodology. The gradual substitution of this approach by other methods responds to a series of inconveniences; such as the requirement for "carbene-friendly" conditions (air- and moisture-free systems), or the inefficiency of this pathway for the preparation of complexes containing certain common ligands, such as IMes or SIMes.[72]

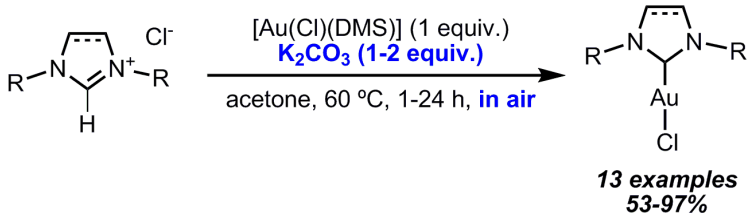


Scheme 1.12. General routes for the synthesis of [Au(Cl)(NHC)] complexes.[72-74]

2) Transmetallation route: the transmetallation route requires the formation of a [M(Cl)(NHC)] precursor that can be then transformed into the desired Au complex *via* NHC transfer (Scheme 1.12, right). Ag[73] or Cu[74] species are commonly used for such

purposes. This methodology has led to a wide range of NHCs being transformed to their corresponding Au(I) chloride complexes in modest yields without the requirement for restrictive air- and moisture-free conditions. The main drawback of this approach is the obviously low atom economy that overprices its applicability, especially at higher scales.

These two methods have established the main pathways towards Au(I)-NHC synthesis, but the drawbacks they present still encourage further work to ease the synthetic access to [Au(Cl)(NHC)] complexes. In this line, one of the most important advances is related to the feasibility of weak bases, such as K_2CO_3, to promote the deprotonation of imidazolium salts for further carbene metallation chemistry. This report represents a great simplification of the synthetic method for chloride complexes, affording moderate to excellent yields for a variety of NHCs in air and using technical-grade acetone as solvent (Scheme 1.13).[75]



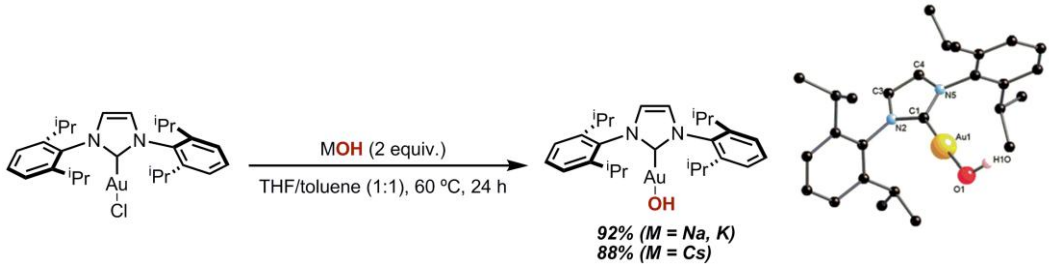
Scheme 1.13. Improved carbene route using K_2CO_3 as base.[75]

The family of Au(I)-NHC chlorides are mainly considered as Au precursors for the preparation of other species. Its reactivity has been considered as restricted for many years, as the use of silver salts to abstract the coordinated halide and generate the catalytically-active species was a strict requirement for their use in catalysis.[46a,50,76] Modern advances in Au(I)-NHC chemistry are currently making progresses along this line of study, having opened a broad field of study about activation and catalysis with these neutral species.

1.3.4.2 [Au(OH)(NHC)] complexes

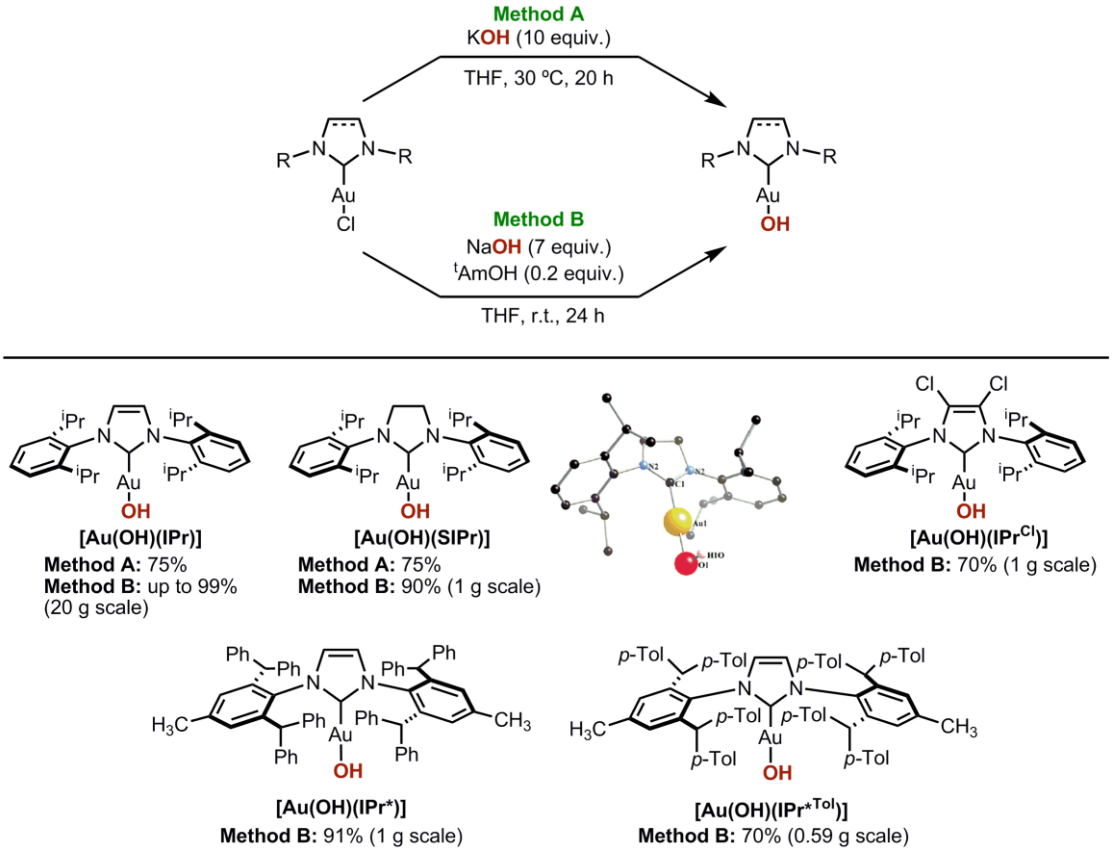
The family of Au(I)-NHC hydroxide complexes, with the general formula [Au(OH)(NHC)], are one of the most common groups of Au(I) complexes obtained from the corresponding chloride counterparts. These species have a very important place in the general chemistry of Au(I)-NHC compounds, exhibiting a higher reactivity than their precursors and being excellent catalysts for a variety of transformations.

The original work for the preparation of Au(I) hydroxides was published in 2010, when Nolan and co-workers accessed this species in excellent yield from [Au(Cl)(IPr)] after reaction with alkali metal salts (MOH, M = Na, K, Cs) in a THF/toluene (1:1) solvent mixture (Scheme 1.14).[77]



Scheme 1.14. First isolated [Au(OH)(NHC)] complex. Crystal structure reproduced from reported literature.[77]

This synthetic methodology was further modified to synthesise [Au(OH)(SIPr)], a complex that could not be prepared using the original methodology. Employing ten equivalents of the alkali hydroxide and reducing the reaction temperature to 30 ºC in THF as the sole solvent, the related SIPr derivative was prepared in 75% yield. X-ray analyses on crystals from this species confirmed the structure of this linear Au(I) species (Scheme 1.15).[78] Lastly, a fairly recent report from Nolan has unveiled the possibility to obtain these species *via* an even milder procedure and to perform scaled-up reactions without any loss of efficiency, thus being a certainly more robust methodology for large-scale catalyst synthesis. The new update consists on the use of an excess of NaOH and catalytic amounts of *t*-amyl alcohol in THF as solvent; under these conditions, room temperature could be used to obtain up to five different [Au(OH)(NHC)] complexes in good to excellent yields, in amounts ranging from 0.5 to 20 g in only 24 h (Scheme 1.15).[79]



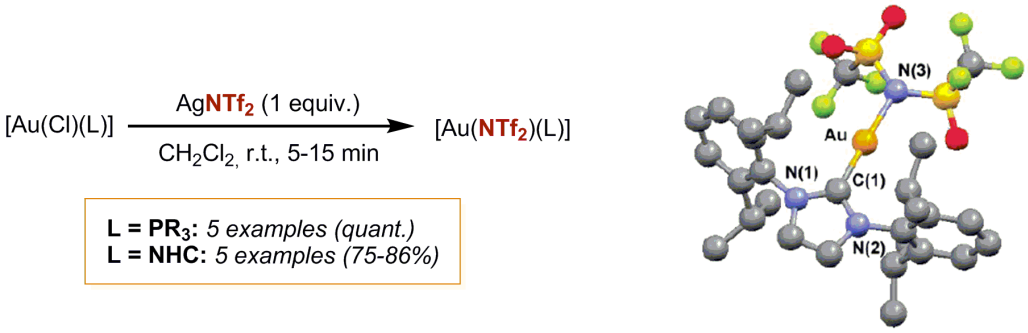
Scheme 1.15. Updated methodologies for the synthesis of Au-NHC hydroxide complexes. Crystal structure reproduced from reported literature.[79]

The interest in providing more general methods for the preparation of [Au(OH)(NHC)] complexes is based on a fast expansion of synthetic protocols employing these species as catalysts. Some examples of this use of hydroxides in catalysis include carboxylation[80] or decarboxylation chemistry,[81] silver-free catalysis based on gold[82] and many other transformations.[83]

1.3.4.3 [Au(NTf$_2$)(NHC)] complexes

The family of Au(I)-triflimide complexes first reported by Gagosz and co-workers is also a representative group of complexes belonging to mono-NHC Au(I) species. These species bear a triflimide unit, (-*NTf$_2$*) as ligand, and have found synthetic applications out of the limitations presented by chloride or hydroxide complexes.

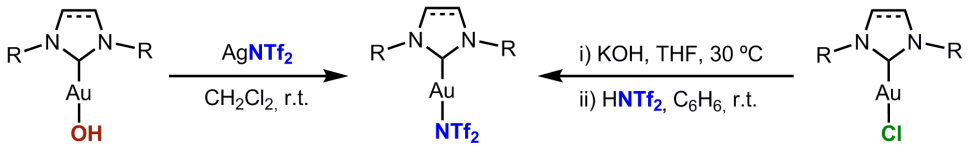
The initial report from 2007 presented the synthesis and isolation of 10 examples of triflimide complexes with either phosphine or NHC ligands (Scheme 1.16);[67] more recently, updated methodologies based on the original synthetic work have extended the amount of tolerated NHCs for the preparation of these complexes with the general formula [Au(NTf$_2$)(NHC)].[84]



Scheme 1.16. First isolated Au(I)-NHC triflimide complexes, and representative crystal structure of [Au(NTf$_2$)(IPr)]. Crystal structure reproduced from reported literature.[67]

The preparation of [Au(NTf$_2$)(NHC)] complexes is not only restricted to the classical use of Au(I)-NHC chlorides as precursors, since the use of Au(I) hydroxides was also proven feasible by Nolan and co-workers in 2010.[85] Together with the advances in silver-free synthesis of Au(I)-NHC triflimides,[86] these alternative pathways offer mild and complementary approaches for the preparation of Au(I)-triflimide species, as shown in Table 1.2. While the use of IPr as NHC in the corresponding Au(I)-NHC chloride or hydroxide complexes provides a better yield using a silver-free protocol (Table 1.2, Entry 1), the use of the SIPr derivative (Table 1.2, Entry 2) affords very similar results by both methods. The use of IPr^{Cl} (Table 1.2, Entry 3) or IPr* (Table 1.2, Entry 4) inverts the observations done with IPr, with a higher yield being reported when silver-based triflamidation is used. These values clearly highlight the necessity for both protocols to be active routes in Au(I)-NHC triflimide species.

Table 1.2. Comparing the synthesis of [Au(OH)(NHC)] complexes through silver or silver-free methods

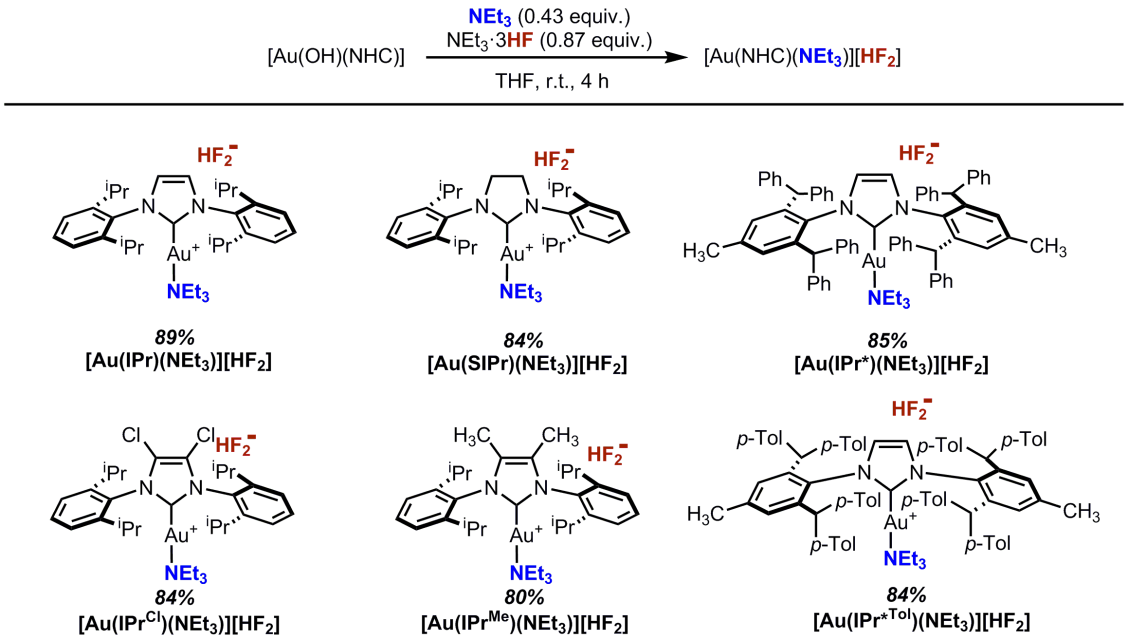


Entry	NHC	Two-step yield (%)	Silver route yield (%)
1	IPr	84	69
2	SIPr	71	73
3	IPr^{Cl}	62	87
4	IPr*	73	93

1.3.4.4 [Au(NHC)(NEt$_3$)][HF$_2$] complexes

This family of complexes is fairly recent (as opposed to the wide diversity of bifluoride complexes available in the literature for many other transition metals),[87] with the first members having been prepared in 2015, and represent the future of Au(I)-NHC chemistry as a "young" family of metal complexes with much to be explored in their reactivity. Some preliminary studies have shown that these species could extend the applications of Au(I)-NHC chemistry in catalysis, therefore calling for more attention in research to unravel their utility.

The first preparation of Au(I)-NHC bifluorides was reported in 2015 by Nolan and co-workers, with a total of six examples of [Au(OH)(NHC)] complexes being transformed into their corresponding bifluorides with the formula [Au(NHC)(NEt$_3$)][HF$_2$], by using a mixture of NEt$_3$·3HF and NEt$_3$ (2:1) in THF at room temperature for 3-4 h.[88] In all cases, good yields of the respective bifluorides were obtained (Scheme 1.17).



Scheme 1.17. First isolated Au(I)-NHC bifluoride complexes.[88]

Other species were prepared by means of exposure of hydroxide complexes to suitable acidic species, as is the case with the two examples of isolated NHC-Au(I)-pyridine bifluorides or the first example of a Au-Se bifluoride species (Figure 1.13). With these studies, a set of new Au(I)-NHC complexes are now accessible for testing in catalysis.

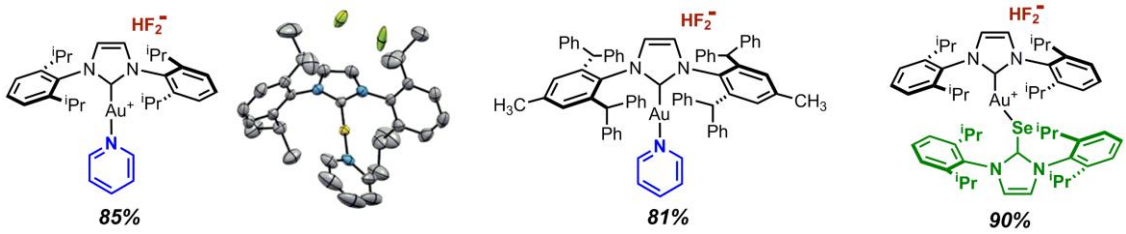


Figure 1.13. Au(I)-NHC bifluoride species bearing other ligands. Crystal structure reproduced from reported literature.[88]

From all reported examples, only the triethylamine adducts have found suitable applications in catalysis so far; more specifically, hydrofluorination of alkynes has been tested, obtaining very interesting results that will be further discussed and used to the advantage of the presented projects in this thesis.

1.4 Au-NHC complexes in C(sp^2)-F bond formation

1.4.1 Fluorination chemistry

1.4.1.1 Historical overview

One of the most prolific fields of study in synthetic chemistry during the last century has been devoted to the preparation of fluorinated compounds. Some early mentions in the late 19th century[89] and a first consistent mention of an organofluorine species dating back to 1900, with the contributions of Swarts,[90] were the precedents of a field which has experienced a massive expansion. Pioneered by the discoveries of Block and co-workers on perfluorinated hydrocarbons[91] during World War II, these novel substances were employed in the development of resistant and thermally-stable materials.

The post-war decades marked the start of a tremendous research activity focusing on the synthesis and applications of fluorinated organic compounds.[92] Different areas, especially biomedicine[93] and agrochemistry[94] have dedicated significant efforts to rationalise the synthesis of fluorocarbons and to find advantageous uses. As an example of that, a wide range of commercialised drugs containing fluorinated moieties are available through industrial-scale production, including compounds such as Gemcitabine, Ezetimibe or Ciprofloxacin, among many others (Figure 1.14). A constant flux of new reviews displaying the fluorinated pharmaceuticals of recent inception and

their status in pharmacological tests, are constantly casted into the available literature.[95] Other applications, such as their use in positron emission tomography (PET)[96] or as radiotracers[97] are also of outstanding importance for biomedicine.

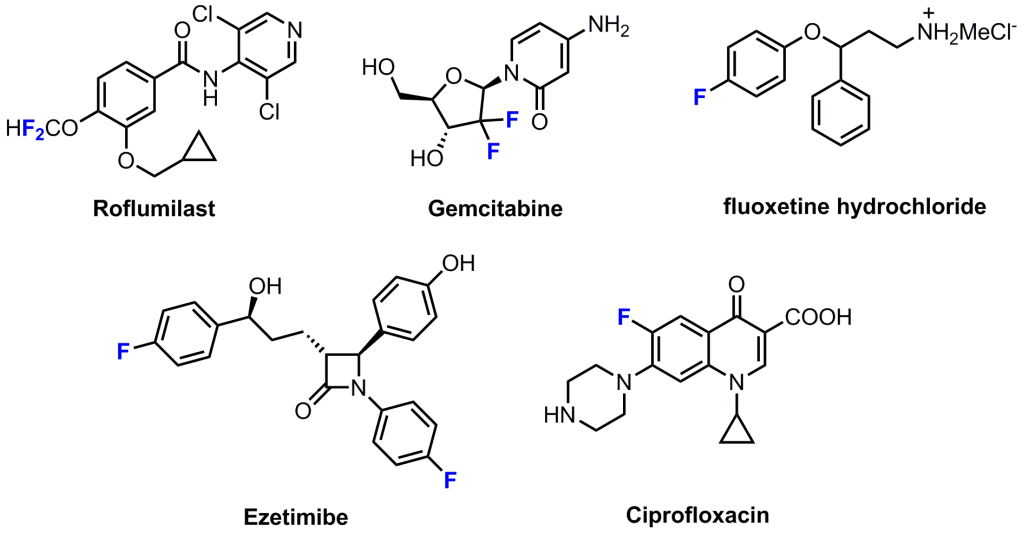


Figure 1.14. Selection of some fluorine-containing "Blockbuster" drugs.

Fluorination chemistry is essentially a "man-powered" area of knowledge, since a very small number of examples of naturally-occurring fluorinated compounds are known,[98] with natural fluorination mechanisms being very rare.[99] Due to the origin of fluorination in human activity, it is not surprising that industrial applications of fluorination currently cover more than 90% of the total fluorination chemistry performed within the scientific world; indeed, industrial manufactures such as optoelectronic materials,[100] lubricants,[101] polymers,[102] refrigerants,[103] dyes[104] or liquid crystals,[105] among many others,[106] are highly developed and profitable.

1.4.1.2 Properties of fluorinated compounds

The peculiarities of the C-F bond are key for the properties of fluorinated compounds. The high electronegativity of the F atom generates a polarised structure which not only creates strong hydrogen bonding with appropriate acceptors,[107] but also alters the dipolar moment of the adjacent centres, as well as their pKa. The result of this is a significant change in the activity of fluorinated moieties as opposed to C-H bonds. It is to be noted that no significant difference in the van der Waals radius (1.35 Å for C-F *vs* 1.10 Å for C-H) and C-bond length (1.26–1.41 Å *vs* 1.08–1.10 Å) can be appreciated between C-F and C-H bonds, with the difference in reactivity being

compatible with an almost perfect structural mimicry of standard C-H bonds in organic molecules. The increased lipophilicity allows a better partitioning into biological membranes, therefore increasing its bioavailability, which represents one of the major interests in their advantageous use in biomedicine and similar areas. Helping with hydrophobic interactions in binding sites and electrostatic bonds with different functionalities is also an important factor of fluorine-containing compounds. The strength of the carbon-fluorine bond and its higher oxidative and thermal stability compared to the hydrogen-based counterpart round up the numerous advantages of fluorinated molecules.

1.4.2 Synthesis of C(sp^2)-F bonds

1.4.2.1 Introduction

The following subchapters will discuss the fundamentals of C(sp^2)-F bond formation, the initial steps and challenges involved in this reaction, and some of the most representative approaches towards the synthesis of fluorovinyl and fluoroaryl species, looking for a better comprehension of this transformation and a better appreciation of the invaluable contributions available thus far.

A basic fluorination reaction consists on the use of a fluorinating reagent to promote C-X cleavage (where X = suitable functionality) and generating a C-F bond in the process. The nature of the displaced functional group is important to determine the type of fluorination reagent to be used, and a good range of these reagents is available to fulfil most chemical requirements. The most common categorisation in fluorination chemistry is done based on the nature of the fluorine source, that is, *electrophilic fluorination* or *nucleophilic fluorination.* A selection of typical compounds for fluorination is shown in Figure 1.15. The use of fluorine gas (F_2) has dominated the field of electrophilic fluorination until very recent decades, [108] when its substitution by easily-handled non-toxic compounds is now evident. Reagents containing N-F moieties are undoubtedly the most used sources of "F^+"; these include F-TEDA derivatives (in particular, the tetrafluoroborate species most commonly known as Selectfluor),[109] as well as NFSI.[110] N-F reagents have been extensively studied, with their fluorination capability being constantly updated with new derivatives and mechanistic insights.[111] On the other hand, the large family of fluoride-based compounds ("F^-") is represented by species such as DAST[113] (belonging to the group of reagents based on S-F

moieties).[112] These reagents have slowly displaced simpler yet less efficient nucleophilic fluorination sources, such as KF or HF. The particular interest in the substitution of HF due to its toxicity and special handling has given room to less toxic surrogates, such as $NEt_3 \cdot 3HF$ or DMPU·HF, which are nowadays very present in HF-promoted chemistry. The use of tetrabutylammonium fluoride (TBAF), despite its simplicity, is still a very useful method for the fluorination of certain substrates.

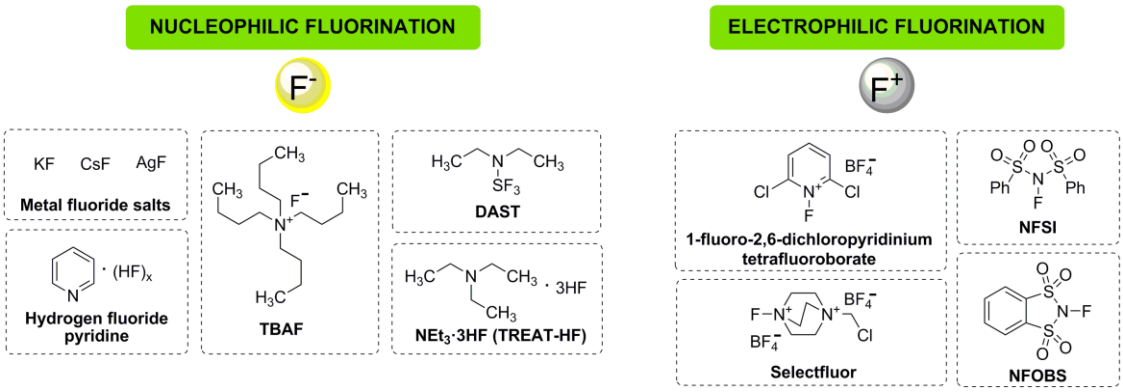


Figure 1.15. Selection of most common fluorination reagents available in the literature.

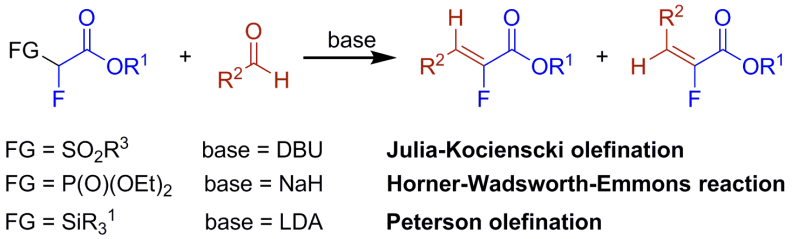
These are only a fraction of the vast amount of fluorine sources that have been successfully used in this reaction, with the use of electrophilic fluorination representing a generally more expensive but more versatile approach[114] than nucleophilic fluorination.[115] As a result of this, the two differentiated routes towards fluorofunctionalisation of chemicals have been studied independently in research, obtaining in both cases useful protocols, which include C(sp^2)-F bond formation reactions.

1.4.2.2 Synthesis of fluoroalkenes: state-of-the-art

The first type of compound containing C(sp^2)-F bonds is the family of fluoroalkenes. The fluorovinyl moiety[116] is a very interesting fragment that has significant presence in chemistry. From unprecedented effects in Diels-Alder cyclisations[117] to strong biological activity as antiviral and enzyme inhibitors[118] (structural mimics of amides)[119] or as suitable co-monomers for polymerisation with ethylene,[120] there is a patent desire in chemistry for the preparation of fluoroalkenes in an efficient and selective way.[121]

The synthetic access to these compounds presents some flexibility, with different approaches being available for their preparation. Traditionally, olefination methods have been used to generate fluorovinyl fragments, with special contribution from three

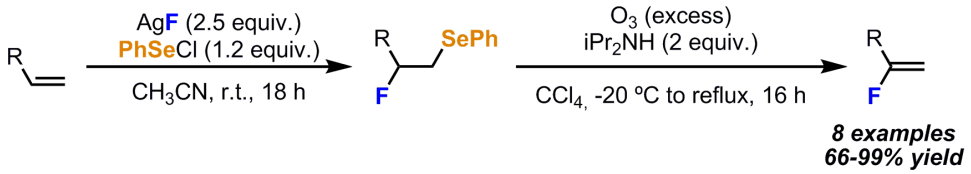
reactions: the Julia-Kocienski olefination,[122] the Horner-Wadsworth-Emmons reaction[123] and the Peterson olefination,[124] as shown in Scheme 1.18. In all three cases, the reaction is based on the functionalisation of aldehydes with appropriate fluorinated esters in the presence of strong bases.



Scheme 1.18. Synthesis of fluoroalkenes using traditional olefination methods based on aldehyde substrates.

While *E*-alkenes are usually obtained as major products using these methods (as described in the original protocols)[125,126] the efficiency of these reactions has proven limited for more general fluoroalkene synthesis. Important substrate dependence, complex synthetic routes for the preparation of the starting materials and overall low yields (<80%) are underlined as the major drawbacks in these reactions.

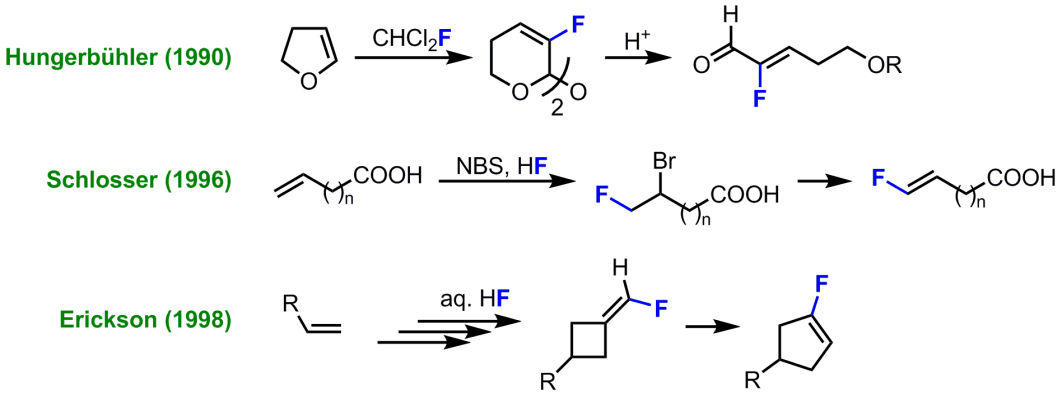
In response to these synthetic problems, new methodologies were extensively tested during the second half of the 20th century, with good results. For example, in 1990, the direct fluorination of alkenes was exploited by McCarthy and co-worker, who reported a sequential fluoroselenation/demetallation reaction of monosubstituted alkenes, yielding 2-fluoro-1-alkenes in moderate to excellent yields (Scheme 1.19).[127]



Scheme 1.19. Fluoroselenation/demetallation of olefins for the synthesis of 2-fluoro-1-alkenes.[127]

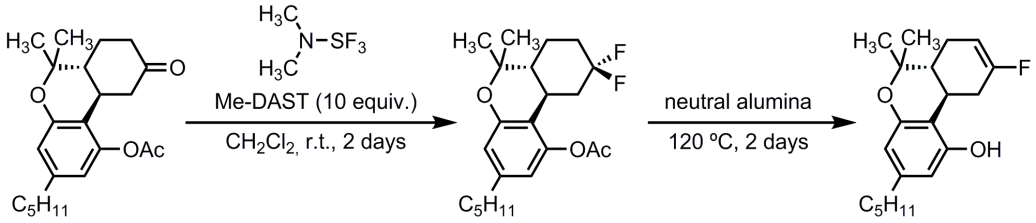
While the reaction is an excellent approach to disubstituted *gem*-fluoroalkenes under mild conditions, the multistep conversion using expensive reagents at high loadings and with a short scope of substrates has not allowed a more extensive use of such a methodology. The synthesis of fluoroalkenes through formal C-H fluorination of olefins is rare, and as shown in the previous example, usually requires big excesses of additives to proceed with good results. During the 1990's, some other examples of C-H

activation/fluorination reactions were discovered, such as the use of fluoroacetals obtained from 2,3-dihydrofuran[128] for the synthesis of fluorinated acrolein derivatives,[129] the studies on fluorobromination-dehydrobromination of alkenes[130] or the preparation of cyclic fluoroalkenes by carbanionic rearrangements on halomethylenecyclobutanes (Scheme 1.20).[131]



Scheme 1.20. Some examples of fluoroolefin synthesis reported during the 1990's.

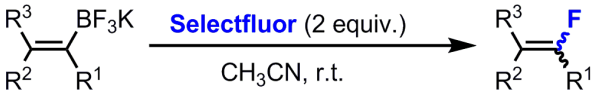
In a similar fashion to the work of McCarthy, multistep processes were required in order to reach the final desired compounds, and the substrate scopes for these protocols were very limited. The presented examples summarise the inherent difficulties of direct fluorination of olefins for an easy access to fluoroalkenes, and the use of different approaches was certainly considered as a good alternative. Indeed, the activation of other moieties for fluorination has found a much more general applicability and a wider range of useful synthetic possibilities. For example, the work from Tius and co-workers shows the advantageous use of ketones as fluoro-olefin precursors in the functionalisation of complex molecules. In their report, a halogenated cannabinoid, (-)-11-nor-9-keto-hexahydrocannabinol (HHC), was treated with ten equivalents of dimethylaminosulfur trifluoride (Me-DAST) in CH_2Cl_2 at room temperature for 2 days, affording the bis-fluoride species which, upon stirring at 120 ºC in the presence of neutral activated alumina in a sealed tube for two days, cleanly afforded the corresponding fluoroalkene (Scheme 1.21).[132]



Scheme 1.21. Difluorination/elimination reaction in cannabinoids promoted by Me-DAST under mild conditions.[132]

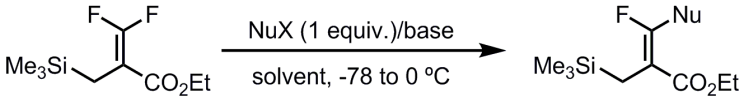
The use of "masked" fluoro-olefins is not strictly necessary for efficient fluorination, and the activation of other functional groups attached to C(sp^2) carbons has also been claimed in this type of chemistry. For example, alkenylboronic acids are suitable fluoroalkene precursors, as shown by the work of Olah in 1997 (Table 1.3).[133] While stereoselectivities were not very high (unless sterically-demanding substituents were present), the simplicity of the method demonstrated a great advantage for synthetic purposes.

Table 1.3. Fluorination of alkenyltrifluoroboronate salts with Selectfluor.[133]



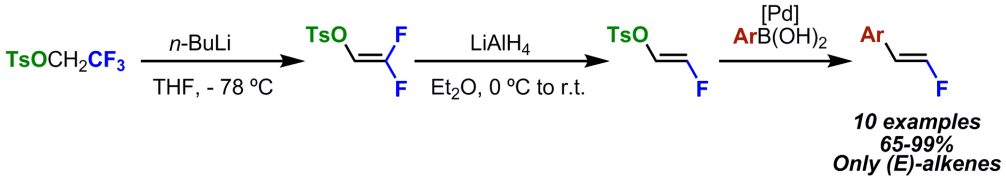
R^1	R^2	R^3	Yield (%)	*E:Z* (%)
H	Ph	H	89	50:50
H	Bu	H	58	50:50
H	4-MeC_6H_4	H	87	50:50
H	4-ClC_6H_4	H	78	50:50
Ph	Ph	H	71	85:15
H	Ph	Br	65	50:50

Since the last decade of the 20th century, a very extensive exploitation of fluoroalkene synthesis has occurred, with many revisited concepts being an important part of successful fluorination attempts. The principles of addition-elimination mechanisms visited in the past for the fluorination of olefins were suitable, for example, for the transformation of *gem*-difluoroalkenes to tetrasubstituted fluoroalkenes in the presence of nucleophiles, as observed by Shi and co-workers in 2000 (Scheme 1.22).[134]



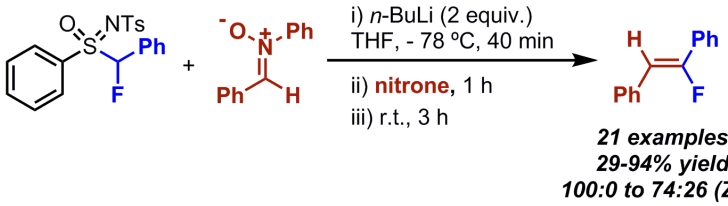
Scheme 1.22. Addition/elimination mechanism for the preparation of fluoroalkenes from *gem*-difluoroalkenes.[134]

Despite bringing the two-step concept back to synthetic proposals, this type of reactions has in fact found good application since the obtained results have compensated for the higher complexity of the route. Another example of this mechanism for the fluorination of olefins is the work reported by Hong and co-workers in 2010, when 2,2,2-trifluoroethyl tosylate was transformed to the corresponding 2-fluorovinyl tosylate in the presence of *n*-BuLi. This intermediate could be then treated with $LiAlH_4$ at low temperatures to selectively perform for the access to selective monodefluorination, yielding *E*-fluorovinyl tosylates. In the last step, the cross-coupling reaction with various boronic acids, catalysed by palladium, afforded disubstituted *E*-fluoroalkenes as reaction products (Scheme 1.23).[135]



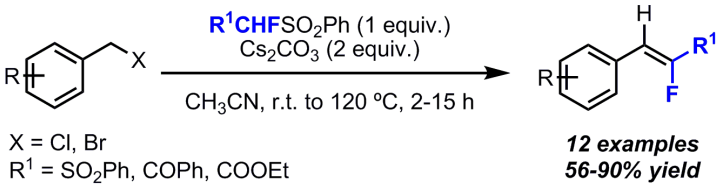
Scheme 1.23. Vicinal disubstituted fluoroalkene synthesis *via* three step fluorination/elimination/cross-coupling with boronic acids.[135]

During the new "golden age" of addition-elimination chemistry, a surprising *renaissance* of the olefination based on aldehydes was witnessed. The inspiration came from previous decades, when Purrington detailed the feasibility of α-fluorosulfoxides as interesting precursors for fluoroalkene synthesis in 1987,[136] overcoming experimental difficulties experienced during the classical fluoroolefination approaches. The use of *S*-containing fluoroalkanes was recovered in later years by Hu, in a methodology that reacted α-fluorosulfoximines and nitrones for the isolation of trisubstituted fluoroalkenes in up to 94% isolated yield and generally good stereoselectivities (Scheme 1.24).[137]



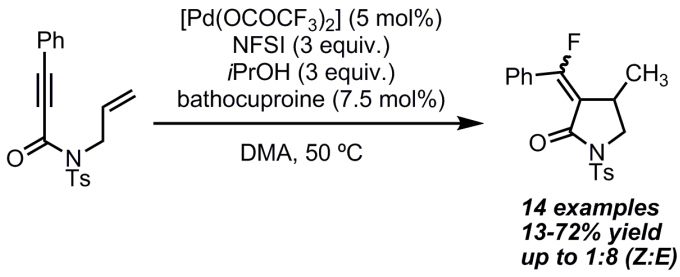
Scheme 1.24. Synthesis of trisubstituted fluoroalkenes from α-fluorosulfoximines and nitrones.[137]

In the same year, Olah and co-workers discussed a very interesting feature of Julia-type conditions: their adaptability to other substrates. In this case, the use of α-fluorobis(phenylsulfonyl)methane efficiently transformed alkyl halides (bromo- or chloro derivatives) into their corresponding fluoroethene derivatives, promoted by the use of Cs_2CO_3 in acetonitrile as solvent (Scheme 1.25).[138] The versatility of sulfur-derived fluoroalkanes as fluorinated fragments was further reinforced with this method, extending the substrate scope and amplifying the synthetic possibilities of this setup.



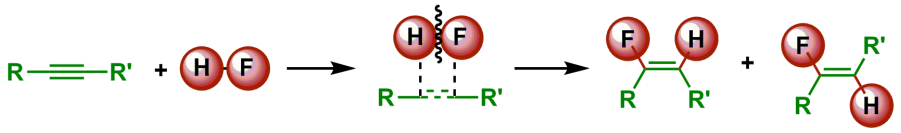
Scheme 1.25. Modification of Julia-Kocienski conditions for the synthesis of fluoroalkenes using benzyl chlorides or bromides.[138]

The use of transition metal catalysts for the fluorination of olefins has been omitted from this fluorination field until recently, when some of the most fresh methodologies involved such type of reaction promoters. One of the first available reports is the use of Pd catalysis in conjunction with NFSI, for setting-up a vinylic C-F bond after a tandem cyclisation/fluorination protocol for enynes, as reported by Liu and co-workers (Scheme 1.26).[139]



Scheme 1.26. Pd-catalysed cyclisation of enynes with concomitant C-F bond formation.[139]

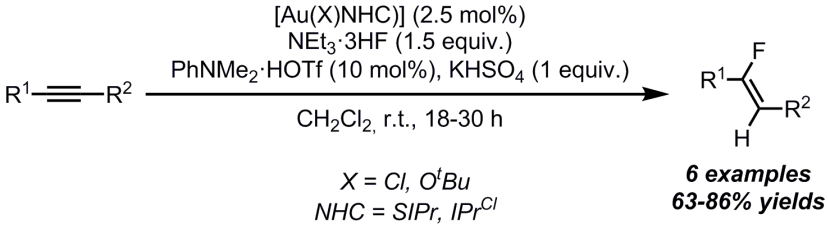
Within the field of transition metal catalysis, the research community has abandoned the old concepts of fluoro-olefin synthesis and has focused on a synthetically different approach: the hydrofluorination of alkynes. This reaction consists on the direct addition of an HF unit to a triple bond, formally reducing the alkyne to an alkene with concomitant C-F and C-H bond formation (Scheme 1.27).



Scheme 1.27. General scheme for the reaction of alkynes with HF for the synthesis of fluoroalkenes.

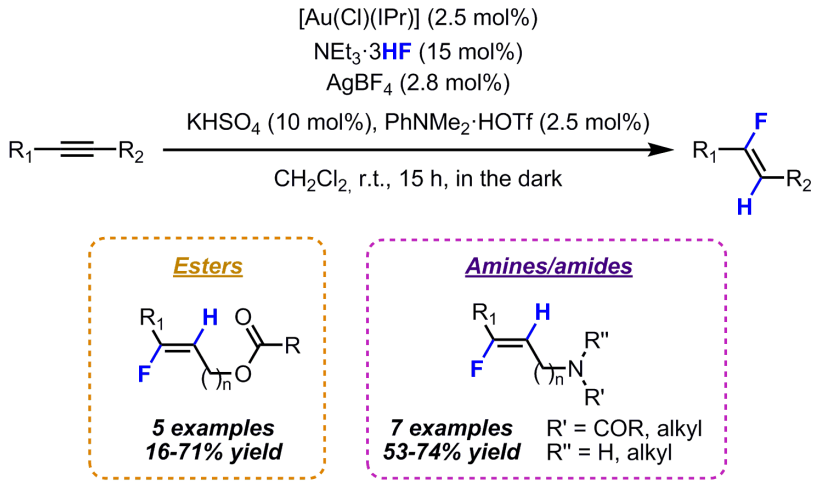
The commercial availability of alkynes covering a wide structural diversity, together with a higher atom economy of the hydrofluorination process and a simple reaction mechanism have facilitated the integration of this alternative methodology into the commonly performed fluorination methods. While the use of HF is decreasing due to its toxicity and handling difficulties, new families of HF surrogates have been synthesised and used for fluorination. Their behaviour in the addition to triple bonds has been proven similar to that of HF, and with the aid of metals, the newly formulated methodologies have responded positively to the demand of more consistent and robust synthetic systems.[140]

The use of Au(I) species has been a major breakthrough in hydrofluorination chemistry, providing unique reactive features for selective synthesis of fluorovinyl moieties. The highest exploitation of this reaction is based on the use of Au(I)-NHC complexes (a reactive feature that will be the foundation for the experimental work detailed in future chapters of this thesis). The pioneering work of Sadighi and co-workers in 2007 initiated the very successful field of hydrofluorination of alkynes promoted by Au(I)-NHC species.[141] Under mild conditions, the conversion of symmetrical and unsymmetrical alkynes to the related fluoroalkenes was achieved (Scheme 1.28). Two different catalysts were used in the presence of various additives for optimal results, but unfortunately a narrow scope of substrates was obtained, with isolated yields of up to 84% and a difficult control of the stereoselectivity of some resulting alkenes, which might explain its limited applicability to the synthesis of complex fluoroalkenes.



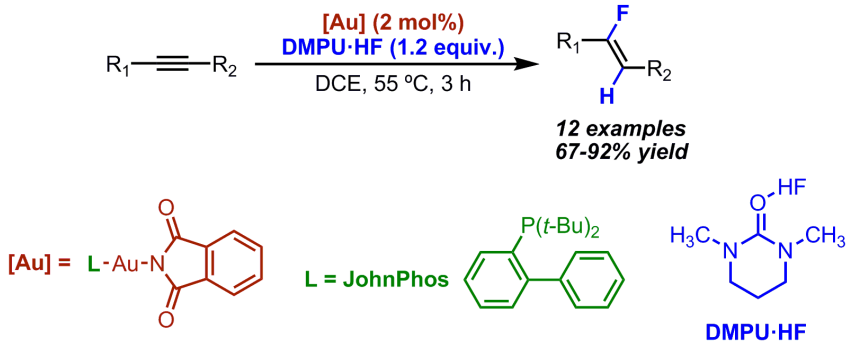
Scheme 1.28. Hydrofluorination of internal alkynes catalysed by [Au(X)(NHC)] complexes.[141]

Despite its limitations, ulterior studies have revealed how powerful this type of Au-catalysed reaction is for the hydrofluorination of alkynes. In 2009, Miller made use of [Au(Cl)(IPr)] as catalyst in the conversion of alkynes to fluoroalkenes in the presence of directing groups for selective HF addition.[142] By the combination of certain additives, the use of NEt_3·3HF as hydrofluorination promoter was again satisfactory, allowing the synthesis of 13 examples of hydrofluorinated alkynes with yields up to 74% (Scheme 1.29). Despite a better general reactivity and selectivity, the strong substrate dependence and the difficulty in obtaining high isolated yields have also precluded this methodology from having a wider scientific diffusion.



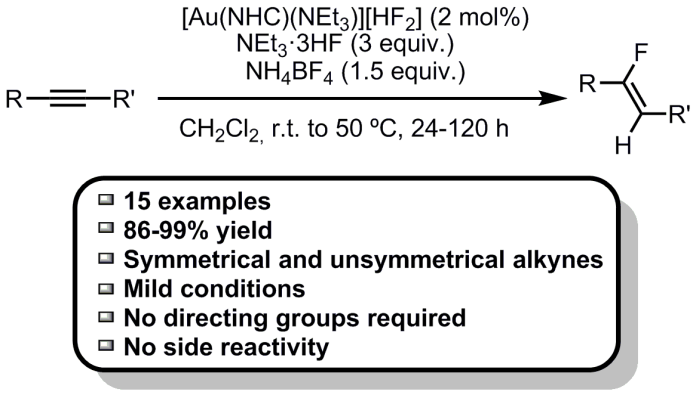
Scheme 1.29. Hydrofluorination of internal alkynes with directing groups catalysed by [Au(Cl)(IPr)].[142]

Moving away from NHC-ligated Au(I) complexes has also provided interesting results. The work of Xu in 2014 is a clear example of the utility of Au(I)-phosphine species for the synthesis of trisubstituted fluoro-olefins. Hydrofluorination of alkynes employing DMPU·HF as hydrofluorination reagent could proceed efficiently only when catalysed by an imidogold(I) complex, with JohnPhos as additional ligand (Scheme 1.30).[143]



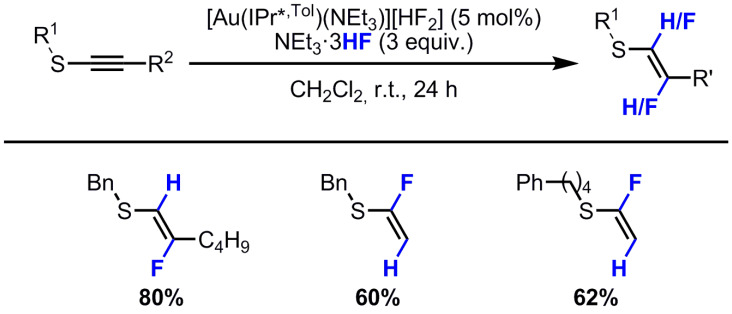
Scheme 1.30. Au(I)-catalysed hydrofluorination of alkynes with DMPU·HF.[143]

In 2015, Nolan and co-workers reported, as part of their investigation on new Au(I) catalysts, an efficient hydrofluorination of alkynes using a new family of Au(I)-NHC species, with the general formula $[Au(NHC)(NEt_3)][HF_2]$. These Au(I) bifluorides provided mild access to the desirable fluoroalkenes using $NEt_3{\cdot}3HF$ as fluorine source. (Scheme 1.31).[88] With a wide substrate scope, including both symmetrical and unsymmetrical alkynes, the need for fewer additives and higher yields, this approach represents the latest and most competitive methodology for the hydrofluorination of internal alkynes available in the literature, highlighting the interest in the use of Au(I)-NHC species for fluorination chemistry.



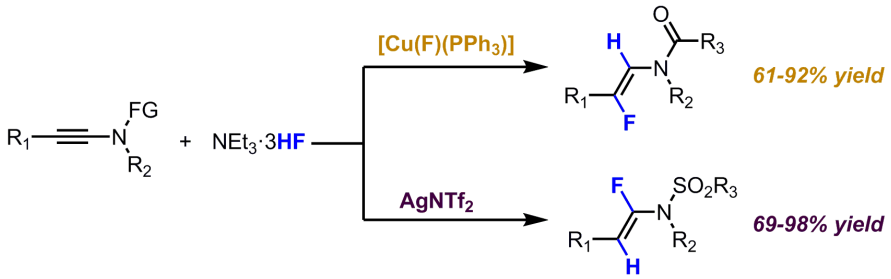
Scheme 1.31. Au(I)-catalysed hydrofluorination of internal alkynes.[88]

While the exploitation of hydrofluorination chemistry has been mainly focused on the use of internal alkynes with aryl or alkyl chains as substituents, other approaches using other alkyne derivatives have some presence in the literature. In the same work from the Nolan group, the application of a variant of the optimised system to alkynyl sulfides as substrates provided an expedient access to selective synthesis of fluorovinyl thioethers (Scheme 1.32).[88] In this case, $[Au(IPr^{*Tol})(NEt_3)][HF_2]$ was chosen as catalyst, expanding the versatility of Au(I)-NHC bifluorides in catalysis.



Scheme 1.32. Au-catalysed hydrofluorination of alkynyl sulfides.[88]

Another report by Zhu has revealed the suitability of hydrofluorination conditions to yield the corresponding fluorinated enamides under Cu(I)- or Ag(I)-catalysed conditions (Scheme 1.33).[144] The stereo- and regioselectivities were strictly controlled by the substituents in the nitrogen atom, affording stereocontrol of the products ranging from 81:19 to >99:1 (*Z:E*).

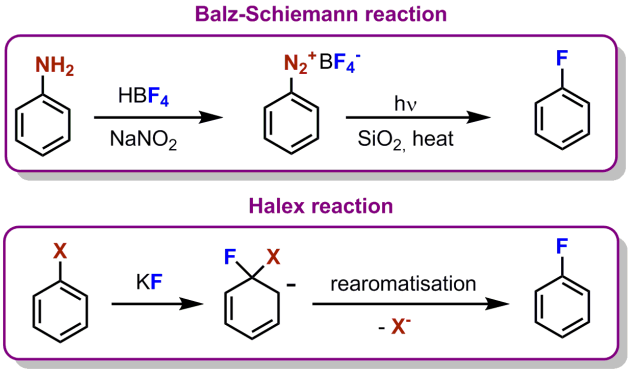


Scheme 1.33. Cu(I)- and Ag(I)-catalysed *trans*-hydrofluorination of ynamides.[144]

1.4.2.3 Synthesis of fluoroarenes: state-of-the-art

The synthesis of aryl fluorides by C(sp^2)-F bond formation on aromatic derivatives has focused more synthetic efforts than the fluorination of olefins, due to a greater interest in aromatic species and their wider presence in valuable chemicals. This field of study has become a very attractive area to the chemistry community due to the associated challenges;[145] nonetheless, the benefits derived from the synthesis of aryl fluorides certainly compensate the dedication of research groups over the years. In a similar fashion to fluoroalkenes, the pharmaceutical and agrochemical industry have certainly taken advantage of the improved solubility, bioavailability and *in vivo* stability of fluorinated aromatic compounds.[146] The use of aryl fluorides as building blocks has been also investigated, with reported reactions such as hydrodefluoration,[147] defluorination/metallation[148] and many other examples[149] being of interest for lesser research activities.

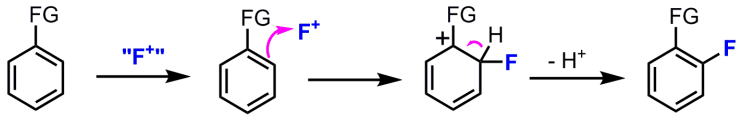
The discussion about aromatic fluorination has been open for decades.[150] In spite of the success of the most recent approaches, it is certainly interesting to witness that the so-called "traditional methods", such as the Balz-Schiemann reaction[151] or the nucleophilic substitution of bromo- or chloroarenes with KF (HALogen EXchange, or *Halex reaction*)[152] (Scheme 1.34) are still valid methods in the recent literature, despite their limited efficiency from a general synthetic perspective. This exposes the lack of good reactivity and selectivity in aromatic fluorination, a major inconvenience that has only been partially assessed over the years and that concentrates a significant amount of efforts to overcome such drawbacks.



Scheme 1.34. Traditional fluorination methodologies: Balz-Schiemann reaction and halide exchange with KF (Halex reaction).[151,152]

1.4.2.3.1 Electrophilic fluorination

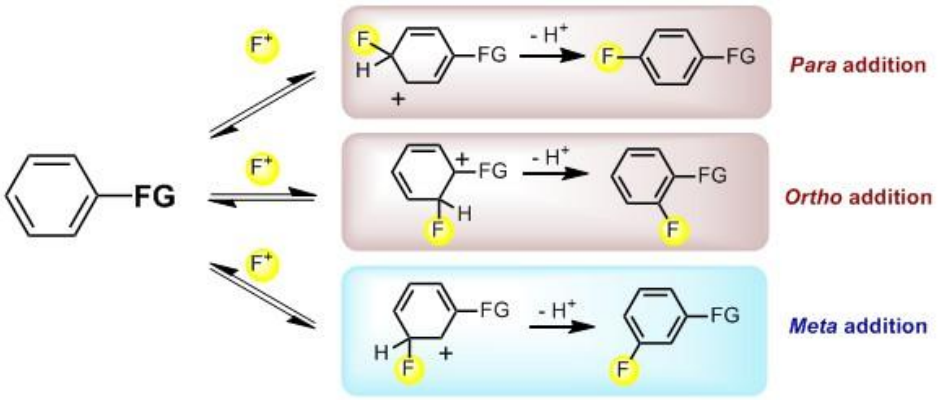
This is the most direct and reactive approach for the synthesis of aryl fluorides. It consists of the direct attachment of an electrophilic fluorine source to an aromatic compound, by means of a temporary dearomatisation of the compound. Further loss of a given entity in the ring (usually hydrogen, but the reactivity can be tuned by the presence of other functional groups) regenerates the aromaticity of the ring, providing the desirable fluoroarene (Scheme 1.35).



Scheme 1.35. General scheme for electrophilic fluorination of arenes.

While significant experimental work has been focused on electrophilic fluorination, important selectivity issues are present based on this mechanism. A strong dependence on the functionalisation of the substrate for selective fluorination can be witnessed. As in typical S_NAr reactions, the directing capability of organic

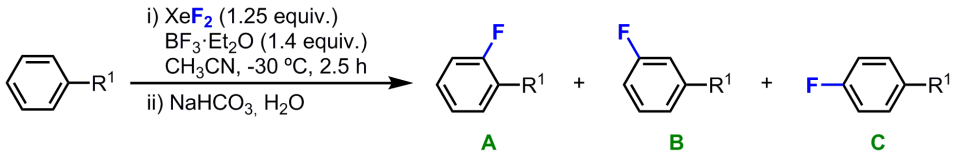
functionalities is key for appropriate reactivity, with electron-donating groups favouring *ortho*- and *para* fluorination, whereas electron-withdrawing groups orientate fluorine addition to *meta* positions (Scheme 1.36). Fundamental resonance and inductive effects apply as well to fluorination chemistry.



Scheme 1.36. General scheme for electrophilic fluorination of arenes.

A very recent and detailed mechanistic study shows how complex electrophilic fluorination can be even in the case of simple compounds.[153] Table 1.4 summarises some of the results obtained for the fluorination of simple monosubstituted benzene derivatives using XeF_2 as fluorinating reagent. These values display how the use of electron donating groups does not promote high selectivities in fluorination, only slightly favouring the *ortho*- and *para* functionalisation due to their intrinsic electronics (Table 1.4, Entries 1-3). On the other hand, the use of electron withdrawing groups seems to have a much larger influence on the site selection for "F^+", as shown by the lower amount of *ortho* and *para* products in comparison to the *meta* adduct (Table 1.4, Entry 4). However, it is noticeable that electron-donating groups greatly reduce the consumption of starting material, leading to only 10% conversion of the substrate.

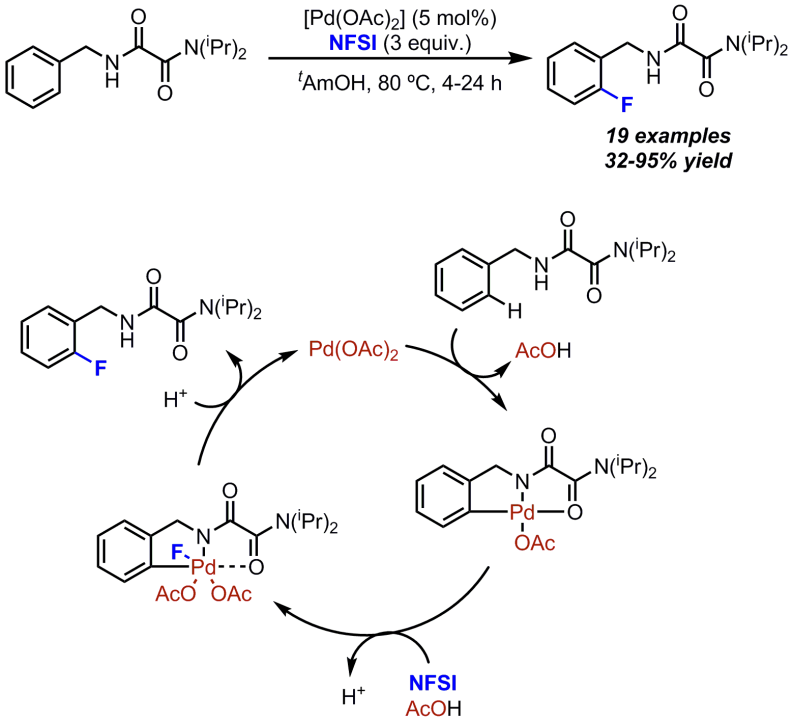
Table 1.4. Studies on the nucleophilic fluorination of monosubstituted benzenes.[153]



Entry	R^1	SM conversion (%)	Yield (%)	Isomer ratio (%)		
				A	B	C
1	Me	94	21	62	9	29
2	Cl	99	42	63	8	29
3	Br	99	56	29	9	62
4	NO_2	10	6	9	89	2

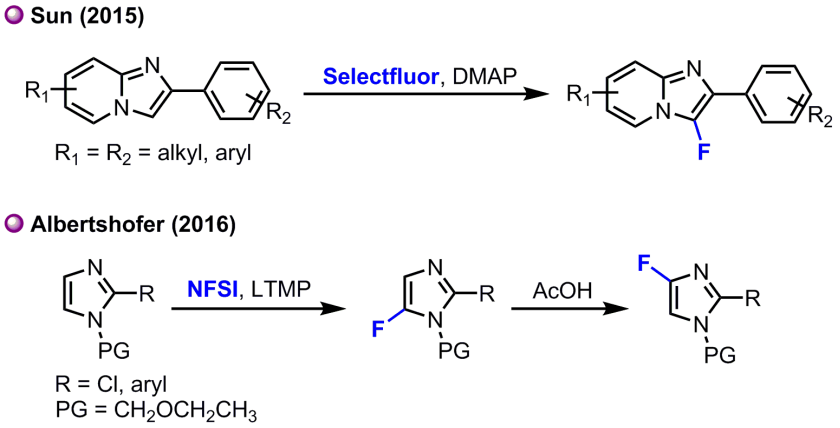
This complexity of electrophilic fluorination has involved great efforts to understand its mechanism, especially in the case of substrates with no directing groups (for example, electrophilic fluorination of benzene). While some reviews have assessed the C-H activation of "naked" arenes towards fluorination,[154] the generated discussion has not provided a consistent set of synthetically useful reactions. On the other hand, it is clear that directed fluorination of C-H bonds is a much more active field, with a reduction of the substrate scope in favour of a better reactivity and selectivity of the fluorination process. This approach has therefore gathered major synthetic efforts for better electrophilic fluorination methods to be unravelled.

Some examples from the recent literature can be presented for a better understanding of the structural parameters that are currently being exploited for efficient electrophilic fluorination of C-H bonds. The first case is the discovery of oxalyl amide-protected benzylamines as good substrates for the *ortho* C-H fluorination of aromatic rings in a very selective manner.[155] The great regioselectivity of the process can be explained by means of the reaction mechanism, which involves a Pd(II) catalyst coordinating to both oxygen and nitrogen in a planar structure favouring the activation of the *ortho* C-H bond in the aromatic moiety. Since the C-H activation of any other aromatic position generates a much more strained intermediate, other regioisomers are precluded in this reaction. The obtained tetrasubstituted Pd(II) intermediate leads to reductive elimination of the corresponding *ortho*-fluorinated aromatic compounds, after oxidation to Pd(IV) and Pd-F bond formation in the presence of NFSI (Scheme 1.37).



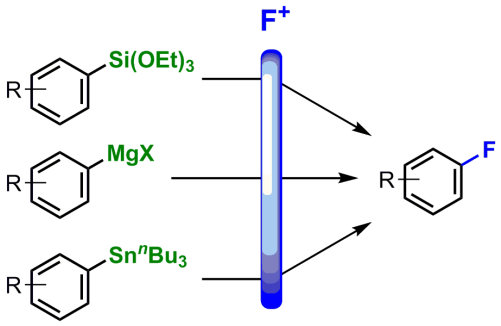
Scheme 1.37. Fluorination of *ortho* C-H bonds in oxalyl amide-protected benzylamines catalysed by $[Pd(OAc)_2]$.[155]

This example clearly shows how important directing groups can be for efficient C-F bond formation, since no side reactivity was observed during the course of the presented reaction. The selective control of the fluorination of imidazole rings by the presence of appropriate protecting/directing groups,[156] or the pKa/aromaticity-directed mild control of the fluorination of imidazo[1,2-a]pyridines using Selectfluor[157] are only a few examples that showcase the abundance of *ortho*-directing chemistry in the synthesis of fluoroarenes (Scheme 1.38).[158] The main problem of this type of reactions is the synthetic restriction to *ortho*-activated positions in aromatic rings, hampering the substrate design for specific fluorination targets.



Scheme 1.38. Other selected examples of substrate-directed fluorination of C-H bonds.[156,157]

Another perspective on directed fluorination can be considered, where a given functional group is directly substituted by fluorine. This pathway makes use of a much easier reaction mechanism, facilitating the design of feasible synthetic routes. In practice, this concept has definitely shown good performance with a variety of functionalities as directing moieties for fluorination; among those, the use of organometallic reagents represent one of the oldest approaches for C-F bond synthesis, and it is still nowadays being used by many researchers. A short summary of some of these reactions is herein described:



- ***Arylsilanes:*** the use of arylsilanes has been showcased in 2011, where the use of over-stoichiometric Ag(I) oxide and barium oxide, in the presence of Selectfluor, could efficiently catalyse the direct fluorination of triethoxysilylarenes using acetone as solvent at 90 ºC for 2 h. A total of 16 examples of aryl fluorides with 60-90% yields were reported.[159]

- ***Grignard reagents:*** despite the historically known substrate dependence of the reactivity of Grignard reagents under electrophilic fluorination conditions,[160] certain Grignard reagents can promote efficient electrophilic fluorination under mild

conditions, as shown by the work reported in 2010. The simple preparation of organomagnesium reagents from aryl bromides, combined with the use of NFSI, afforded clean conversion of 19 examples of the LiCl adducts in a CH_2Cl_2:perfluorodecalin solvent mixture (4:1), after only 2 h at room temperature, with yields of up to 94%.[160] During the same year, Beller also reported the utility of these adducts for fluorination using a different fluorination reagent (*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, F-TMP-BF_4) in heptane or $CH_3OC_4F_5$ as solvent, at 0 ºC for 1.5 h, to obtain a similar number of selectively fluorinated aromatic compounds in good yields.[162]

- ***Aryl stannanes:*** electrophilic fluorination using F-TEDA-PF_6 in the presence of overstoichiometric AgOTf afforded 12 examples of aryl fluorides in 63-83% yields after stirring for 20 minutes at 23 ºC in acetone, as reported in 2009.[163] A slight modification of this system has been applied to the efficient fluorination of small molecules of chemical interest, including flavanone, taxol or quinine, among others (Figure 1.16).[164]

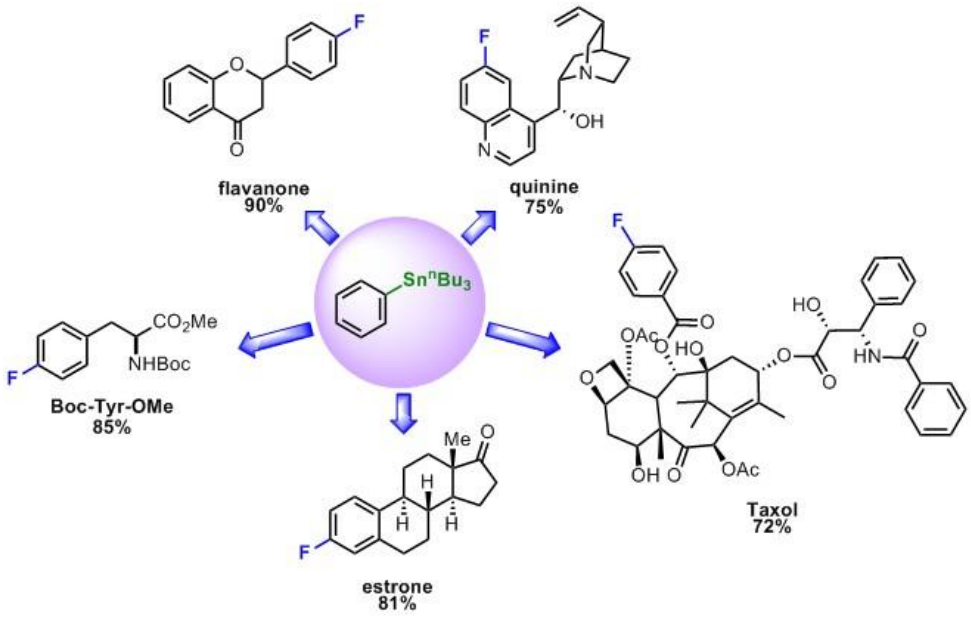
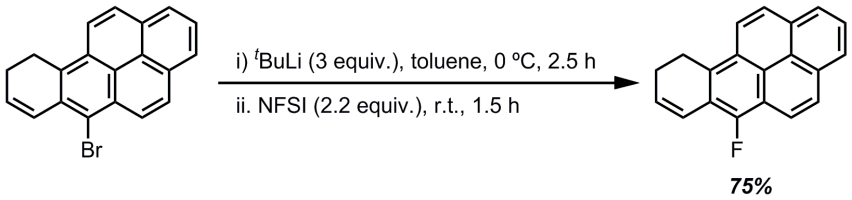


Figure 1.16. Selected examples of fluorinated small molecules using aryl stannanes as substrates *via* a modified procedure from the original work by Ritter.[164]

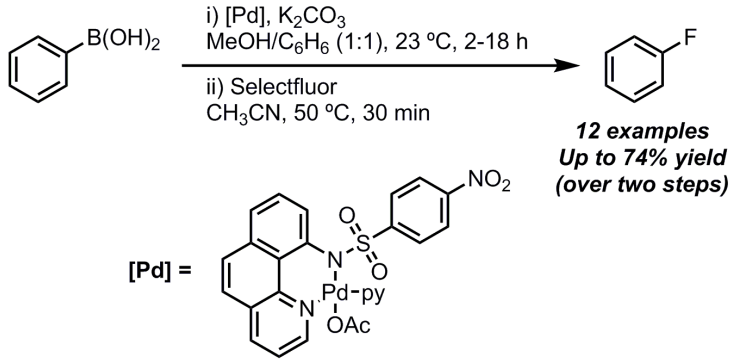
- ***Other metallated aryl derivatives:*** other metal-based species have been used as precursors for fluorination, although most of these adducts are prepared and reacted *in situ*, and therefore present little to no competitiveness with previously analysed substrates. As an example, aryllithium compounds are reactive towards electrophilic fluorination sources, as it has been shown by the *in situ* generation of a lithium adduct

of a bromopyrene derivative, followed by reaction with NFSI, providing moderate yield of the related fluoropyrene (Scheme 1.39).[165]



Scheme 1.39. Simple fluorination of boronic acids and salts with Selectfluor under mild conditions in acetonitrile as solvent.[165]

Overcoming the inconveniences of preparing complex starting materials is always a priority in the simplification of synthetic routes; to do so, the use of cheap commercially available substrates with great structural diversity is greatly desirable. The impractical use of organometallic species has been revised in order to access better directing groups with a higher availability. As a result, boronic acids have been acknowledged as suitable substrates for aromatic fluorination. Ritter initially explored the reactive features of these substrates in 2008, discovering the utility of arylpalladium (II) complexes for the reductive elimination of aryl fluorides in the presence of Selectfluor.[166] After these preliminary results, they rapidly reported the application of this methodology to a broader scope of arylboronic acids, obtaining acceptable results (Scheme 1.40).[167]



Scheme 1.40. Pd(II)-catalysed two-step fluorination of boronic acids.[167]

These results were certainly interesting, and have attracted much attention due to the easy access to boronic acids. A brief parenthesis to the use of transition metals for this reaction is to be mentioned, with the work of Lemaire showing the conversion of certain boronic acids and organotrifluoroborates with Selectfluor as a sole reagent in acetonitrile as solvent.[168] Despite the great efficiency of this system, a very restricted and specific substrate scope was presented (Figure 1.17). On the other hand, this

investigation encouraged the use of trifluoroborate chemistry in fluorination reactions, with some interesting approaches now available.[169]

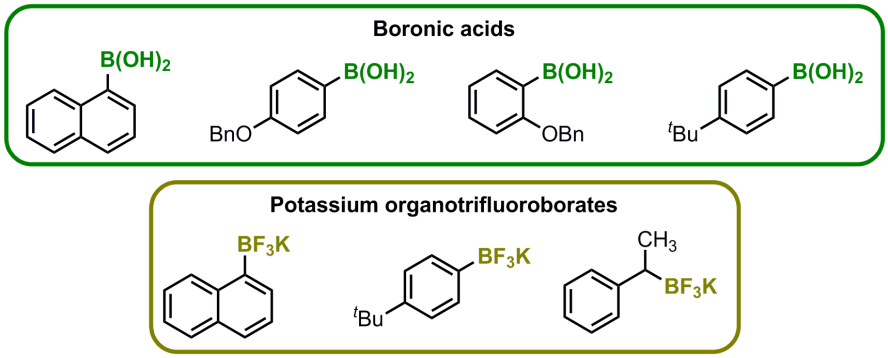
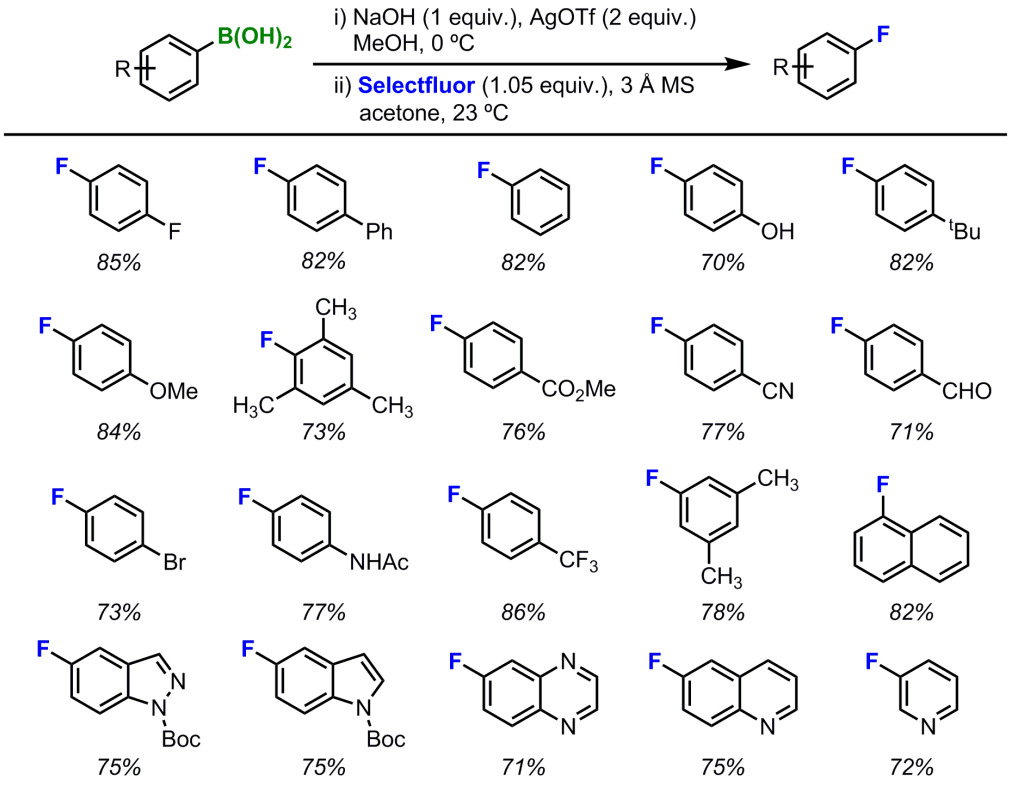


Figure 1.17. Studied substrates undergoing simple fluorination using Selectfluor in acetonitrile under catalyst-free conditions.[169]

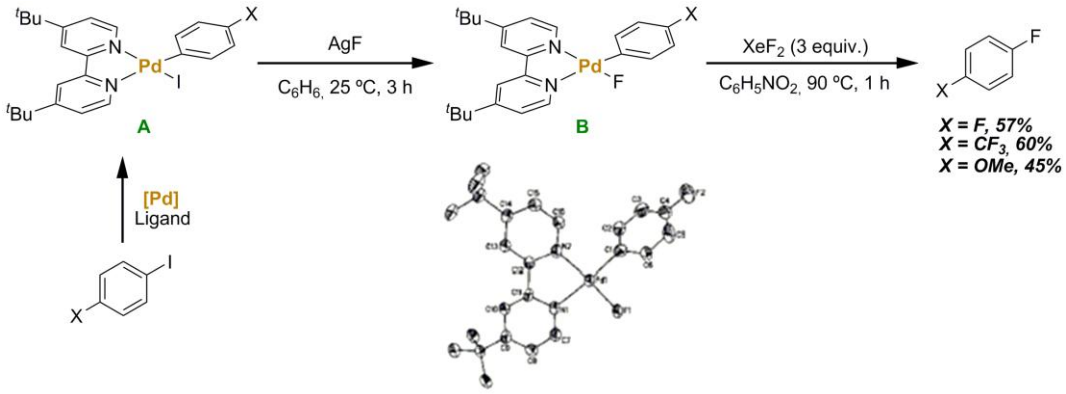
With the emergence of transition metal catalysis, Ritter re-investigated the opportunities generated by boronic acids in fluorination, and in this case, using a simple Ag(I) salt and Selectfluor, 20 examples of fluorinated molecules with moderate yields were accessed from the corresponding boronic acids.[170] The broader scope of substrates certainly justifies the use of a more complex system, as both electron-rich and electron-poor aromatic rings were tolerated by this system (Scheme 1.41), therefore proving to be one of the most general methodologies for fluoroarene synthesis available in the literature to date.



Scheme 1.41. Scope of aryl fluorides prepared through Ag(I)-promoted fluorination of arylboronic acids in the presence of Selectfluor.[170]

While Ritter moved away from palladium chemistry with this approach, this metal has not been yet disregarded as an alternative approach to silver, with the interest in reducing the metal loading to catalytic quantities (as opposed to the use of over-stoichiometric amounts of AgOTf in the aforementioned report). The research of Sanford and co-workers has been of central importance for this purpose. In 2006, a Pd(II) salt was discovered to be an efficient catalyst for the C-H activation of C(sp^3)-H bonds in quinoline derivatives and promoting straightforward fluorination in the presence of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as "F^+" source. This transformation could be further extended to the formation of C(sp^2)-F bonds, albeit in moderate yields.[171] Reasonable oxidative addition of functionalised aromatic compounds to palladium, followed by fluorine transfer from the electrophilic fluorination source, can occur in these systems. This can concomitantly take place by either oxidation of the Pd centre (for an example of this route, see Scheme 1.37) or by simple ligand displacement (Scheme 1.42). Reductive elimination could then lead to the desired compound. Sanford studied the reaction intermediates involved in this type of cycle, in an attempt to acknowlede such elementary steps.[172] Indeed, a tetracoordinated arylpalladium(II) iodide species (Scheme 1.42, **A**) could be reacted with AgF under

sonicating conditions to obtain the corresponding monofluoride unsymmetrical square planar complex (Scheme 1.42, **B**). This species was further reacted with XeF_2 in nitrobenzene as solvent, affording the expected aryl fluoride as product. Different substrates were run, obtaining equivalent results and isolating the corresponding fluoroarenes in moderate yields.



Scheme 1.42. Mechanistic studies on the fluorination of aryl iodides using a Pd(II) complex. Crystal structure of **B** reproduced from reported literature.[172]

Despite these results, Sanford discovered that the critical C-F bond formation step from complex **B** was not the only feasible approach. In fact, another Pd species could be isolated after treating **B** with three equivalents of XeF_2 at 70 ºC for a couple of minutes. The resulting Pd(IV) complex was further identified as the octahedral bifluoride complex shown in Figure 1.18, which also proved active for the release of aryl fluorides when reacted with XeF_2. These results represent important mechanistic insights into the synthesis of fluoroarenes in the presence of transition metal complexes.

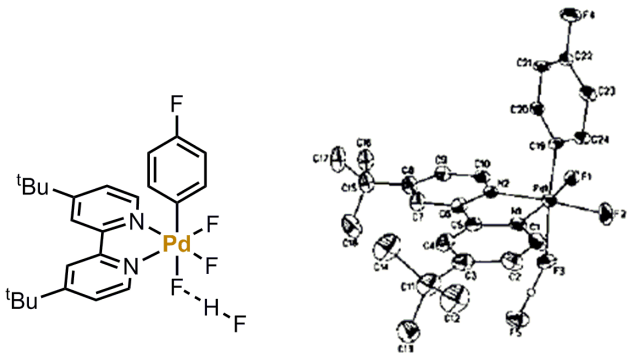
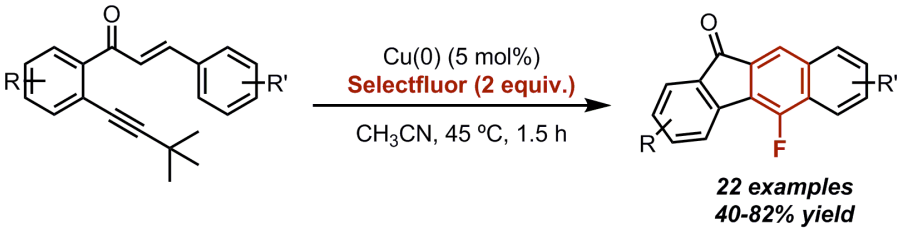


Figure 1.18. Pd(IV) bifluoride complex obtained during the mechanistic studies of C-F bond formation in appropriately substituted Pd(II) complexes. Crystal structure reproduced from reported literature.[172]

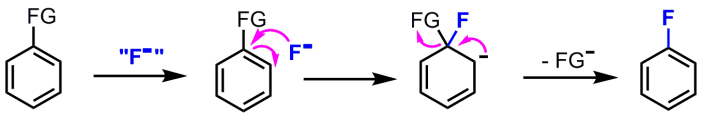
Lastly, the *in situ* preparation of fluorinated aromatic rings from aliphatic species also has some presence in the literature. Among these, cyclisation reactions accompanied by the addition of nucleophiles or electrophiles are very typical in compounds containing suitable arrays of alkene/alkyne functionalities, with fluorine incorporation being one possibility. The work from Liu in 2015 displays an example of the mentioned reactive path, where 1,6-enynes were used for multicyclization studies in the presence of Selectfluor, ultimately providing fluorinated polyaromatic scaffolds in up to 82% isolated yield (Scheme 1.43).[173] This complex C-C bond cleavage/annulation/fluorination sequence under very mild conditions represents a good example of the utility of electrophilic fluorination for complex systems when appropriate systems are used.



Scheme 1.43. Synthesis of fluorinated aromatic rings *via* Cu-catalysed cyclization of 1,6-enynes.[174]

1.4.2.3.2 Nucleophilic fluorination

The methods employing nucleophilic fluorination are based on the reaction of a nucleophilic fluorine source with an aromatic compound, generating a carbanion intermediate that, similarly to the case of electrophilic fluorination, temporarily disrupts the aromaticity of the ring. The extrusion of an anion with lower nucleophilicity drives the regeneration of the aromatic character, releasing the desired fluoroarenes in the process (Scheme 1.44).

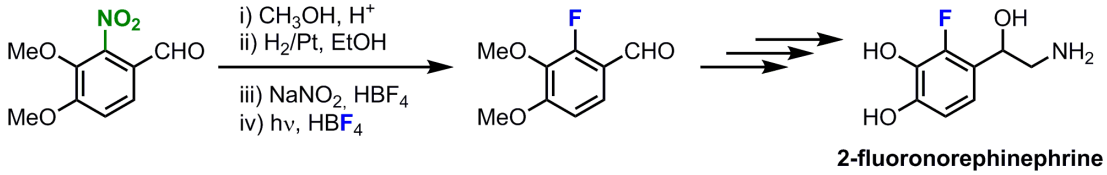


Scheme 1.44. General scheme for nucleophilic fluorination of aryl derivatives.

Some important fundamentals concerning nucleophilic fluorination can be understood from this diagram. First, the selectivity of the process is again an important issue,[154] and equally important mesomeric and inductive effects can also be represented

for the carbanionic intermediate to predict the most likely positions for C-F bond formation. These effects seem to be very pronounced, with only the presence of electron-withdrawing groups being a suitable directing force. Moreover, the strict removal of hydrogen bond donors is required to amplify the nucleophilic character of "F^-" entities, restricting the usable systems. Vigorous stirring and high temperatures are usually needed to avoid complex product distribution and to accelerate the fluorination of easily accessible C-H bonds. As a result of these observations, a much decreased functional group tolerance and the strict control of reaction conditions seriously limits the application of non-directed C-H bond fluorination in arenes. Some discussion about general features of nucleophilic fluorination can be found in the literature.[174]

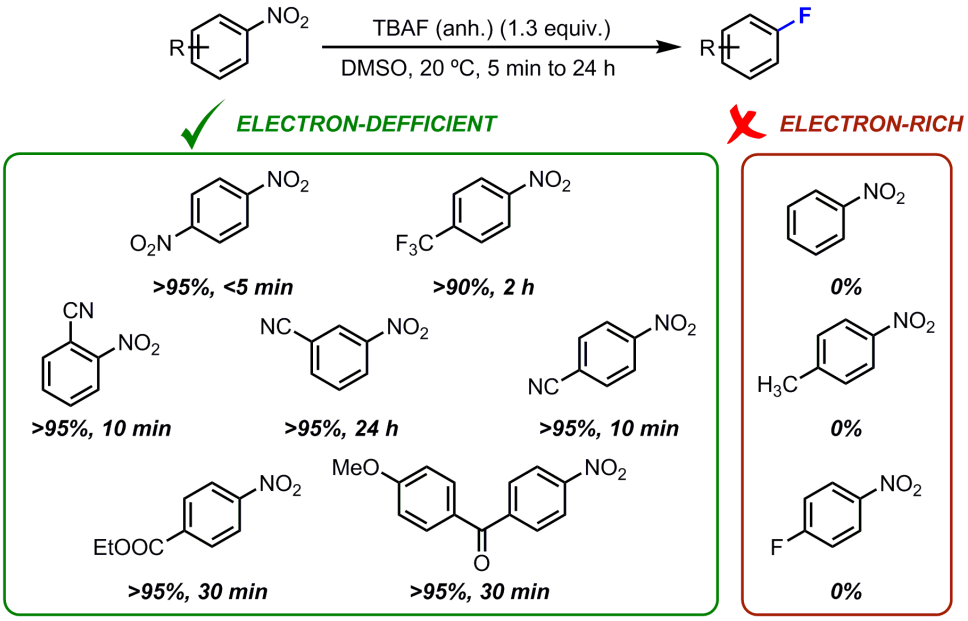
Nonetheless, the use of directing functional groups has been much more extensively used for this type of fluorination chemistry, especially with compounds containing electron-withdrawing groups. The use of nitroarenes can be cited as one of the oldest and most common routes based on this approach. Using such compounds for fluorination dates back to the 1950's,[175] and the various modes of reactivity being available have further increased their presence in the field. For example, nitroarenes are one of the most employed substrates to access anilines, the starting substrates for Balz-Schiemann fluorination.[151] The specificity of this method has been very useful for the synthesis of complex fluorinated compounds; for example, Kirk reported in 1979 a synthetically useful and selective fluorination pathway for the preparation of 2-fluoronorephinephrine starting from a functionalised nitroarene (Scheme 1.45).[176]



Scheme 1.45. Selective fluorination of a nitroarene into the corresponding aryl fluoride for the synthesis of 2-fluoronorephinephrine.[176]

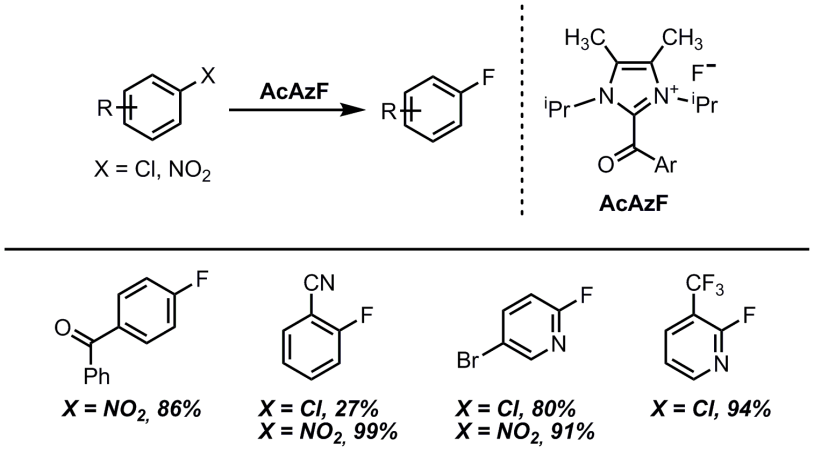
The high selectivity of this method for substrates with non-hydrogenatable functionalities is outstanding, having created a main trend in fluorination based on nitro group substitution. However, the use of nitroarenes has not only been linked to their reduction properties; in fact, the use of -NO_2 moieties, as a "throw-away" group, is very useful for mild fluorination conditions. As an example, fluoride sources such as anhydrous tetrabutylammonium fluoride (a highly nucleophilic fluorination source that

has found good use in the field of S_NAr reactions involving fluorine)[177] have been reported to displace nitro groups and replace them with fluorine at room temperature in the absence of any other additive or catalyst, as reported by DiMagno in 2006.[178] While the efficiency of the fluorination procedure with electron-defficient arenes was very high, electron-rich arenes were completely unreactive under their reported conditions, as expected from their lower tendency to react with nucleophilic fluoride sources (Scheme 1.46).



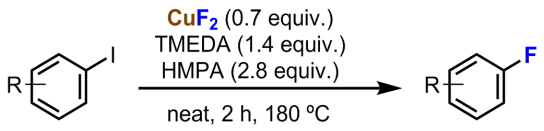
Scheme 1.46. Nucleophilic fluorination of electron-defficient nitroarenes with TBAF.[178]

Appropriate activation of nitro groups affords fluorination with no requirements for any special catalysts or additives, with a variety of fluorination sources having being explored. One interesting example, within the background of the chemistry presented in this chapter, is the use of free carbenes in conjunction with acyl fluorides for the *in situ* generation of acyl azolium fluoride salts, a powerful fluorination reagent for nitroarenes (Scheme 1.47).[179] This methodology has also proven efficient for aryl chlorides as substrates.



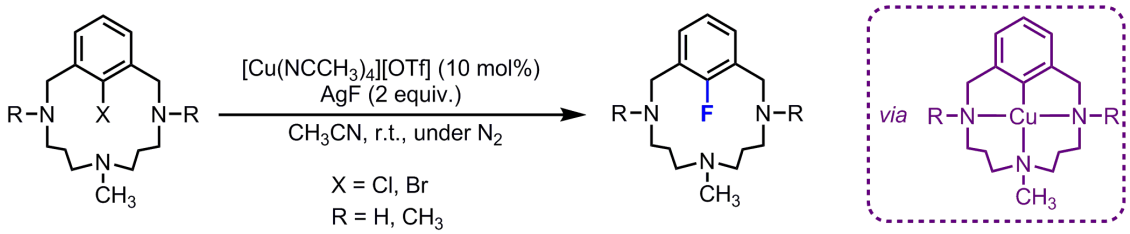
Scheme 1.47. Synthesis of an acyl-NHC fluoride salt and application to fluorination of aryl chlorides and nitroarenes.[179]

Aryl halides were used in the *"Halex"* reaction to access ArF compounds, and the methodologies involving such substrates have been updated in recent decades. With a main interest in the use of aryl chlorides (the least reactive members of the halide family),[152] bromides and iodides have not been underestimated for their inclusion in optimal methods. The use of transition metal complexes is mainly required for this chemistry to be effective, with a particular attention to the high number of reports using copper salts. Grushin has dedicated significant efforts to unravel the mysteries behind halide exchange reactions in aromatic compounds using fluorination sources and copper salts. A preliminary study of the use of copper(II) fluoride as the single catalyst/F^- source for the conversion of iodoarenes into aryl fluorides was later patented, becoming one of the standard approaches for Cu-catalysed fluorination of aryl iodides (Scheme 1.48).[180]



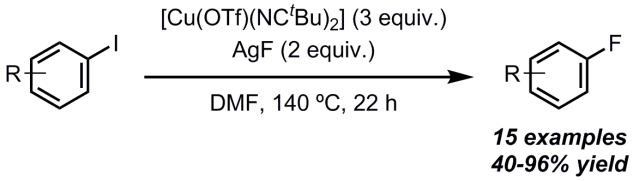
Scheme 1.48. Cu(II)-catalysed fluorination of aryl iodides.[180]

Other copper-catalysed fluorination reactions of aryl iodides have been also presented in the literature in recent times, improving the requirement for high temperatures and various stoichiometric additives imposed in Grushin's system. Ribas studied the Cu(I)-catalysed halogen exchange in macrocyclic aromatic halides with chelating structure,[181] promoting easy fluorination in the presence of AgF (Scheme 1.49).



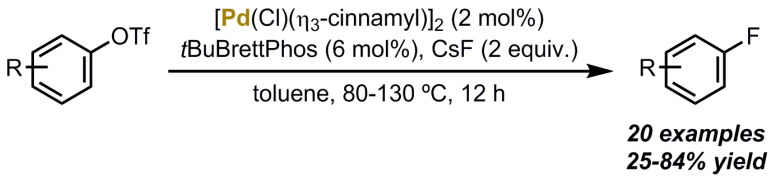
Scheme 1.49. Cu(I)-catalysed fluorination of macrocyclic aryl bromide and chlorides.[181]

Based on this Cu(I) complex, Hartwig developed a more general methodology using AgF in DMF at 140 ºC, obtaining a good number of examples of fluoroarenes in moderate to excellent yields and simplifying the reaction system described by Grushin. The use of over-stoichiometric amounts of the copper species is still regarded as an important inconvenience for this method (Scheme 1.50).[182]



Scheme 1.50. Additive-free Cu(I)-mediated of aryl iodides.[182]

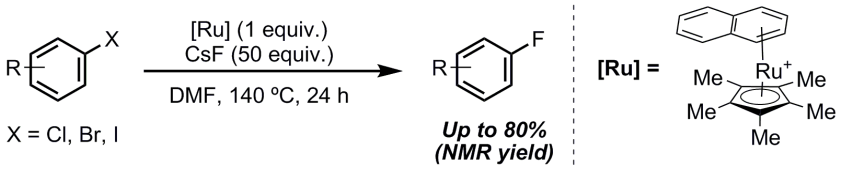
Aside from copper, the ability of other metals to promote C-F bond formation has also been tested. For example, palladium complexes have been used for this reaction, with an outstanding example in the work reported by Buchwald and co-workers in 2009. The use of a Pd(II) dimer as catalyst, in the presence of 6 mol% of a phosphine ligand (*t*BuBrettPhos), allowed the conversion of a variety of aromatic triflates into the corresponding aryl fluorides with excellent performance.[183]



Scheme 1.51. Pd(II)-catalysed nucleophilic fluorination of aryl triflates.[183]

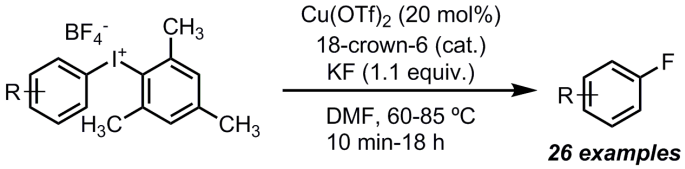
Despite his early work on copper, Grushin is well-known for his contributions to the literature about the application of rhodium and palladium in fluorination chemistry,[184] with his most recent reports being in this area. The use of aryl chlorides has still attracted the attention of his research group, exploring more deeply into its reactivity. The use of CsF in the presence of a Ru-Cp* complex was reported as a very

interesting fluorination approach in 2015 (Scheme 1.52).[185] While only few substrates were tested, a metal species optimisation was carried out, showing the suitability of these adducts for fluorination and claiming a new approach that can eventually emerge as a very powerful synthetic route in the next years.



Scheme 1.52. Preliminary studies in the application of Ru for the fluorination of aryl halides.[185]

Interestingly, the use of iodoarenes provided a different reactive approach that has been successfully exploited, which other aryl halides failed to perform equally. This method, based on the generation of iodonium salts as reactive starting materials, have been used since the 1980's,[186] with interesting results. The group of Sanford has reported several reactions using such compounds; for example, in 2013, the preparation of a variety of fluoroarenes starting from mesityl-based iodonium salts was disclosed, using $Cu(OTf)_2$ as catalyst in the presence of 18-crown-6.[187] The use of KF as fluorination source afforded a number of examples after very short periods of time under at T < 100 ºC (Scheme 1.53).



Scheme 1.53. Selective nucleophilic fluorination of iodonium salts.[187]

Since this example, the Sanford group has fine-tuned the synthesis of the involved substrates and the catalytic conditions to prepare fluoroarenes. A mechanistic proposal based on a Cu(I)/Cu(III) cycle, supported with extensive computational studies, was also presented in 2014 (Figure 1.19).[188] The application of these Cu-based methods could also be adjusted for radiofluorination purposes, adding a great value to this approach.[189] Finally, and transcending from Sanford's group, the work of Wirth in 2015 showed a modification in which iodonium salts were supported on resins and subjected to nucleophilic fluorination conditions, affording good preliminary results in this heterogeneous-based fluorination chemistry for the synthesis of aryl fluorides.[190]

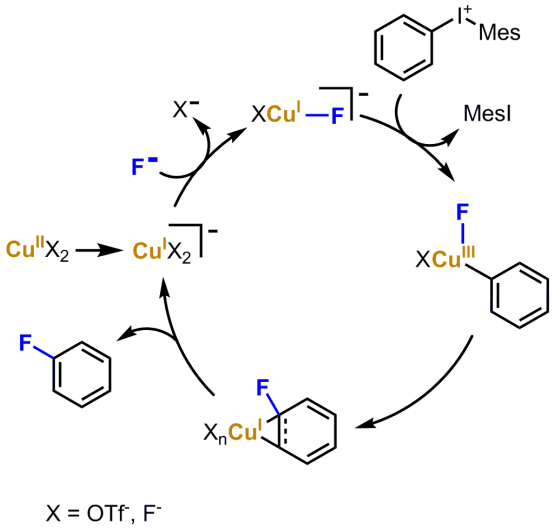
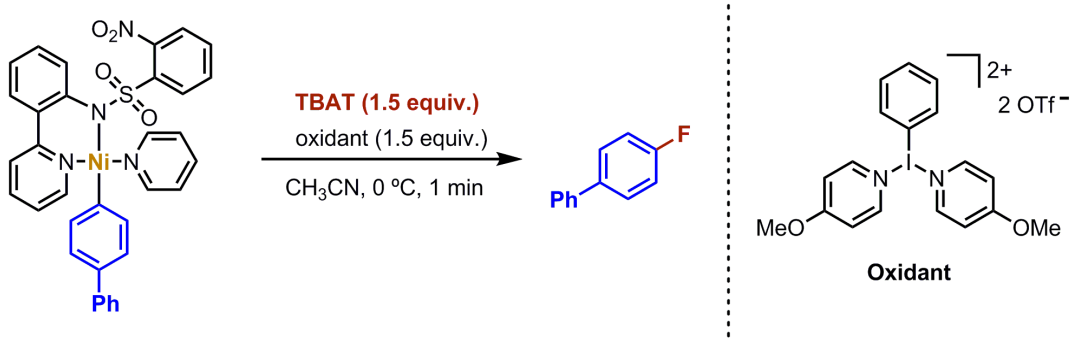


Figure 1.19. Proposed catalytic cycle for the Cu-catalysed nucleophilic fluorination of iodonium salts.[188]

A final group of substrates showing good fluorination reactivity under nucleophilic conditions, in the presence of copper, is the family of boron-based compounds (boronic acids, esters and salts), which presented some application in electrophilic fluorination and have also found use in nucleophilic approaches. The work of Gouverneur on aryl pinacolboronic esters[191] or the use of boronic acids by Sanford[192] in radiofluorination with $K^{18}F$ and Cu(II) systems, are some of the few examples reported in this area.

The fluorination of functionalised arenes is not limited to copper catalysts, although it presents the widest studied field among transition metal-catalysed fluorination reactions of arene derivatives.[193] Stepping towards new metals to provide parallel approaches also requires some critical evaluation.[194] For example, Ritter has demonstrated that arylnickel species can be possible substrates for fluoroarene synthesis. By reacting aryl bromides with $[Ni(cod)_2]$ and further transmetallation with a Ag-sulfonamide complex, the resulting tetracoordinated Ni(II) species (Scheme 1.54) can release ArF compounds upon oxidation with an hypervalent iodine reagent in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) and 18-crown-6. Using these conditions, radiofluorination is also possible for a variety of small molecules.[195]



Scheme 1.54. One-step oxidative fluorination of arylnickel(II) complexes.[195]

Despite the intense work on transition metal-catalysed fluorination of arene derivatives, catalyst-free systems are still discovered and provide access to limited yet highly valuable conversion of certain functionalities into fluoroarenes. That is the case with phenols and the extensive work of Ritter in the development of deoxyfluorination reagents. This reaction can be performed by using NHC derivatives in the absence of catalysts or additives. The first fluorination promoter was discovered in 2011, having the structure of a geminal difluorinated imidazole-based compound. This species, known today as PhenoFluor, has provided excellent results for the deoxofluorination of phenols (Figure 1.20).[196,197] After this initial report, and in an attempt to further improve the performance of this system, another imidazole-based reagent, named PhenoFluorMix, was prepared in 2015. This compound has also afforded fluoroarenes from their corresponding phenols with very practical conditions (Figure 1.20).[198] The use of PhenoFluorMix is nowadays highly encouraged over PhenoFluor, due to its higher stability to moisture, and the possibility to store it in air. Also, its synthesis can be scaled up to decagram quantities without any special requirements. The mechanistic details have not been yet discussed, although nucleophilic fluorination is suspected to be operating in this reaction.

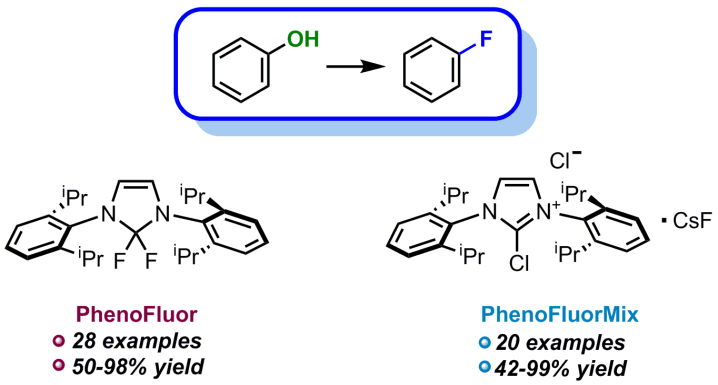
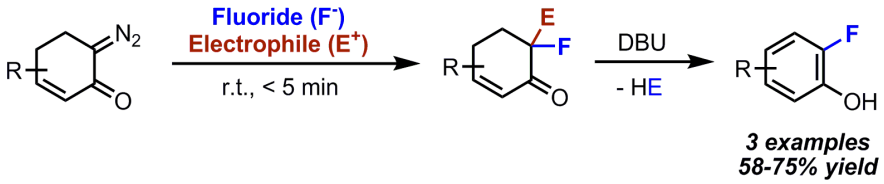


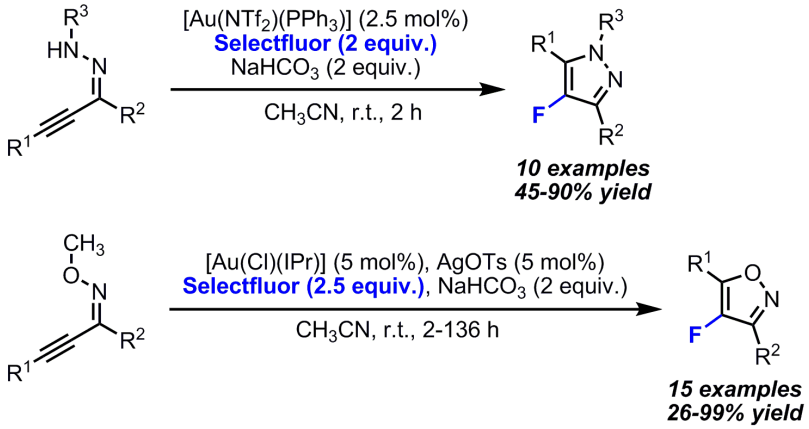
Figure 1.20. General scheme for nucleophilic fluorination of aryl derivatives.[196-198]

Some examples of the use of non-aromatic substrates for fluoroarene synthesis have also been reported. This is the case of the nucleophilic fluorination of cyclic azoketones in the presence of a non-nucleophilic base and an auxiliary electrophile.[199] Using this methodology, Katzenellenbogen and co-workers provided a great access to *o*-fluorophenols at room temperature, and the good performance was inspiring for its application in radiolabelling studies (Scheme 1.55).



Scheme 1.55. General scheme for nucleophilic fluorination of aryl derivatives.[199]

In line with the interests of this thesis, it is noticeable that, to the best of our knowledge, the only reported fluorination methodologies involving gold catalysis are limited to tandem heterocycle synthesis/C-F bond formation. Fluorinated pyrazoles[200] and isoxazoles[201] can be efficiently synthesised using these methods (Scheme 1.56). In the case of isoxazoles, the first report of a reaction forming C(sp^2)-F bonds using a Au(I)-NHC species encourages further study of its mediation in similar reactions. Since no similar strategies are available for simple arenes, the presented background ascertains the need for new efficient methodologies for the preparation of such compounds, which will dedicate some discussion in this thesis.



Scheme 1.56. Au-catalysed synthesis of fluorinated heterocycles.[200,201]

1.5 References

(1) D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.* 2000, **100**,

39.

(2) For some selected reviews about N-heterocyclic carbenes, see: a) W. A. Herrmann and C. Köcher, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 2162; b) W. A. Herrmann, *Angew. Chem. Int. Ed.* 2002, **41**, 1290; c) F. E. Hahn and M. C. Jahnke, *Angew. Chem. Int. Ed.* 2008, **47**, 3122; d) P. de Fremont, N. Marion and S. P. Nolan, *Coord. Chem. Rev.* 2009, **253**, 862; e) W. Kirmse, *Angew. Chem. Int. Ed.* 2010, **49,** 8798; f) Cazin, C. S. J.; in: *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, Springer: New York, **2011**.

(3) a) L. Tschugaeff and P. Teearu, *Ber.* 1914, **47**, 568; b) L. Tschugajeff, M. Grigorjewa and A. Z. Posnjak, *Anorg. Allg. Chem.* 1925, **148**, 37.

(4) W. Wanzlick and E. Schikora, *Angew. Chem.* 1960, **72**, 494.

(5) H. W. Wanzlick and H-J. Schönherr, *Angew. Chem. Int. Ed.* 1962, **1**, 75.

(6) For some selected references, see: a) D. M. Lemal and K. I. Kawano, *J. Am. Chem. Soc.* 1962, **84**, 1761; b) W. Wanzlick, *Angew. Chem. Int. Ed.* 1962, **1**, 75.

(7) H.-W. Wanzlick and H.-J. Schonherr, *Angew. Chem. Int. Ed*. 1968, **7**, 141.

(8) K. Öfele, *J. Organomet. Chem.* 1968, **12**, 42.

(9) a) A. Igau, H. Grutzmacher, A. Baceiredo and G. Bertrand, *J. Am. Chem. Soc.* 1988, **110**, 6463; b) A. J. Arduengo III, R. L. Harlow and M. Kline, *J. Am. Chem. Soc*. 1991, **113**, 361.

(10) a) O. Schuster, L. Yang, H. G. Raubenheimer and M. Albrecht, *Chem. Rev.* 2009, **109**, 3445; b) R. H. Crabtree, *Coord. Chem. Rev.* 2013, **257**, 755.

(11) A. A. Tukow, A. T. Normand and M. S. Nechaev, *Dalton Trans*. 2009, 7015.

(12) a) G. Frenking, M. Solà and S. F. Vyboishchikov, *J. Organomet. Chem.* 2005, **690**, 6178; b) H. Jacobsen, A. Correa, C. Costabile and L. Cavallo, *J. Organomet. Chem.* 2006, **691**, 4350; c) R. Tonner, G. Heydenrych and G. Frenking, *Chem. Asian. J.* 2007, **2**, 1555; d) H. Jacobsen, A. Correa, A. Poater, C. Costabile and L. Cavallo, *Coord. Chem. Rev.* 2009, **253**, 687.

(13) N. M Scott, R. Dorta, E. D, Stevens, A. Correa, L. Cavallo and S. P. Nolan, *J. Am. Chem. Soc.* 2005, **127**, 3516.

(14) a) X. L. Hu, Y. J. Tang, P. Gantzel and K. Meyer, *Organometallics*, 2003, **22**, 612; b) X. L. Hu, I. Castro-Rodriguez, K. Olsen and K. Meyer, *Organometallics*, 2004, **23**, 755.

(15) Nolan, S. P.; in: *N-Heterocyclic Carbenes in Synthesis*; Wiley, **2006**.

(16) C. A. Tolman, *Chem. Rev.* 1977, **77**, 313.

(17) a) J. Huang, H. J. Schanz, E. D. Stevens and S. P. Nolan, *Organometallics,* 1999, **18**, 2370; b) Nolan, S. P.; in: *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*; Wiley-VCH, **2014**.

(18) H. Clavier and S. P. Nolan, *Chem. Commun.* 2010, **46**, 841.

(19) A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano and L. Cavallo, *Eur. J. Inorg. Chem.* 2009, 1759.

(20) L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano and L. Cavallo, *Organometallics,* 2016, **35**, 2286**.**

(21) F. Ragone, A. Poater and L. Cavallo, *J. Am. Chem. Soc.* 2010, **132**, 4249.

(22) a) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer and J. H. Teles, *Angew. Chem. Int. Ed.* 2012, **71**, 12370; b) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.* 2013, **42**, 4906.

(23) For some selected examples for intramolecular reactivity, see: a) E. M. Phillips, M. Wadamoto, A. Chan and K. A. Scheidt, *Angew. Chem. Int. Ed.* 2007, **46**, 3107; b) M. Wadamoto, E. M. Phillips, T. E. Reynolds and K. A. Scheidt, *J. Am. Chem. Soc.* 2007, **129**, 10098; c) Y. Li, X. Q. Wang, C. Zheng and S. L. You, *Chem. Commun.* 2009, 5823.

(24) For some selected examples for intermolecular reactivity, see: a) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.* 2006, **128**, 8418; b) C. Burstein, S. Tschan, X. L. Xie and F. Glorius, *Synthesis*, 2006, 2418; d) V. Nair, R. R. Paul, K. C. S. Lakshmi, R. S. Menon, A. Jose and C. R. Sinu, *Tetrahedron Lett.* 2011, **52**, 5992; e) X. Q. Fang, X. K. Chen and Y. R. Chi, *Org. Lett.* 2011, **13**, 4708.

(25) For some selected examples, see: a) C. Burstein and F. Glorius, *Angew. Chem. Int. Ed.* 2004, **43**, 6205; b) V. Nair, S. Vellalath, M. Poonoth and E. Suresh, *J. Am. Chem. Soc.* 2006, **128**, 8736; c) J. Kaeobamrung and J. W. Bode, *Org. Lett.* 2009, **11**, 633; d) D. E. A. Raup, B. C. David, D. Holte and K. A. Scheidt, *Nat. Chem.* 2010, **2**, 766; e) B. C. David, D. E. A. Raup and K. A. Scheidt, *J. Am. Chem. Soc.* 2010, **132**, 5345; f) X. Fang, K. Jiang, C. Xing, L. Hao and Y. R. Chi, *Angew. Chem. Int. Ed.* 2011, **50**, 1910; g) X. D. Zhao, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.* 2011, **133**, 12466; h) Y. M. Zhao, Y. Tam, Y. J. Wang, Z. Li and J. Sun, *Org. Lett.* 2012, **14**, 1398.

(26) For some selected examples, see: a) S. Singh, V. K. Rai, P. Singh and L. D. S.

Yadav, *Synthesis*, 2010, 2957; b) L. D. S. Yadav, V. K. Rai, S. Singh and P. Singh, *Tetrahedron Lett.* 2010, **51**, 1657; c) L. D. S. Yadav, S. Singh, V. K. Rai, *Synlett*, 2010, 240; d) D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.* 2011, **133**, 10402; e) G. Liu, P. D. Wilkerson, C. A. Toth and H. Xu, *Org. Lett.* 2012, **14**, 858.

(27) For the original description of the reaction, see F. Wohler, J. Liebig, *J. Ann. Pharm.* 1832, **3**, 249.

(28) For some selected examples, see: a) J. C. Sheehan and T. Hara, *J. Org. Chem.* 1974, **39**, 1196; b) W. Tagaki, Y. Tamura and Y. Yano, *Bull. Chem. Soc. Jpn.* 1980, 478; c) R. L. Knight and F. J. Leeper, *Tetrahedron Lett.* 1997, 3611; d) A. U. Gerhard and F. J. Leeper, *Tetrahedron Lett.* 1997, **38**, 3615; e) C. A. Dvorak and V. H. Rawal, *Tetrahedron Lett.* 1998, **39**, 2925; f) R. L. Knight and F. J. Leeper, *J. Chem. Soc. Perkin Trans. I*, 1998, 1891; g) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.* 2003, **125**, 8432; h) M.-Q. Jia and S.-L. You, ACS Catal. 2013, **3**, 622.

(29) For the original description of the reaction, see: H. Stetter, *Angew. Chem. Int. Ed.* 1976, **15**, 639.

(30) For some selected examples, see: a) D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899; b) M. S. Kerr and T. Rovis, *Synlett*, 2003, 1934; c) M. S. Kerr, J. R. de Alaniz and T. Rovis, *J. Org. Chem.* 2005, **70**, 5725; e) Y. Matsumoto and K. Tomioka, *Tetrahedron Lett.* 2006, **47**, 5843.

(31) For some other selected references, see: a) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit and A. Alexakis, *J. Am. Chem. Soc.* 2006, **128**, 8416; b) J. Douglas, J. E. Taylor, G. Churchill, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.* 2013, **78**, 3925.

(32) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. Scheidt, *Angew. Chem. Int. Ed.* 2012, **51**, 11686.

(33) For further review on ligand types, their identification and properties, see: J. F. Hartwig, in: *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, **2010.**

(34) W. A. Herrmann, K. Öfele, M. Elison, F. E. Kühn and P. W. Roesky, *J. Organomet. Chem.* 1994, **480**, C7.

(35) H. Díaz-Velazquez and F. Verpoort, *Chem. Soc. Rev.* 2012, **41**, 7032.

(36) T. Weskamp, V. P. W. Böhm and W. A. Herrman, *J. Organomet. Chem.* 1999, **585**, 348.

(37) D. Munz, D. Meyer and T. Strassner, *Organometallics,* 2013, **32**, 3469.

(38) For some selected examples, see: a) W. A. Herrmann, M. Elison, J. Fischer, C-Köcher and G. R. J. Artus, *Angew. Chem. Int. Ed.* 1995, **34**, 2371; b) J. Huang and S. P. Nolan, *J. Am. Chem. Soc.* 1999, **121**, 9889; c) H. M. Lee and S. P. Nolan, *Org. Lett.* 2000, **2**, 2053; d) R. A. Batey, M. Shen and A. J. Lough, *Org. Lett.* 2002, **4**, 1411; e) M. S. Viciu, R. A. Kelly III, E. D. Stevens, F. Naud, M. Studer and S. P. Nolan, *Org. Lett.* 2003, **5**, 1479; f) S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem. Int. Ed.* 2004, **43**, 1871; g) N. Hadei, E. Assen, B. Kantchev, C. J. O'Brie and M. G. Organ, *Org. Lett.* 2005, **7**, 3805; h) Y.-C. Lin, H.-H. Hsueh, S. Kanne, L.-K. Chang, F.-C. Liu and I. J. B. Lin, *Organometallics,* 2013, **32**, 3859.

(39) J. DePasquale, M. Kumar, M. Zeller and E. T. Papish, *Organometallics* 2013**, 32**, 966.

(40) H. Song, D. Fan, Y. Liu, G. Hou and G. Zi, *J. Organomet. Chem*. 2013, **729**, 40.

(41) For a selection of other transformations catalysed by transition metal-NHC complexes, see: a) S. P. Nolan, *Organometallics,* 2001, **20**, 3607; b) A. Fürstner and G. Seidel, *Org. Lett.* 2002, **4**, 541; c) L. Ackermann, *Org. Lett.* 2005, **7**, 439.

(42) M.-L. Teyssot, A.-S. Jarrousse, M. Manin, A. Chevry, S. Roche, F. Norre, C. Beaudoin, L. Morel, D. Boyer, R. Mahiou and A. Gautier, *Dalton Trans.* 2009**,** 6894.

(43) Q.-X. Liu, Z..Q. Yao, X.-J. Zhao, Z.-X. Zhao and X.-G. Wang, *Organometallics,* 2013, **32**, 3493.

(44) For some selected references, see: a) K. Öfele, *Angew. Chem. Int. Ed.* 1968, **7**, 950; b) S. Diez-González, N. Marion and S. P. Nolan, *Chem. Rev.* 2009, **109**, 3612.

(45) For some selected reviews, see: a) A. S. K. Hashmi, *Gold Bull.* 2004, **37**, 51; b) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* 2005, **44**, 6990; c) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed.* 2006, **45**, 7896; d) A. S. K. Hashmi, *Chem. Rev.* 2007, **107**, 3180*;* e) S. P. Nolan, *Nature*, 2007, **445**, 496; f) A. S. K. Hashmi, *Chem. Rev.* 2007, **107**, 3180; g) A. S. K. Hashmi, *Chem. Rev.* 2007, **107**, 3180; h) A. Arcadi, *Chem. Rev.* 2008, **108**, 3266; i) A. S. K. Hashmi and M. Rudolph,

Chem. Soc. Rev. 2008, **37**, 1766; j) H. Schmidbaur and A. Schier, *Chem. Soc. Rev.* 2008, **37**, 1931; k) Z. Li, C. Brouwer and C. He, *Chem. Rev.* 2008, **108**, 3239; l) A. S. K. Hashmi, and M. Rudolph, *Chem. Soc. Rev.* 2008, **37**, 1766; m) D. J. Gorin, B. D. Sherry, and F. D. Toste, *Chem. Rev.* 2008, **108**, 3351; n) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885; o) H. C. Shen, *Tetrahedron*, 2008, **64**, 7847; p) Z. G. Li, C. Brouwer and C. He, *Chem. Rev.* 2008, **108**, 3239; q) A. S. K. Hashmi and C. Hubbert, *Angew. Chem. Int. Ed.* 2010, **49**, 1010; r) A. S. K. Hashmi, *Pure Appl. Chem.* 2010, **82**, 657; s) T C. Boorman and I. Larrosa, *Chem. Soc. Rev.* 2011, **40**, 1910; t) A. Corma, A. Leyva-Perez and M. J. Sabater, *Chem. Rev.* 2011, **111**, 1657; u) C. D. Pina, E. Falletta and M. Rossi, *Chem. Soc. Rev.* 2012, **41,** 350.

(46) For some selected examples, see: a) J. H. Teles, S. Brode, and M. Chabanas, *Angew. Chem. Int. Ed.* 1998, **37**, 1415; b) A. S. K. Hashmi, J. P. Weyrauch, W. Frey and J. W. Bats, *Org. Lett.* 2004, **6**, 4391; c) A. S. K. Hashmi, A. M. Schuster and F. Rominger, *Angew. Chem. Int. Ed.* 2009, **48**, 8247.

(47) For some selected examples, see: a) A. S. K. Hashmi, L. Schwarz, J.-H. Choi and T. M. Frost, *Angew. Chem. Int. Ed.* 2000, **39**, 2285; b) G. Zhang, Y. Peng, L. Cui and L. Zhang, *Angew. Chem. Int. Ed.* 2009**, 48**, 3112; c) P. Garcia, M Malacria, C. Aubert, V. Gandon and L. Fensterbank, *Chem. Cat. Chem.* 2010, **2**, 493.

(48) For some selected examples on other functionalisation reactions involving gold catalysts, see: a) J. P. Markham, S. T. Staben and F. D. Toste, J. *Am. Chem. Soc.* 2005, **127**, 9708; b) N. Morita, N. Krause, *Angew. Chem. Int. Ed.* 2006, **45**, 1897.

(49) R. O. C. Norman, W. J. E. Parr and C. B. Thomas, *J. Chem. Soc. Perkin. Trans. 1*, 1976, 1983.

(50) Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.* 1986, **108**, 6405.

(51) For some selected references, see: a) R. A. Widenhoefer, *Chem. Eur. J.* 2008, **14**, 5382; b) Y.-M. Wang, A. D. Lackner and F. D. Toste, *Acc. Chem. Res.* 2014, **47**, 889; c) W. Zi and F. D. Toste, *Chem. Soc. Rev.* 2015, **45**, 4567.

(52) B. Ranieri, I. Escofet and A. M. Echavarren, *Org. Biomol. Chem.* 2015, **13**, 7103.

(53) A comparative study of the relativistic effects in some transition metals can be found at: A. Leyva-Pérez and A. Corma, *Angew. Chem. Int. Ed.* 2012, **51**, 614.

(54) P. Pyykkö, *Angew. Chem. Int. Ed.* 2004, **43**, 4412.

(55) For a summary of the consequences of relativistic effects in homogeneous gold catalysis, see: D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395.

(56) R. G. Pearson, *J. Am. Chem. Soc.* 1963, **85,** 3533.

(57) For some selected reviews, see: a) A. S. K. Hashmi, *Gold Bull.* 2003, **36**, 3; b) A. Fürstner and P. W. Davies, *Angew. Chem. Int. Ed.* 2007, **46**, 3410; c) R. E. M. Brooner, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* 2013, **52**, 11714.

(58) a) H. Schmidbaur, S. Cronje, B. Djordjevic and O. Schuster, *Chem. Phys.* 2005, **311**, 151; b) Picture taken from ref. 55, and adapted from: P. Pyykko and J. P. Desclaux, *Acc. Chem. Res.* 1979, **12**, 276.

(59) a) H. Schmidbaur, *Gold. Bull.* 2000, **33(1)**, 3; b) H. Schmidbaur and A. Schier, *Chem. Soc. Rev.* 2012, **41**, 370.

(60) F. G. Mann, A. F. Wells and D. Purdie, *J. Chem. Soc.* 1937, 1828.

(61) P. Pyykkö, *Chem. Soc. Rev.* 2008, **37**, 1967.

(62) Chiusoli, G. P.; Maitlis, P. M.; in: *Metal-catalysis in industrial organic processes; Softback ed.;* RSC Publishing: Cambridge, **2008**.

(63) For some selected reviews, see: a) N. Marion and S. P. Nolan, *Chem. Soc. Rev.* 2008, **37**, 1776; b) S. P. Nolan, *Acc. Chem. Res.* 2011, **44**, 91.

(64) I. Ott, *Coord. Chem. Rev.* 2009, **253**, 1670.

(65) F. Bonati, A. Burini and B. R. Pietroni, *J. Organomet. Chem.* 1989, **375**, 147.

(66) M. V. Baker, P. J. Barnard, S. K. Brayshaw, J. L. Hickey, B. W. Skelton and A. H. White, *Dalton Trans.* 2005, 37.

(67) N. Mézailles, L. Ricard and F. Gagosz, *Org. Lett.* 2005, **7,** 4133.

(68) P. de Frémont, E. D. Stevens, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez and S. P. Nolan, *Chem. Commun*. 2006, 2045.

(69) N. Marion, P. de Frémont, G. Lemière, E. D. Stevens, L. Fensterbank, M. Malacria and S. P. Nolan, *Chem. Commun.* 2006, 2048.

(70) P. de Frémont, N. Marion, S. P. Nolan, *J. Organomet. Chem.* 2009, **694**, 551.

(71) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.* 2008, **47,** 5224.

(72) P. de Frémont, N. M. Scott, E. D. Stevens and S. P. Nolan, *Organometallics,* 2005, **24**, 2411.

(73) J. C. Garrison and W. J. Youngs, *Chem. Rev.* 2005, **105**, 3978.

(74) a) M. R. L. Furst and C. S. J. Cazin, *Chem. Commun.* 2010, **46**, 6924; b) O. Santoro, F. Lazreg, D. B. Cordes, A. M. Z. Slawin and C. S. J. Cazin, *Dalton Trans.* 2016, **45**, 4970.

(75) A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin, and S. P. Nolan, *Chem. Commun.* 2013, **49**, 5541.

(76) For more seminal studies related to this activation, see: a) G. C. Bond, *Gold Bull.* 1972, **5,** 11; b) G. J. Hutchings, *J. Catal.* 1985, **96**, 292.

(77) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.* 2010, **46**, 2742.

(78) A. Gómez-Suárez, R. S. Ramón, A. M. Z. Slawin and S. P. Nolan, *Dalton Trans.* 2012, **41**, 5461.

(79) F. Nahra, S. R. Patrick, A. Collado and S. P. Nolan, *Polyhedron*, 2014, **84**, 59.

(80) I. I. F. Boogaerts and S. P. Nolan, *J. Am. Chem. Soc.* 2010, **132,** 8858.

(81) S. Dupuy, F. Lazreg, A.M.Z. Slawin, C.S.J. Cazin and S.P. Nolan, *Chem. Commun.* 2011, **47**, 5455.

(82) a) S. Gaillard, J. Bosson, R.S. Ramón, P. Nun, A.M.Z. Slawin and S.P. Nolan, *Chem. Eur. J.* 2010, **16,** 13729; b) P. Nun, R.S. Ramón, S. Gaillard and S.P. Nolan, *J. Organomet. Chem.* 2011, **696,** 7.

(83) a) S. Gaillard, P. Nun, A.M.Z. Slawin and S.P. Nolan, *Organometallics*, 2010, **29**, 5402; b) P. Nun, S. Gaillard, A.M.Z. Slawin and S.P. Nolan, *Chem. Commun.* 2010, **46**, 9113; c) E. Brulé, S. Gaillard, M.-N. Rager, T. Roisnel, V. Guérineau, S. P. Nolan and C. M. Thomas, *Organometallics*, 2011, **30**, 2650; d) D. Konkolewicz, S. Gaillard, A. G. West, Y. Y. Cheng, A. Gray-Weale, T. W. Schmidt, S. P. Nolan and S. Perrier, *Organometallics*, 2011, **30**, 1315; e) P. Nun, S. Dupuy, S. Gaillard, A. Poater, L. Cavallo and S. P. Nolan, *Catal. Sci. Technol.* 2011, **1,** 58; f) P. Nun, S. Gaillard, A. Poater, L. Cavallo and S. P. Nolan, *Org. Biomol. Chem.* 2011, **9**, 101; g) S. R. Patrick, I. I. F. Boogaerts, S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Beilstein J. Org. Chem.* 2011, **7**, 892.

(84) L. Ricard, and F. Gagosz, *Organometallics* 2007, **26**, 4704

(85) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.* 2010, **46**, 2742

(86) S. R. Patrick, A. Gómez-Suárez, A. M. Z. Slawin and S. P. Nolan, *Organometallics*, 2013, **33**, 421.

(87) F. Nahra, M. Brill, A. Gómez-Herrera, C. S. J. Cazin and S. P. Nolan, *Coord. Chem. Rev.* 2016, **307**, 65.

(88) F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan and S. P. Nolan, *Chem. Cat. Chem.* 2015, **7**, 240.

(89) a) A. Borodine, *Justus Liebigs Ann. Chem.* 1863, **126**, 58; b) O. Wallach, *Justus*

Liebigs Ann. Chem. 1886, **235**, 233.

(90) F. Swarts, *Bull. Acad. Roy.Belg.* 1892, **24,** 474.

(91) J. H. Simons and L. P. Block, *J. Am. Chem. Soc.* 1937, **59**, 1407.

(92) For some selected reviews, see: a) M. R. C. Gerstenberger and A. Haas, *Angew. Chem. Int. Ed. Engl.* 1981, **20**, 647; b) W. G. M. Jones, *Organofluorine Compounds,* ed. R. E. Banks, Ellis Horwood, Chichester, **1982**; c) J. A. Wilkinson, *Chem. Rev.* 1992, **92**, 505; d) W. R. Dolbier, *Chem. Rev.* 1996, **96**, 1557; e) D. L. S. Brahms and W. P. Dailey, *Chem. Rev.* 1996, **96**, 1585; f) D. J. Burton, Z. Y. Yang, W. M. Qiu, *Chem. Rev.* 1996, **96**, 1641; g) T. Umemoto, *Chem. Rev.* 1996, **96**, 1757; h) M. Schlosser, *Angew. Chem. Int. Ed.* 1998, **37**, 1496; i) T. Hiyama, in: *Organofluorine compounds, chemistry and applications;* Springer-Verlag, Berlin, **2000**; j) P. Kirsch, in: *Modern fluoroorganic chemistry;* Wiley-VCH, Weinheim, **2004**; k) V. A. Soloshonok, in: *Fluorine-containing synthons, ACS symposium series,* Oxford University Press, Washington, D.C, **2005**; l) K. Uneyama, in: *Organofluorine Chemistry;* Blackwell publishing: Oxford, **2006**; m) T. Furuya, C. A. Kuttruff and T. Ritter, *Curr. Op. Drug. Disc. Dev.* 2008, **11**, 803; n) D. O'Hagan, *Chem. Soc. Rev.* 2008, **37**, 308; o) M. Schuler, F. Silva, C. Bobbio, A. Tessier and V. Gouverneur, *Angew. Chem. Int. Ed.* 2008, 47, 7927; p) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.* 2013, **52**, 8214; q) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme and J.-F. Paquin, *Chem. Rev.* 2015, **115**, 9073.

(93) For some selected reviews, see: a) D. F. Halpern, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,* ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993; b) M. P. Krafft, *Adv. Drug Deliv. Rev*, 2001, **47**, 209; c) J. G. Riess, *Chem. Rev.* 2001, **101**, 2797; d) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637; e) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.* 2006, **127**, 303; f) K. L. Kirk, *Curr. Top. Med. Chem.* 2006, **6**, 1445; g) M. Cametti, B. Crousse, P. Metrangolo, R. Milani and G. Resnati, *Chem. Soc. Rev.* 2012, **41**, 31.

(94) For some selected reviews, see: a) P. Jeschke, *Chem. Bio. Chem.* 2004, **5**, 570; b) P. Maienfisch and R. G. Hall, *Chimia*, 2004, **58**, 93; k) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.* 2008, **37**, 320.

(95) For some selected examples, see: a) F. M. D. Ismail, *J. Fluorine Chem.* 2002, **118**, 27; b) J.-P. Bégué and D. Bonnet-Delpon, *J. Fluorine Chem.* 2006, **127**, 992; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.* 2016, **116**, 422.

(96) For some selected examples, see: a) S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.* 2008, **108**, 1501; b) L. Cai, S. Lu and V. W. Pike, *Eur. J. Org. Chem.* 2008, 2853; c) P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem. Int. Ed.* 2008, **47**, 8998; d) R. Littich and P. J. H. Scott, *Angew. Chem. Int. Ed.* 2012, **51**, 1106.

(97) For selected examples, see: a) Y.-S. Ding, C.-Y. Shiue, J. S. Fowler, A. P. Wolf and A. Plenevaux, *J. Fluorine Chem.* 1990, **48**, 189; b) M. E. Sergeev, F. Morgia, M. Lazari, C. Wang, Jr. and R. M. van Dam, *J. Am. Chem. Soc.* 2015, **137**, 5686; c) B. D. Zlatopolskiy, J. Zischler, P. Krapf, F. Zarrad, E. A. Urusova, E. Kordys, H. Endepols and B. Neumaier, *Chem. Eur. J.* 2015, **21**, 5972; d) M. B. Haskali, S. Telu, Y.-S. Lee, C. L. Morse, S. Lu and V. W. Pike, *J. Org. Chem.* 2016, **81**, 297; e) M. S. Sanford and P. J. H, Scott, *ACS Cent. Sci.* 2016, **2**, 128.

(98) a) Chambers, R. D. in: *Fluorine in Organic Chemistry*, John Wiley & Sons, New York, **1973**; b) D. B. Harper and D. O'Hagan, *Nat. Prod. Rep.* 1994, **11**, 123; c) C. D. Murphy, C. Schaffrath and D. O'Hagan, *Chemosphere*, 2003, **52**, 455.

(99) a) C. Schaffrath, S. L. Cobb and D. O'Hagan, *Angew. Chem. Int. Ed.* 2002, **41**, 3913; b) C. J. Dong, F. L. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan and J. H. Naismith, *Nature*, 2004, **427**, 561.

(100) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Chem. Commun.* 2007, 1003.

(101) Lagow, R. J.; Bierschenk, T. R.; Juhlke, T. J.; Kawa, H.; in: *Synthetic Fluorine Chemistry*, ed. G. A. Olah, R. D. Chambers and G. K. S. Prakash, Wiley, New York, **1992**, p. 402.

(102) For some selected examples, see: a) M. Hudlicky, in: *Chemistry of Organic Fluorine Compounds II*, Ellis Horwood, Chichester, **1992**; b) C. M. Kassis, J. K. Steehler, D. E. Betts, Z. B. Guan, T. J. Romack, J. M. DeSimone and R. W. Linton, *Macromolecules*, 1996, **29**, 3247; c) Y. Li, *Acc. Chem. Res.* 2012, **45**, 723; d) D. Anton, *Adv. Mater.* 1998, **10**, 1197; e) M. G. Dhara and S. Banerjee, *Prog. Polym. Sci.* 2010, **35**, 1022.

(103) a) T. Midgely and A. L. Henne, *Ind. Eng. Chem.* 1930, **22,** 542.; b) Banks, R. E.;

in: *Fluorocarbons and Their Derivatives*, MacDonald, London, **1970**.

(104) J. O. Hendricks, *Ind. Eng. Chem.* 1950, **45,** 99.

(105) a) F. Guittard, E. T. de Givenchy, S. Geribaldi and A. Cambon, *J. Fluorine Chem.* 1999, **100**, 85; b) P. Kirsch and A. Hahn, *Eur. J. Org. Chem.* 2005, 3095.

(106) For other examples of applications of organofluorine compounds, see: a) I. T. Horvath and J. Rabai, Science, 1994, **266**, 72; b) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.* 2011, **40**, 3496.

(107) J. Emsley, *Chem. Soc. Rev.* 1980, **9**, 91.

(108) G. Sandford, *J. Fluorine Chem.* 2007, **128**, 90.

(109) For some essential knowledge about this reagent, see: a) R. E. Banks, S. N. Mohialdinkhaffaf, G. S. Lal, I. Sharif and R. G. Syvret, *J. Chem. Soc. Chem. Commun.* 1992, 595; b) R. P. Singh, J. M. Shreeve, *Acc. Chem. Res.* 2004, **37**, 31; c) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent and C.-H. Wong, *Angew. Chem. Int. Ed.* 2004, **44**, 192; d) S. Stavber and M. Zupan, *Acta Chim. Slov.* 2005, **52**, 13.

(110) For some essential knowledge about this reagent, see: a) Poss, A. J. in: *N-Fluorobenzenesulfonimide.* e-EROS Encyclopedia of Reagents for Organic Synthesis, **2003**; b) H. Teare, E. G. Robins, E. Årstad, S. K. Luthra and V. Gouverneur, *Chem. Commun.* 2007, 2330; c) V. Bizet, *Synlett*, 2012, **23**, 2719.

(111) a) J. Baudoux and D. Cahard, *Org. React.* 2007, **69**, 347; b) X.-S. Xue, Y. Wang, M. Li and J.-P. Cheng, *J. Org. Chem.* 2016, **81**, 4280; c) R. Pereira, J. Wolstenhulme, G. Sandford, T. D. W. Claridge, V. Gouverneur and J. Cvengroš, *Chem. Commun.*, 2016, **52**, 1606.

(112) C. Ni, M. Hu and J. Hu, *Chem. Rev.* 2015, **115**, 765.

(113) a) W. J. Middleton, *J. Org. Chem.* 1975, **40**, 574; b) W. J. Middleton, E. M. Bingham, *Org. Synth.* 1988, **50**, 440.

(114) a) G. Sankar Lal, G. P. Pez and R .G. Syvret, *Chem. Rev.* 1996, **96**, 1737; b) S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron*, 1999, **55**, 12431

(115) For selected reviews, see: a) M. A. Tius, *Tetrahedron*, 1995, **51**, 6605; b) C. Hollingworth and V. Gouverneur, *Chem. Commun.* 2012, **48**, 2929; c) A. J. Cresswell, S. F. Davies, P. M. Roberts and J. E. Thomson, *Chem. Rev.* 2015, **115**, 566.

(116) For essential information about this motif, see: a) Filler, R.; Kobayashi, Y.; in:

Biomedicinal Aspects of Fluorine Chemistry, Elsevier, Amsterdam, **1982**; b) *Fluorine in Bioorganic Chemistry* (Eds.: J. T. Welch, S. Eswarakrishman), Wiley, New York, **1991**; c) *Organofluorine Chemistry: Principles and Commercial Applications*, (Eds.: R.E. Banks, B. E. Smart, J. C. Tatlow), Plenum, New York, **1994**.

(117) T. Ernet, A. H. Maulitz, W.-U. Würthwein and G. Haufe, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1929.

(118) S. F. Wnuk, C.-S. Yuan, R. T. Borchardt, J. Balzarini, E. De Clercq and M. J. Robins, *J. Med. Chem.* 1994, **37**, 3579.

(119) Uneyama, K.; in: *Organofluorine Chemistry,* Blackwell, Oxford, **2006.**

(120) W. Weng, Z. L. Shen and R. F. Jordan, *J. Am. Chem. Soc.* 2007, **129**, 15450.

(121) For some selected examples, see: a) C. E. Jakobsche, G. Peris and S. J. Miller, *Angew. Chem. Int. Ed.* 2008, **47**, 6707; b) H. Yanai and T. Taguchi, *Eur. J. Org. Chem*, 2011, 5939; c) G. Landelle, M. Bergeron, M.-O. Turcotte-Savard and J.-F. Paquin, *Chem. Soc. Rev.* 2011, **40**, 2867.

(122) a) A. K. Ghosh and B. Zajc, *Org. Lett.* 2006, **8**, 1553; b) E. Pfund, C. Lebargy, J. Rouden and T. Lequeux, *J. Org. Chem.* 2007, **72**, 7871; c) M. He, A. K. Ghosh and B. Zajc, *Synlett*, 2008, 999; d) D. A. Alonso, M. Fuensanta, E. Gómez-Bengoa and C. Nájera, *Adv. Synth. Catal.* 2008, **350**, 1823; e) A. K. Ghosh, S. Banerjee, S. Sinha, S. B. Kang and B. Zajc, *J. Org. Chem.* 2009, **74**, 3689; f) B. Zacj and R. Kumar, *Synthesis*, 2010, **11**, 1822.

(123) H.-J. Tsai, *Tetrahedron Lett.* 1996, **37**, 629.

(124) J. Lin and J. T. Welch, *Tetrahedron Lett.* 1998, **39**, 9613.

(125) For the original description of the Horner-Wadsworth-Emmons reaction, see: W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.* 1961, **83**, 1733.

(126) For the original description of the Peterson olefination, see: D. J. Peterson, *J. Org. Chem.* 1968, **33**, 780.

(127) J. R. McCarthy, D. P. Matthews and C. L. Barney, *Tetrahedron Lett.* 1990, **31**, 973.

(128) For the original reaction description of the fluoroacetal synthesis from 2,3-dihydrofuran, see: E. V. Dehmlow and K. Franke, *Liebigs. Ann. Chem.* 1979, 1456.

(129) T. Allmendinger, P. Furet and E. Hungerbühler, *Tetrahedron Lett.* 1990, **31**, 7297.

(130) D. Michel and M. Schlosser, *Synthesis*, 1996, 1007.

(131) Z. Du, M. J. Haglund, L. A. Pratt and K. L. Erickson, *J. Org. Chem.* 1998, **63**, 8880.

(132) M. A. Tius, G. S. K. Kannangara, M. A. Kerr and K. J. S. Grace, *Tetrahedron*, 1993, **49**, 3291.

(133) N. A. Petasis, A. K. Yudin, I. A. Zavialov, G. K. S. Prakash and G. A. Olah, *Synlett* 1997, 606.

(134) X.-H. Huang, P.-Y. He and G.-Q. Shi, *J. Org. Chem.* 2000, **65**, 627.

(135) H. Zhang, C-B. Zhou, Q-Y. Chen, J-C. Xiao and R. Hong, *Org. Lett*, 2010, **13**, 560.

(136) S. T. Purrington and J. H. Pittman, *Tetrahedron Lett.* 1987, **28**, 3901.

(137) W. Zhang, W. Huang and J. Hu, *Angew. Chem. Int. Ed.* 2009, **48**, 9858.

(138) G. K. S. Prakash, S. Chacko, H. Vaghoo, N. Shao, L. Gurung, T. Mathew and G. A. Olah, *Org. Lett.* 2009, **11**, 1127.

(139) H. Peng and G. Liu, *Org. Lett.* 2011, **13**, 772.

(140) G. Liu, *Org. Biomol. Chem.* 2012, **10**, 6243.

(141) J. A. Akana, K. X. Bhattacharyya, P. Miller and J. P. Sadighi, *J. Am. Chem. Soc*. 2007, **129**, 7736.

(142) B. J. Gorske, C. T. Mbofana and C. J. Miller, *Org. Lett.* 2009, **11**, 4318.

(143) O. E. Okoromoba, J. Han, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.* 2014, **136**, 14381.

(144) G. He, S. Qiu, H. Huang, G. Zhu, D. Zhang, R. Zhang, H. Zhu, *Org. Lett.* 2016, **18**, 1856.

(145) T. Furuya, J. E. M. N. Klein and T. Ritter, *Synthesis*, 2010, **11**, 1804.

(146) For some selected examples, see: a) P. Jeschke, *Chem. Bio. Chem.* 2004, **5**, 570; b) A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15; c) K. Müller, C. Faeh and F. Diederich, F. *Science*, 2007, **317**, 1881; d) W. K. Hagmann, *J. Med. Chem.* 2008, **51**, 4359; e) K. L. Kirk, *Org. Process Res. Dev.* 2008, **12**, 305; f) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.* 2008, **37**, 320; g) P. Jeschke, *Pest. Manage. Sci.* 2010, **66**, 10.

(147) W.-B. Wu, M.-L. Li and J.-M. Huang, *Tetrahedron Lett.* 2015, **56**, 1520.

(148) B. Z. Li, Y. Y. Qian, J. Liu and K. S. Chan, *Organometallics*, 2014, **33**, 7059.

(149) For some selected examples, see: a) P. S. Fier and J. F: Hartwig, *J. Am. Chem.*

Soc. 2014, **136**, 10139; b) T. Niwa, H. Ochiai, Y. Watanabe and T. Hosoya, *J. Am. Chem. Soc.* 2015, **137**, 14313; c) X.-W. Liu, J. Echavarren, C. Zárate and R. Martin, *J. Am. Chem. Soc.* 2015, **137**, 12470; d) Y. Mizukami, Z. Song and T. Takahashi, *Org. Lett.* 2015, **17**, 5942; e) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder and U. Radius, *J. Am. Chem. Soc.* 2016, **138**, 5250.

(150) a) Clark, J. H.; Wails, D.; Bastock, T. W.; in: *Aromatic Fluorination;* CRC Press; Boca Raton, FL, **1996**; b) Kirsch, P.; in: *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications;* Wiley: Weinheim, Germany, **2004**.

(151) G. Balz and G. Schiemann, *Ber. Dtsch. Chem. Ges*. 1927**, 60**, 1186.

(152) a) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.* 1956**, 78**, 6034; b) Langlois, B.; Gilbert, L.; Forat, G.; Fluorination of aromatic compounds by halogen exchange with fluoride anions ("halex" reaction). In: *Industrial Chemistry Library*; Jean-Roger, D., Serge, R., Eds.; Elsevier: **1996**; *pp* 244−292.

(153) A. E. Fedorov, A. A. Zubarev, V. Y. Mortikov, L. A. Rodinovskaya and A. M. Shestopalov, *Russ. Chem. Bull. Int. Ed.* 2015, **64,** 1049.

(154) A. Lin, B. Huehls and J. Yang, *Org. Chem. Front.* **2014**, *1*, 434.

(155) C. Chen, C. Wang, J. Zhang and Y. Zhao, *J. Org. Chem.* 2015, **80**, 942.

(156) K. Albertshofer and N. S. Mani, *J. Org. Chem.* 2016, **81**, 1269.

(157) P. Liu, Y. Gao, W. Gu, Z. Shen and P. Sun, *J. Org. Chem.* 2015, **80**, 11559.

(158) For some selected examples, see: a) V. Snieckus, F. Beaulieu, K. Mohri, W. Han, C. K. Murphy and F. A. Davis, *Tetrahedron Lett.* 1994, **35**, 3465; b) X. Wang, T.-S. Mei and J. Q. Yu, *J. Am. Chem. Soc.* 2009, **131**, 7520.

(159) P. Tang and T. Ritter, *Tetrahedron,* 2011, **67**, 4449.

(160) a) W. E. Barnette, *J. Am. Chem. Soc.* 1984, **106**, 452; b) E. Differding and M. Wehrli, *Tetrahedron Lett.* 1991, **32**, 3819.

(161) S. Yamada, A. Gavryushin and P. Knochel, *Angew. Chem. Int. Ed.* 2010, **49**, 2215.

(162) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* 2010, **49**, 2219.

(163) T. Furuya, A. E. Strom and T. Ritter, *J. Am. Chem. Soc.* 2009, **131**, 1662.

(164) P. P. Tang, T. Furuya and T. Ritter, *J. Am. Chem. Soc.* 2010, **132**, 12150.

(165) B. Zajc, *J. Org. Chem.* 1999, **64**, 1902.

(166) T. Furuya and T. Ritter, *J. Am. Chem. Soc.* 2009, **130**, 10060.

(167) T. Furuya, H. M. Kaiser and T. Ritter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

(168) C. Cazorla, E. Métay, B. Andrioletti and M. Lemaire, *Tetrahedron Lett.* 2009, **50**, 3936.

(169) a) S. Darses and J.-P. Genêt, *Chem. Rev.* 2008, **108**, 288; b) S. R. Dubbaka, S. Gadde and V. R. Narreddula, *Synthesis*, 2015**, 47**, 854.

(170) T. Furuya and T. Ritter, *Org. Lett.* 2009, **11**, 2860.

(171) K. L. Hull, W. Q. Anani and M. S. Sanford, *J. Am. Chem. Soc.* 2006, **128**, 7134.

(172) N. D. Ball and M. S. Sanford, *J. Am. Chem. Soc.* 2009**, 131**, 3796.

(173) J. Zhang, H. Wang, S. Ren, W. Zhang and Y. Liu, *Org. Lett.* 2015, **17**, 2920.

(174) D. J. Adams and J. H. Clark, *Chem. Soc. Rev.* 1999, **28**, 225.

(175) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.* 1956, **78**, 6034.

(176) K. L. Kirk, D. Cantacuzene, Y. Nimitkitpaisan, D. McCulloh, W. L. Padgett, J. W. Daly and C. R. Creveling, *J. Med. Chem*. 1979, **22**, 1493.

(177) For some other examples, see: a) J. H. Clark and D. Walls, *J. Fluorine Chem.* 1995, **70**, 201; b) S. D. Kuduk, R. M. DiPardo and M. G. Bock, *Org. Lett.* 2005, **7**, 577; c) H. Sun, S. G. DiMagno, *Chem. Commun.* 2007, 528.

(178) H. Sun and S. G. DiMagno, *J. Am. Chem. Soc.* 2005, **127**, 2050; d) H. Sun and S. G. DiMagno, *Angew. Chem. Int. Ed.* 2006, **45**, 2720.

(179) S. J. Ryan, S. D. Schimler, D. C. Bland and M. S. Sanford, *Org. Lett.* 2015, **17**, 1866.

(180) V. V. Grushin (EI DuPont de Nemours & Co) US 7202388, **2007**; *Chem. Abstr*. 2007, **144**, 331137.

(181) A. Casitas, M. Canta, M. Solà, M. Costas and X. Ribas, *J. Am. Chem. Soc.* 2011, **133**, 19386.

(182) P. S. Fier and J. F. Hartwig, *J. Am. Chem. Soc.* 2012, **134**, 10795.

(183) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fontanet, T. Kinzel and S. L. Buchwald, *Science*, 2009, **325**, 1661.

(184) V. V. Grushin, *Acc. Chem. Res.* 2010, **43**, 160.

(185) A. I. Konovalov, E. O. Gorbacheva, F. M. Miloserdov and V. V. Grushin, *Chem. Commun.* 2015, **51**, 13527.

(186) M. van der Puy, *J. Fluorine Chem.* 1982, **21**, 385.

(187) N. Ichiishi, A. J. Canty, B. F. Yates and M. S. Sanford, *Org. Lett. 2013*, **15(19)**, 5134.

(188) N. Ichiishi, A. J. Canty, B. F. Yates and M. S. Sanford, *Organometallics*, 2014,

33, 5525.

(189) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford and P. J. H. Scott, *Org. Lett.* 2014, **16**, 3224.

(190) R. Edwards, W. de Vries, A. D. Westwell, S. Daniels and T. Wirth, *Eur. J. Org. Chem.* 2015, 6909.

(191) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, and V. Gouverneur, *Angew. Chem. Int. Ed.* 2014, **53**, 7751.

(192) A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Org. Lett.* 2015, **17**, 5780.

(193) For some other selected examples, see: a) M. A. Subramanian and L. E. Manzer, *Science,* 2002, **297**, 1665; b) K. M. Janmanchi and W. R. Dolbier Jr. *Org. Process Res. Dev.* 2008, **12**, 349; c) X. Mu and G. Liu, *Org. Chem. Front.* 2014, **1**, 430.

(194) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F. R. Leroux, *Beilstein, J. Org. Chem.* 2013, **9**, 2476.

(195) E. Lee, M. H. Hooker and T. Ritter, *J. Am. Chem. Soc.* 2012, **134**, 17456.

(196) For the original description of the synthesis of PhenoFluor, see: P. P. Tang, W. K. Wang, and T. Ritter, *J. Am. Chem. Soc.* 2011, **133**, 11482.

(197) For some selected examples of the application of PhenoFluor, see: a) F. Sladojevich, S. I. Arlow, P. Tang and T. Ritter, *J. Am. Chem. Soc.* 2013, **135**, 2470; b) M. G. Campbell and T. Ritter, *Org. Process Res. Dev.* 2014, **18**, 474; c) T. Fujimoto, F. Becker and T. Ritter, *Org. Process Res. Dev.* 2014, **18**, 1041.

(198) T. Fujimoto and T. Ritter, *Org. Lett.* 2015, **17**, 544.

(199) N. Yasui, C. G. Mayne and J. A. Katzenellenbogen, *Org. Lett.* 2015, **17**, 5540.

(200) J. Qian, Y. Liu, J. Zhu, B. Jiang and Z. Xu, *Org. Lett.* 2011, **13**, 4220.

(201) Y. Jeong, B.-I. Kim, J. K. Lee and J.-S. Ryu, 2014, **79**, 6444.

CHAPTER 2

Arylsulfonic Acids: Substrates in Fluorination Chemistry

2.1 Introduction

The previous chapter has presented the state-of-the-art in the synthesis of aryl fluorides, displaying the main advantages and inconveniences of the methods available up to date. Despite the wide variety of methods, only few of the important inconveniences associated with this reaction have been addressed by these protocols,[1] and therefore the discovery of new methodologies for the synthesis of aryl fluorides is still highly desirable.

A few aromatic derivatives were discussed earlier as suitable molecules for the preparation of aryl fluorides, such as nitroarenes, haloarenes or phenols. Nonetheless, many other derivatives with interesting chemical features for fluorination remain untested in this transformation. Among these, arylsulfonic acids can be discussed. While these compounds are active acidic catalysts and precursors for important molecules, the study of the sulfonic acid/sulfonate moiety as a "leaving group", providing access to site-selective functionalisation of arenes, is scarce. The chemical properties of this molecular fragment, together with the most recent advances in fluorination chemistry involving functional group substitution, have encouraged us to test these substrates in the challenging field of electrophilic fluorination. This is still an unexplored area of research for this type of transformation. Their synthetic availability, ease of handling and reactive properties certainly warranted exploring the feasibility of C-S activation towards the generation of aryl fluorides in the presence of "F^+" sources.

This chapter will present the preliminary results of the study of the reactivity of arylsulfonic acids in the presence of electrophilic fluorination sources. Both catalyst-free and transition metal-catalysed systems will be discussed, with a special attention to Au(I)-NHC complexes and their possible mediation in substituting the sulfonic acid moiety for a fluorine atom.

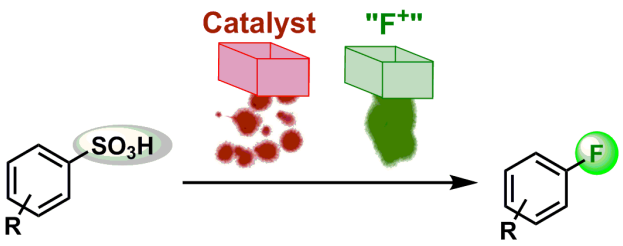


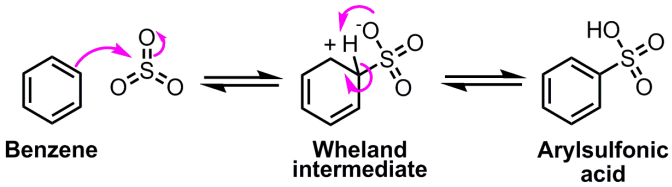
Figure 2.1. General scheme for the electrophilic fluorination of arylsulfonic acids.

2.2 Arylsulfonic acids

2.2.1 Introduction

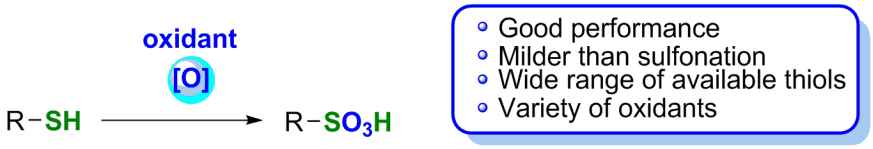
Sulfonic acids constitute a family of organosulfur compounds whose main structure is based on the presence of a sulfonyl hydroxide group (-SO_3H) attached to an alkyl or aryl chain. These compounds are highly polar molecules and strong acids (benzenesulfonic acid has a pKa of -2.8, about a million times higher than that of common carboxylic acids, and within the range of common strong inorganic acids such as HCl, HNO_3 or H_2SO_4). These compounds can be used in a variety of roles, ranging from acidic organic catalysts to surfactants, materials and drugs, among others,[2] and are therefore regarded as interesting substances in chemistry.

Sulfonic acids are generally prepared by direct electrophilic sulfonation of benzene derivatives with various sulfonation reagents, sulfur trioxide in fuming H_2SO_4 being the most employed methodology for such purpose. This synthesis follows the general electrophilic substitution mechanism, with sulfur trioxide being added to benzene and the corresponding Wheland intermediate getting rearomatised by proton abstraction which is promoted by the generated sulfonate (Scheme 2.1). This sulfonation pathway has been extensively studied, and it is especially important for the industrial production of alkylated benzenesulfonic acids.



Scheme 2.1. Mechanism of the electrophilic sulfonation of benzene using sulfur trioxide.

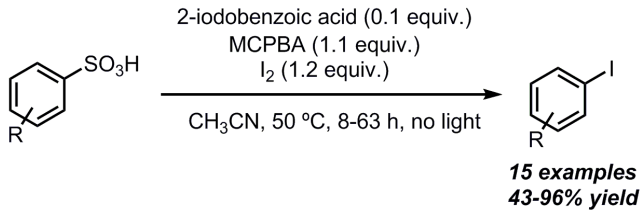
Sulfonic acids can be alternatively prepared through oxidation of thiols (Scheme 2.2). Mechanistic studies and well-documented experimental data are available for this transformation.[3] The latter became a suitable alternative to the hazardous use of sulfur trioxide, providing a useful synthetic method for arylsulfonic acids.[4]



Scheme 2.2. Oxidation of thiols for the synthesis of sulfonic acids.

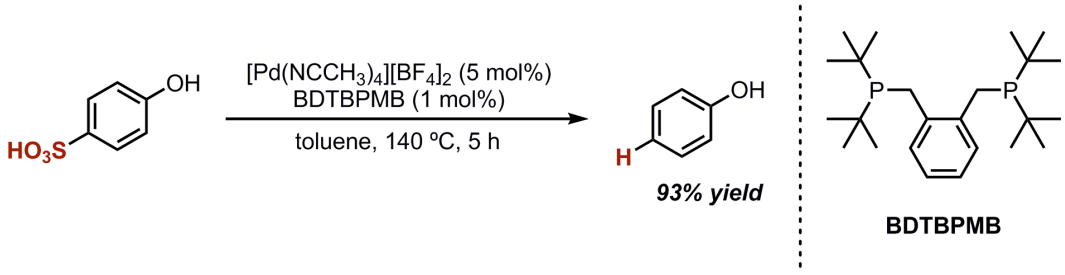
2.2.2 Arylsulfonic acids in substitution reactions

Several reports have shown that arylsulfonic acids could be converted into other aromatic derivatives. For example, Togo and co-workers reported in 2010 a system for the conversion of arylsulfonic acids into their corresponding aryl iodides after reaction with iodine in the presence of *meta*-chloroperbenzoic acid (MCPBA) (Scheme 2.3).[5]



Scheme 2.3. Iodination of arylsulfonic acids with iodine.[5]

The C-S bond cleavage featured in this reaction represents only one example of the range of reports showing the high interest in the use of sulfur-containing compounds for the formation of new chemical bonds.[6] The use of transition metal catalysts in this chemistry has provided a more consistent approach towards simplified and optimised synthetic routes. Among these examples, one interesting report by Cole-Hamilton and co-workers from 2010 attracted our attention. In this work, the use of a Pd(II) catalyst promoted SO_3 extrusion in 4-hydroxybenzenesulfonic acid upon warming to 140 ºC for 5 h (Scheme 2.4), releasing phenol in 93% yield.[7] The methodology required an electron-rich metal centre (in this case, obtained *via* the use of a particular bis-phosphine ligand) to perform efficiently.



Scheme 2.4. Pd(II)-catalysed desulfonation of arylsulfonic acids.[7]

The proposed elimination of SO_3 using this transition metal system was very intriguing, and correlates quite nicely with the well-known desulfonation process which usually requires slightly acidic conditions and high temperatures.

2.2.3 Fluorination of arylsulfonic acids

The exploitation of desulfonation/substitution chemistry for the preparation of other aromatic derivatives using a similar concept is still in its infancy, and thus further work is needed to expand this interesting area of research. In particular, and in the context of the growing importance of fluorinated compounds (and more specifically, aryl fluorides, see Chapter 1.4.3.3 for further information about synthesis and applications of these molecules), a desulfonation/fluorination reaction would be of great utility for synthesis (Figure 2.2). To the best of our knowledge, no example of this transformation has been reported to date.

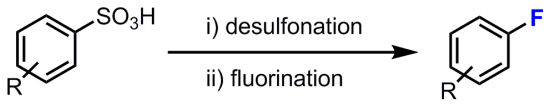
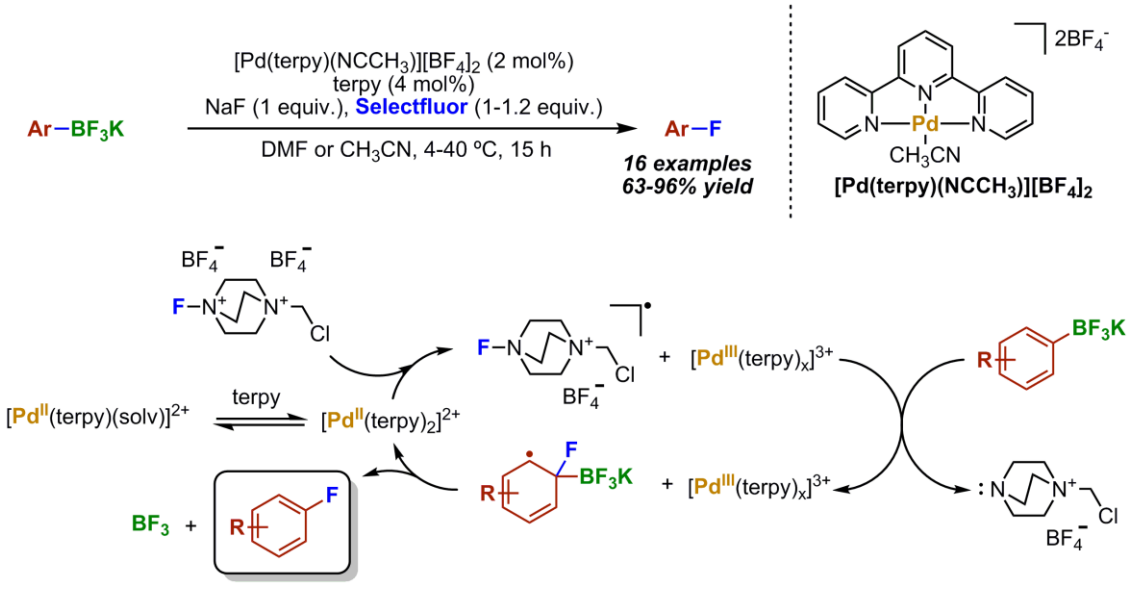


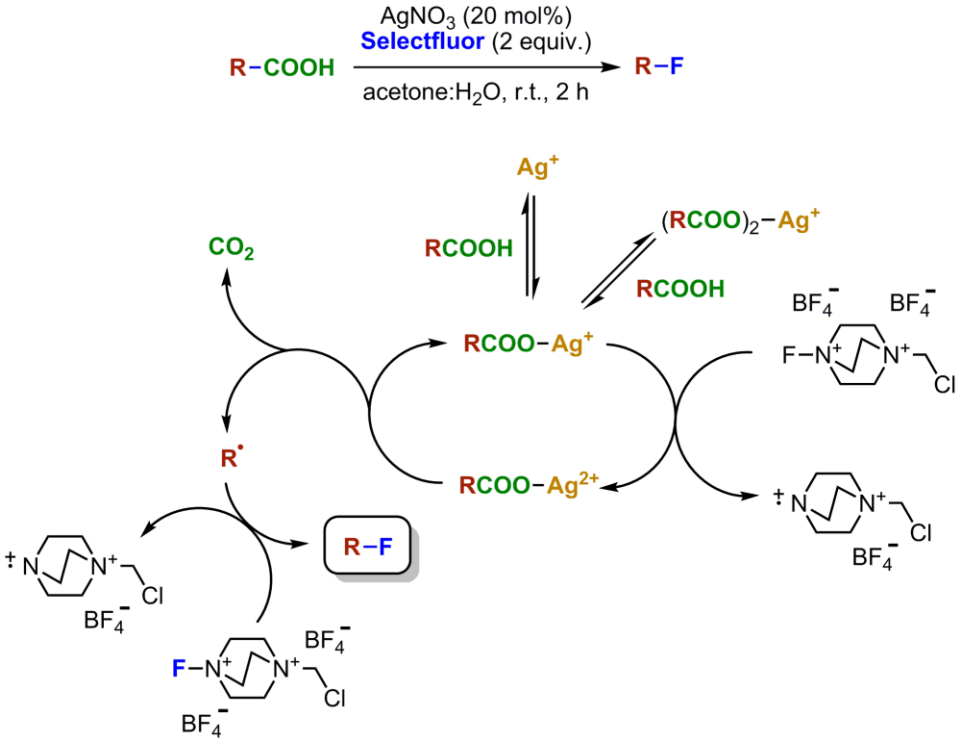
Figure 2.2. Proposed desulfonation/fluorination of arylsulfonic acids for the synthesis of aryl fluorides.

The idea of functional group extrusion followed by fluorination is not new, although only a few reports have discussed similar mechanisms. In 2013, Ritter presented the fluorination of aryl trifluoroborate salts using a Pd(II) catalyst. The mechanistic pathway proposed in this work suggested a radical fluorination of aryl trifluoroborates followed by extrusion of BF_3 with concomitant release of the desired aryl fluoride (Scheme 2.5). Isolated yields up to 96% were obtained using this mild methodology.[8]



Scheme 2.5. Proposed mechanism for the Pd-catalysed fluorination of aryl trifluoroborate salts.[8]

Due to the complexity of the catalytic system, the search for easier alternatives for similar reactions has not ceased. The conversion of aliphatic carboxylic acids into their corresponding fluoroalkanes, *via* a decarboxylation procedure catalysed by a Ag(I) salt, is another outstanding example within this area of chemistry.[9] The mechanism of this reaction has been thoroughly studied;[10] with Selectfluor acting as both a fluorinating reagent and single-electron oxidant (Scheme 2.6).

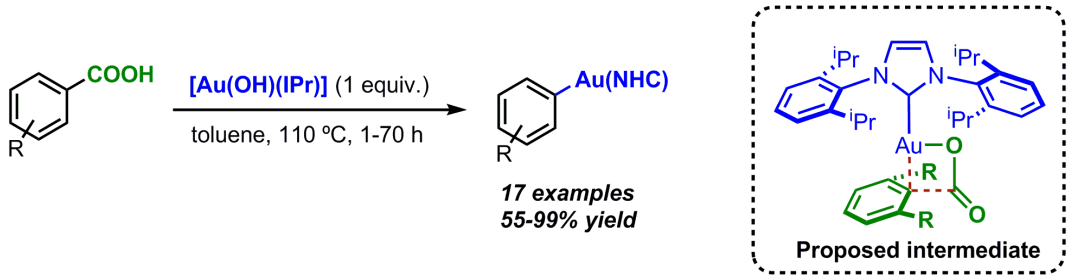


Scheme 2.6. Proposed mechanism for the Ag-catalysed decarboxylation/fluorination of aliphatic carboxylic acids.[10]

Despite featuring a very simple and desirable set of reaction conditions, the inefficiency of the method with aromatic substrates, and the use of a toxic silver salt as catalyst are still inconveniences to be addressed.

Inspired by these two methodologies, we were highly interested in exploring similar chemistry with arylsulfonic acids. Our research strategies mainly focus on the synthesis and applications of transition metal-NHC complexes to new synthetic pathways, and within that context, fluorination chemistry is definitely an interesting area of study. It should be noted that, to date, no examples involving NHC-based complexes have been reported for the fluorination of aryl derivatives. Nevertheless, encouraging work is available in the literature. A report by Nolan and co-workers showed that the reaction between [Au(OH)(IPr)] and benzoic acids generated stable

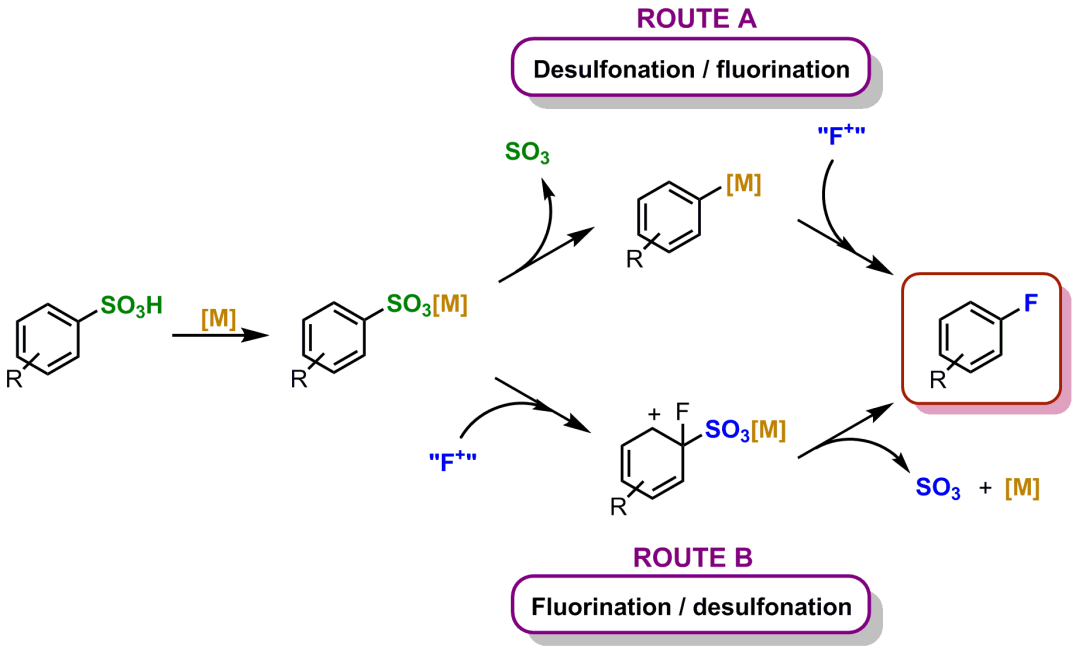
NHC-Au(I)-carboxylato complexes. These complexes, upon warming to 110 ºC in toluene, successfully underwent decarboxylation to yield the corresponding arylgold(I)-NHC species in good to excellent yields (Scheme 2.7).[11]



Scheme 2.7. Decarboxylative synthesis of arylgold(I)-NHC complexes starting from [Au(OH)(IPr)] and aromatic carboxylic acids.[11]

While this work only presented the generation of arylgold(I) species, the reactivity of these complexes towards aryl functionalisation can be an interesting addition to the field of gold catalysis. The ease of access to these NHC-based arylgold(I) species and the relatively simple CO_2 extrusion suggested to us a more than feasible application of these complexes for the fluorination of arylsulfonic acids. With an easy access to these compounds (mainly through sulfonation of arene derivatives) and a better late-stage functionalisation that that of carboxylic acids, sulfonic acids would make for a more attractive leaving group for industrial synthesis.

Considering the previously discussed literature, analogous reaction sequences can be proposed as suitable approaches for the synthesis of aryl fluorides starting from arylsulfonic acids (Scheme 2.8). First, a desulfonation/fluorination strategy can be discussed (Scheme 2.8, top). In analogy with the work from Nolan,[11] the synthesis of metal-sulfonato species, followed by SO_3 extrusion and electrophilic fluorination could afford an efficient synthesis of aryl fluorides. Alternatively, the order of the steps could be reversed (Scheme 2.8, bottom). In this case, the sequence will involve an *ipso*-directed fluorination step taking place prior to the desulfonation stage, following a similar mechanism to that described by Ritter.[8] The preliminary studies of these two mechanisms for the desulfonative fluorination of arylsulfonic acids will now be presented.



Scheme 2.8. Proposed mechanistic pathways for the fluorination of arylsulfonic acids: desulfonation/fluorination (top) and fluorination/desulfonation (bottom).

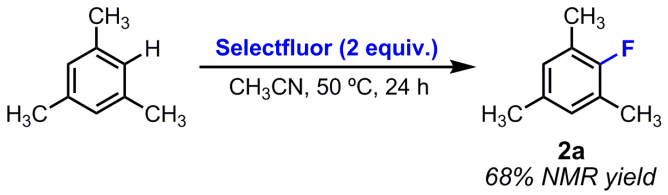
2.2.4 Results and discussion

2.2.4.1 Initial tests

p-Toluenesulfonic acid monohydrate was initially selected as model substrate for the optimisation studies; however, preliminary reactions showed that unselective fluorination was taking place on this substrate. This fact made the identification of the expected product, by spectroscopic analyses, highly difficult. In addition, the low boiling point of the expected compound, 4-methylbenzene fluoride, was also an important drawback for analysis and isolation. In order to circumvent these drawbacks, 2,4,6-trimethylbenzenesulfonic acid dihydrate (**1a**) was selected as a better model substrate for optimisation. The resulting product, 1-fluoro-2,4,6-trimethylbenzene (**2a**), has a higher boiling point and a clearly distinguishable signal by ^{19}F NMR at approximately -127 ppm, making it suitable for optimal analyses. Selectfluor was chosen as the electrophilic fluorine source due to its commercial availability and wide use in fluorination processes.

The accessibility to the corresponding fluorinated product, **2a**, through simple electrophilic fluorination was first assessed. The mechanism for this reaction has been well studied,[12] and was shown to undergo classical electrophilic addition/proton elimination process. To support such reactivity, mesitylene was reacted with two

equivalents of Selectfluor in CH_3CN at 50 ºC for 24 h. **2a** was obtained as the sole fluorinated product in 68% NMR yield, according to ^{19}F NMR analysis using 1-bromo-3-fluorobenzene as an internal standard (Scheme 2.9).

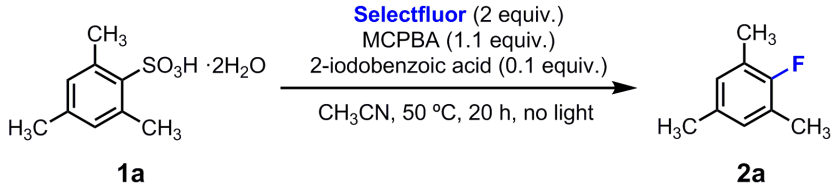


Scheme 2.9. Catalyst-free synthesis of **2a** through electrophilic fluorination of mesitylene.

While this moderate reactivity is generally acceptable for such simple systems, it does not represent a general approach for the fluorination of other substrates. This is due to the highly-substituted symmetrical structure of mesitylene, which strongly favours selective monofluorination. This methodology cannot be successfully applied to other substrates with the same efficiency, thus limiting its applicability. Other approaches to the fluorination of mesitylene, such as the use of *N*-fluorobenzenesulfonimide (NFSI) as a fluorinating reagent,[13] generally provide lower yields and mixtures of the derived mono- and difluorinated species. Due to these drawbacks, non-catalysed fluorination is rendered impractical for a general substrate scope, further supporting the use of more suitable substrates and reaction systems for our experimental studies.

Before testing our mechanistic hypotheses, the use of previously published conditions for desulfonation/functionalisation of arylsulfonic acids seemed logical. Considering the previously presented work from Togo and co-workers for the desulfonative iodination of arylsulfonic acids,[5] an analogous reaction system employing an electrophilic fluorinating source instead of I_2 was discussed. Unfortunately, the use of their optimised conditions using **1a** as substrate and Selectfluor as fluorine source led to only 2% NMR yield of the expected compound **2a** (Table 2.1, Entry 1). The removal of 2-iodobenzoic acid afforded equally low NMR yield of the desired molecule (Table 2.1, Entry 2). Complete removal of these additives led to no traces of **2a** being detected (Table 2.1, Entry 3).

Table 2.1. Desulfonation/fluorination of **1a** promoted by MCPBA/iodobenzoic acid.



1a **2a**

Entry	MCPBA	2-iodobenzoic acid	NMR yield 2a (%)[b]
1	✓	✓	2
2	✓	---	5
3	---	---	0

[a] Reaction conditions: **1a** (0.1 mmol), [Au] (5 mol%), Selectfluor (0.2 mmol), toluene (0.3 mL), 80 ºC, 20 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent), using 1-bromo-3-fluorobenzene as internal standard.

In view of these results, a new methodology needs to be studied for the desulfonative fluorination of arylsulfonic acids. The two proposed routes will be now discussed and tested.

2.2.4.2 Route A: desulfonation/fluorination

Our first proposal was to investigate the suitability of a desulfonation/fluorination strategy for the preparation of aryl fluorides. In order to do so, the use of transition metal-NHC complexes as catalysts was proposed. Our first rational mechanism for this reaction using the aforementioned metal species is depicted in Figure 2.3, and will be based on the use of Au(I)-NHC complexes with the formula [Au(OH)(NHC)] (for further insights into the preparation and reactivity of these species, the Reader is referred to Chapter 1.3). The basic character of Au(I) hydroxide species (Figure 2.3, **A**) can promote acid-base reaction with arylsulfonic acids, $ArSO_3H$, yielding the corresponding NHC-Au(I)-sulfonato species [Au(OSO_2Ar)(NHC)] (Figure 2.3, **B**). In an analogous fashion to Au(I)-carboxylato species reported by Nolan and co-workers,[11] desulfonation with concomitant formation of an aryl-Au bond could then proceed, affording the corresponding NHC-Au(I)-aryl complex (Figure 2.3, **C**), enhancing the nucleophilicity of the *ipso* carbon of the aromatic ring, which could then react with an electrophilic fluorine source. This last step will yield the desired aryl

fluoride together with a Au(I)-NHC reactive intermediate (Figure 2.3, **D**) which could regenerate the active hydroxide species in the presence of a hydroxide base, thus closing the catalytic cycle.

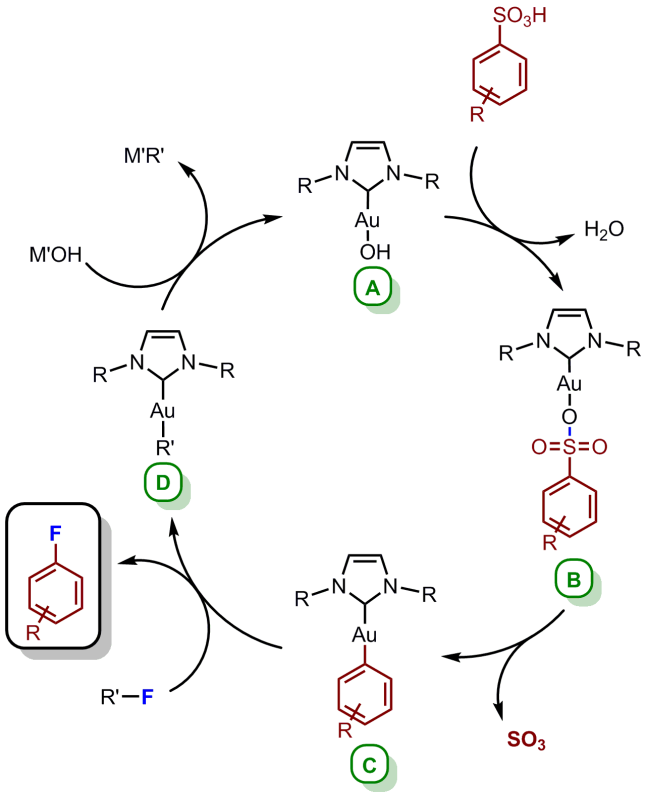
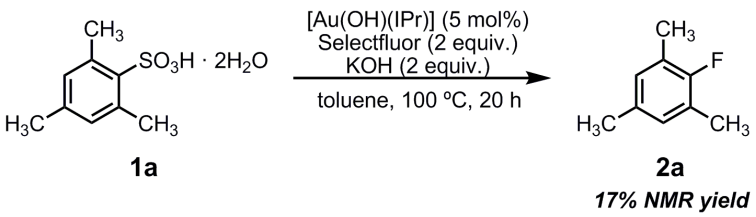


Figure 2.3. Proposed catalytic cycle for the fluorination of arylsulfonic acids catalysed by [Au(OH)(NHC)] complexes.

Based on this proposal, preliminary tests were conducted. **1a** was initially reacted with two equivalents of Selectfluor in the presence of 5 mol% of [Au(OH)(IPr)] and two equivalents of KOH in toluene at 100 ºC for 20 h. Under these reaction conditions, an encouraging 17% of the expected product **2a** was observed (Scheme 2.10). The species was further confirmed by comparison with a pure sample of **2a**, providing a proof of concept of the feasibility of a desulfonative fluorination mechanism.



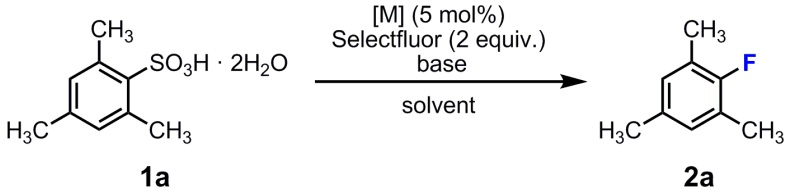
1a **2a**

17% NMR yield

Scheme 2.10. Preliminary test on the Au-catalysed desulfonative fluorination of **1a**.

Inspired by this result, extensive optimisation studies were conducted, with some representative results being summarised in Table 2.2 (complete experimental data can be found in the Supporting Data CD, Experimental Annex - Chapter 2, Table S1). The use of NaOH instead of KOH as base showed a slight decrease in the NMR yield of **2a** (Table 2.2, Entries 1-2). The use of an alternative metal-NHC hydroxide species based on Cu(I) afforded no reaction under the same experimental conditions (Table 2.2, Entries 3-4), thus proving that the nature of the metal is key for its mediation in the desulfonation/fluorination process. Decreasing the amount of base to one equivalent afforded a slightly higher NMR yield of **2a (**Table 2.2, Entry 5), strongly contrasting to what could be expected in a system where the base can be consumed through either acid-base reaction with **1a** or *via* catalyst regeneration. This suggests that a more complex catalytic cycle might be taking place in this reaction. Decreasing the reaction temperature to 80 ºC afforded similar results (Table 2.2, Entry 6) to those obtained previously, and thus was kept for further testing. The variation of the NHC (Table 2.2, Entry 7), the "F^+" source (Table 2.2, Entry 8) or the use of polar aprotic (Table 2.2, Entry 9) or protic solvents (Table 2.2, Entry 10) did not afford better results. Finally, to favour the shift of the chemical equilibrium towards the formation of products, a reflux system was used in order to facilitate SO_3 elimination from the reaction mixture; however, lower performance of the system was obtained under these conditions (Table 2.2, Entry 11).

Table 2.2. Optimisation of the desulfonative fluorination of **1a** using transition metal-NHC hydroxide complexes.



1a **2a**

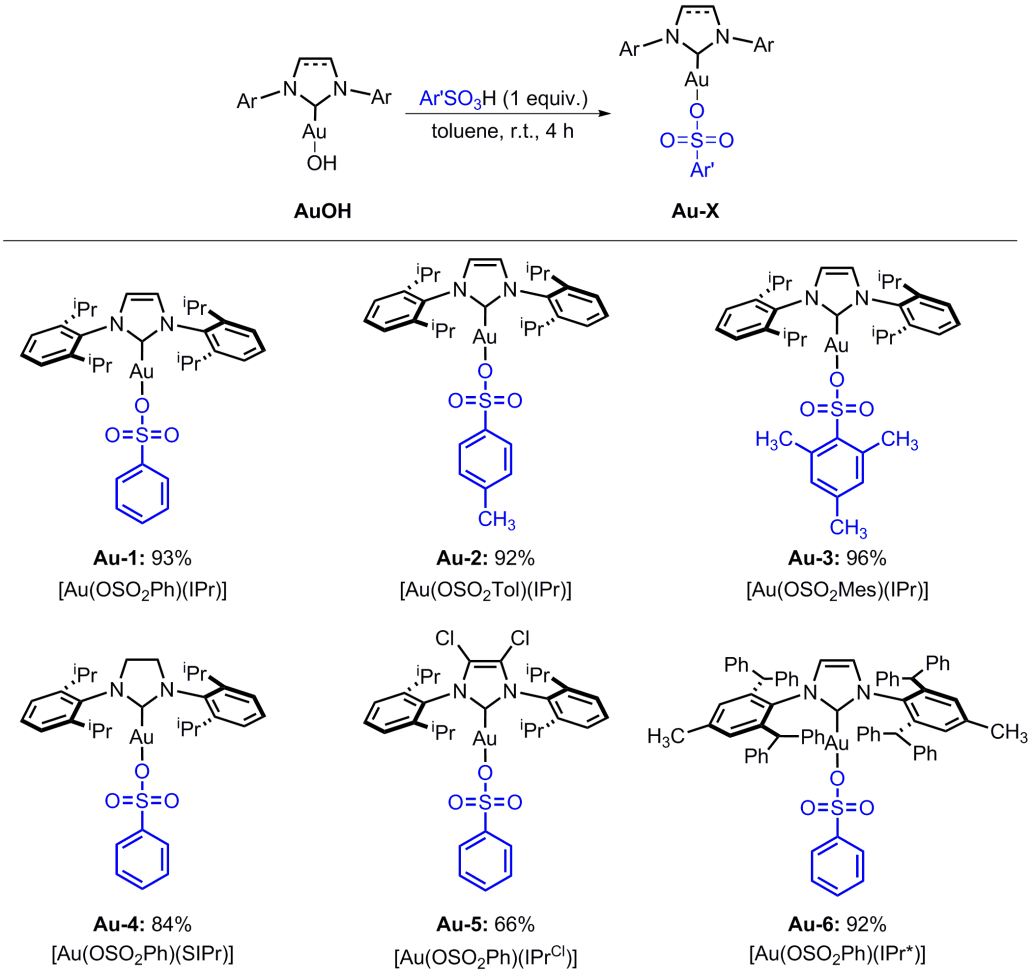
Entry	[M]	Base	Solvent	T (ºC)	Time (h)	2a (%)[b]
1	[Au(OH)(IPr)]	KOH (2)	toluene	100	20	17
2	[Au(OH)(IPr)]	NaOH (2)	toluene	100	20	11
3	[Cu(OH)(IPr)]	KOH (2)	toluene	100	20	< 1
4	[Cu(OH)(IPr)]	NaOH (2)	toluene	100	20	< 1
5	[Au(OH)(IPr)]	KOH (1)	toluene	100	20	20
6	[Au(OH)(IPr)]	KOH (1)	toluene	80	20	21
7	[Au(Cl)(IMes)]	KOH (1)	toluene	80	20	13
8[c]	[Au(OH)(IPr)]	KOH (1)	toluene	80	20	0
9	[Au(OH)(IPr)]	KOH (1)	CH_3CN	80	20	0
10	[Au(OH)(IPr)]	KOH (1)	EtOH	80	20	0
11[d]	[Au(OH)(IPr)]	KOH (1)	toluene	80	20	12

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (5 mol%), Selectfluor (0.2 mmol), base (0.2 mmol), solvent (0.3 mL). [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent), using 1-bromo-3-fluorobenzene as internal standard. [c] *N*-fluorobenzenesulfonimide (NFSI) (0.2 mmol) used instead of Selectfluor. [d] Open system (reflux).

Before re-evaluating the involved reaction mechanism, as suggested by the mismatch of the obtained results with such a pathway, a deeper study of the proposed catalytic steps was performed to discover any hurdles that could be individually addressed.

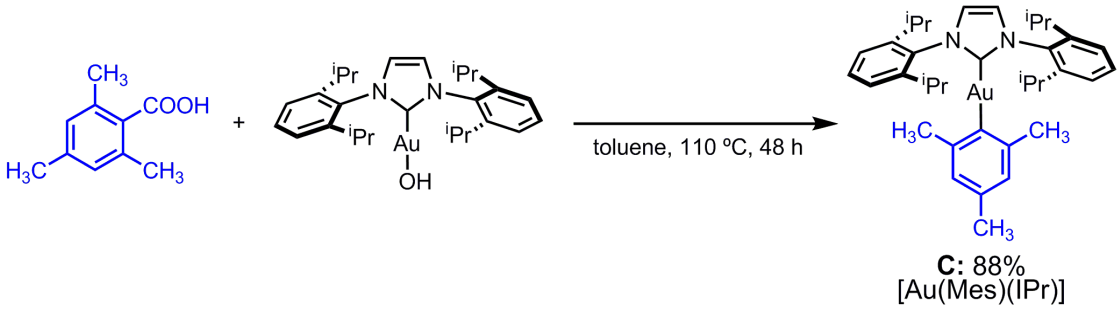
First, the accessibility to Au(I)-NHC species **B** from hydroxide complexes **A** was tested. The preparation of this NHC-Au(I)-sulfonato species was a simple acid-base reaction that could be achieved by reacting [Au(OH)(IPr)] with **1a** in stoichiometric amounts. After 4 h in toluene at room temperature, complex **Au-3** was isolated in 96% yield (Scheme 2.11). This synthetic method could be successfully extended to other arylsulfonic acids (Scheme 2.11, **Au-1** and **Au-2**), and different NHCs were also tolerated (Scheme 2.11, **Au-4** and **Au-6**). Water present in the hydrated form of sulfonic

acids did not have a marked effect on the outcome of this reaction, thus facilitating the synthesis of these complexes from readily available arylsulfonic acid hydrates (a typical commercial form for these substrates). These complexes are air- and moisture-stable white solids, and can be stored for months without any trace of noticeable decomposition.



Scheme 2.11. Synthesis of NHC-Au(I)-sulfonato species.

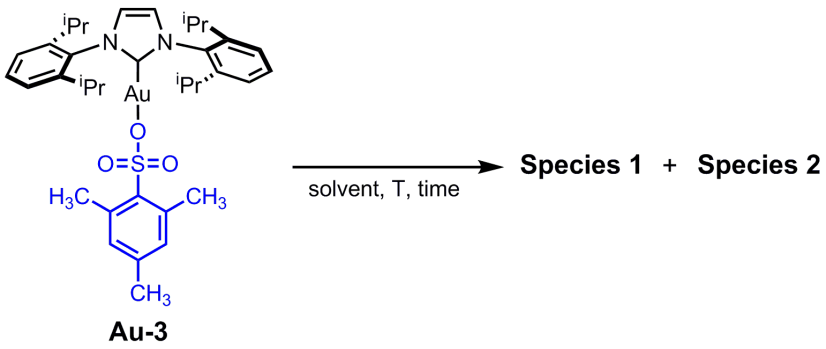
The desulfonation of species **B** into species **C** (Figure 2.3) was then examined. **Au-3** was selected for such studies, representing the appropriate intermediate of our model reaction. For an adequate reaction profiling, the corresponding species **C** was independently prepared by reacting [Au(OH)(IPr)] with stoichiometric 2,4,6-trimethylbenzoic acid in toluene at 110 ºC for 48 h, using the methodology reported by Nolan and co-workers.[11] The corresponding mesitylgold(I)-IPr species was obtained cleanly in 88% yield (Scheme 2.12).



Scheme 2.12. Synthesis of [Au(Mes)(IPr)] from [Au(OH)(IPr)] and 2,4,6-trimethylbenzoic acid.

With this species in hand, the reactivity of **Au-3** was tested (Table 2.3). Stirring the latter complex in toluene at 110 ºC for 24 h afforded no reaction according to NMR analysis (Table 2.3, Entry 1). The use of 1,4-dioxane (a solvent that was also successfully used during the decarboxylation studies of Nolan) provided the same observations, with starting material being detected as the only species (Table 2.3, Entry 2). However, when the reaction solvent was changed to xylenes and the temperature was increased to 130 ºC, two new IPr-based species could be detected after 24 h, in a ratio of 64% and 12% of the mixture, respectively (Table 2.3, Entry 3). These species did unfortunately not match the spectroscopic data for [Au(Mes)(IPr)]. By increasing the reaction time to 48 h, a relative ratio of 89% could be obtained for one of these species, with only 8% of **Au-3** remaining in the mixture (Table 2.3, Entry 4). The reaction time could be again reduced to 24 h when using 140 ºC, with a ratio of 80% for this major species (Table 2.3, Entry 5). However, very surprisingly, when scaling up to 150 mg of **Au-3** for product isolation, the ratio of this desired side product diminished again, with only 18% being detected (Table 2.3, Entry 6). Performing the reaction under nitrogen atmosphere drastically reduced the conversion rate of this reaction, with 83% of the major side product being observed only after 96 h of reaction time (Table 2.3, Entry 7).

Table 2.3. Reactivity of **Au-3** in solution at moderate temperatures.



Au-3

Entry	Solvent	T (ºC)	Time (h)	Au-3 (%)	Species 1 (%)	Species 2 (%)
1	toluene	110	24	100	---	---
2	1,4-dioxane	110	24	100	---	---
3	xylenes	130	24	24	64	12
4	xylenes	130	48	8	89	3
5	xylenes	140	24	15	80	5
6[b]	xylenes	130	72	77	18	5
7[c]	xylenes	130	96	10	83	7

[a] Reaction conditions: **Au-3** (30 mg), solvent (0.3 mL). [b] 150 mg of **Au-3.** [c] Under N_2 atmosphere.

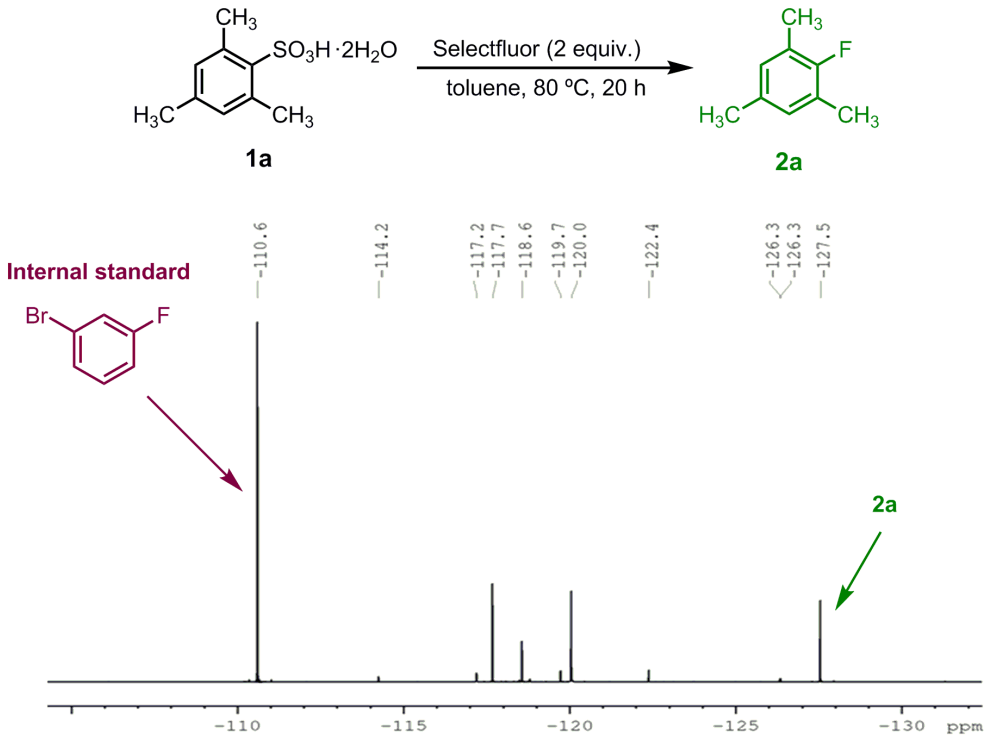
The use of other high-boiling-point solvents, such as DMF, DMA, DMSO or NMP afforded complex signal patterns, although in all cases extensive depletion of **Au-3** was observed, with no desirable intermediate **C** being detected and only minor proportions of species 1 and 2.

Since among all performed tests, no traces of desulfonated species **C** could ever be detected, the desulfonation/fluorination pathway can be regarded as less likely to occur under the tested reaction conditions for the fluorination of arylsulfonic acids. Alternative mechanistic pathways for the conversion of **1a** into **2a** must now be discussed.

2.2.4.3 Route B: fluorination/desulfonation

Considering the lack of success on promoting desulfonation in sulfonato species, the examination of a mechanistic pathway involving other individual steps was

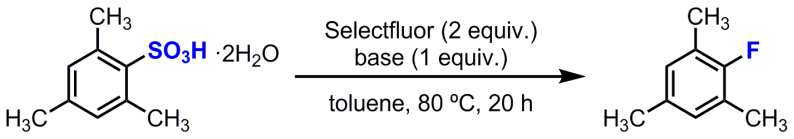
discussed. Initially, metal-free systems were considered, to assess the native reactivity of **1a** in the presence of electrophilic fluorine sources. Surprisingly, when **1a** was reacted with two equivalents of Selectfluor in toluene at 80 ºC for 20 h, a mixture of various fluorinated species could be observed by ^{19}F NMR analysis. This mixture included **2a**, which was observed in 28% NMR yield (Scheme 2.13).



Scheme 2.13. Metal-free desulfonative fluorination of **1a** in the presence of Selectfluor (^{19}F-{^{1}H} NMR spectrum, $CDCl_3$ as solvent).

This result was certainly important, since it displayed a higher reactivity towards the synthesis of **2a** than in the absence of a metal catalyst (see previous subchapter). The effect of the reaction conditions in this reaction was tested under metal-free conditions. First, the use of bases was again considered (Table 2.4). Despite the use of various inorganic bases, conversion of **1a** into **2a** remained unsatisfactory (Table 2.4, Entries 2-8), obtaining in all cases significantly lower NMR yields for the desired product. Low fluorination performance was also observed (negligible amounts of unidentified fluorination products). Considering that nucleophilic aromatic substitution with hydroxide bases is unlikely at 80 ºC (usually requiring up to 300-350 ºC), other reasons are to be invoked for the decrease in reactivity, such as the acid-base neutralisation of the substrate, which can now be highlighted as an inconvenience for the preparation of **2a**.

Table 2.4. Preliminary tests: base-promoted fluorination of mesitylenesulfonic acid dihydrate.[a]

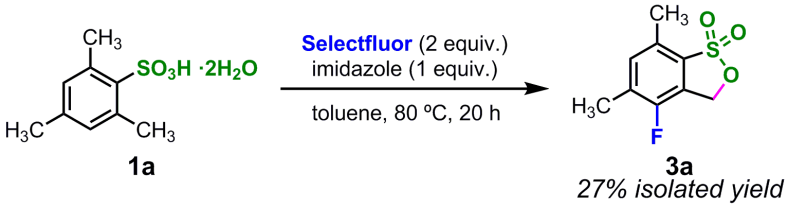


1a **2a**

Entry	Base	NMR yield (%)[b]
1	---	28
2	KOH	10
3	$KHCO_3$	12
4	K_2CO_3	13
5	NaOH	6
6	$NaHCO_3$	10
7	Na_2CO_3	6
8	K_3PO_4	7
9	Imidazole	3

[a] Reaction conditions: **1a** (0.1 mmol), Selectfluor (0.2 mmol), base (0.1 mmol), toluene (0.3 mL), 80 ºC, 20 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent), using 1-bromo-3-fluorobenzene as internal standard.

However, during the base optimisation, the use of imidazole displayed very interesting reactivity. While **2a** was only observed in 3% NMR yield (Table 2.4, Entry 9), a different major species could be detected at -118 ppm by ^{19}F NMR analysis. Despite its low overall NMR yield (25%) and lack of good selectivity, this species could be isolated and analysed by NMR techniques, and the fluorinated sultone **3a** was suggested as the possible reaction product, as the result of an oxidative cyclisation-fluorination sequence (Scheme 2.14). This *one-pot* reaction and the related product have no precedents in the literature.

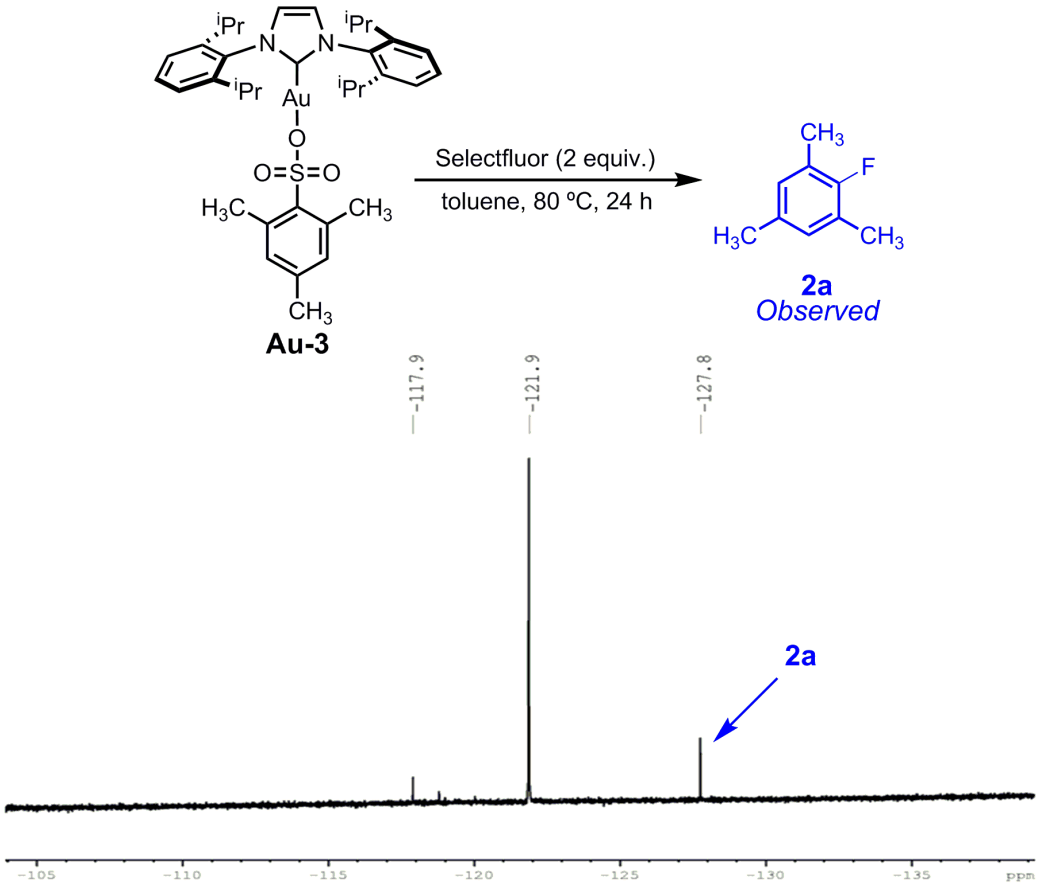


Scheme 2.14. Proposed *one-pot* oxidative cyclisation-fluorination of **1a** for the synthesis of fluorinated sultone **3a**.

Unfortunately, despite the good reproducibility of this reaction, further optimisation of the synthesis of **3a** has yet to be achieved (for the complete experimental data on the optimisation of this reaction, the Reader is referred to the Supporting Data CD, Experimental Annex - Chapter 2, Table S3). The study of this reaction is currently in progress within our research group.

Our synthetic efforts were again concentrated on the optimisation of a methodology to selectively prepare **2a**. Keeping a base-free system, the effect of other parameters, such as solvent, temperature, reaction time or equivalents of Selectfluor, was assessed; however, no improvement of the reactivity towards **2a** could be observed in any case, with no clear reactivity trends for appropriate discussion (for the complete experimental data, the Reader is referred to the Supporting Data CD, Experimental Annex - Chapter 2, Tables S1 and S4). This highlights the fact that, despite the catalyst-free electrophilic fluorination of arylsulfonic acids being feasible, it cannot provide full conversion and selectivity towards the desired compound.

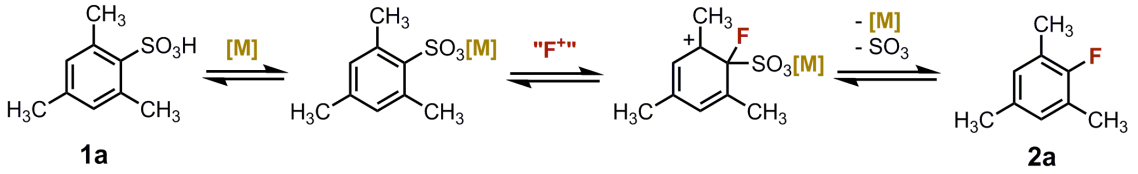
However, an interesting observation encouraged the re-evaluation of metal catalysis in this reaction, despite its failure during the desulfonation/fluorination studies. While it has already been reported that stirring the Au(I) sulfonato species **Au-3** in toluene at 110 ºC for 24 h does not afford any desulfonation product (Table 2.3, Entry 1), when two equivalents of Selectfluor were added to this reaction system, low quantities of **2a** were detected by ^{19}F NMR (8%; Scheme 2.15).



Scheme 2.15. Evidence for the release of **2a** *via* the reaction of **Au-3** with Selectfluor.

This reaction could not be further optimised to increase the NMR yield of **2a**, and the secondary fluorinated product could also not be isolated using standard workup techniques, leading to extensive decomposition into multiple fluorinated species. Despite these inconveniences, this observation showcases a formal elimination of SO_3 together with the fluorination of the aryl fragment in **Au-3**, which was unexpected considering the failure in the desulfonation of **Au-3**. As a result, a different reaction mechanism, aided by the presence of Selectfluor, must be proposed. Different alternatives can be presented along these lines:

1) Similarly to the mechanistic pathway presented by Ritter for the fluorination of aryl trifluoroborates,[9] an *ipso* fluorination of **1a**, followed by elimination of sulfur trioxide, can be proposed (Scheme 2.16).

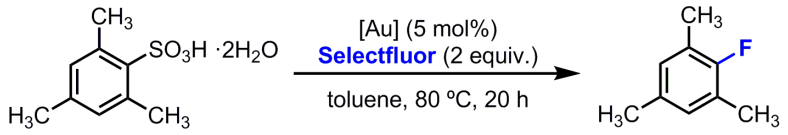


Scheme 2.16. Proposed fluorination/desulfonation mechanism for the conversion of **1a** into **2a.**

This mechanism is in agreement with the conversion of **1a** into **2a** using Selectfluor as the sole reagent. The incomplete conversion in this case is most probably due to insufficient activation of the *ipso*-carbon, and thus the use of metal catalysts to modify this property through complexation of the sulfonic acid group could be a suitable way to overcome this drawback.

For that purpose, a variety of transition metal species were tested as catalysts for this reaction. First, Au(I)-NHC species were considered (Table 2.5). Since Au(I) sulfonato species afforded some conversion towards **2a** in stoichiometric tests, evaluating their performance in catalytic conditions was a straightforward consideration. The use of [Au(OH)(IPr)] (Table 2.5, Entry 1) was compared with our reported sulfonato species (Table 2.5, Entries 2-6), with **Au-1** and **Au-4** behaving similarly to the hydroxide species, and slightly better than in the metal-free system (28%, see Table 2.4, Entry 1). The use of the more defficient IPr^{Cl} as ligand (**Au-5**) led to lower NMR yield of **2a** (Table 2.5, Entry 6). Other active gold complexes were next tested to establish more complete trends. While [Au(OTf)(IPr)] (Table 2.5, Entry 7) afforded similar NMR yields to that obtained by **Au-5**, the chloride species raised the observed yield to 38% (Table 2.5, Entry 8). This certainly demonstrates that a completely different mechanism to that based on SO_3 extrusion from sulfonato intermediates, is involved in our system. The NEt_3-based bifluoride based on IPr was also tested, showing no reactivity amplification (Table 2.5, Entry 9).

Table 2.5. Optimisation of Au(I)-NHC catalyst.[a]



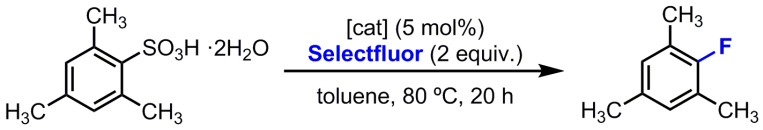
1a **2a**

Entry	[Au] (mol%)	NMR yield (%)[b]
1	[Au(OH)(IPr)]	32
2	Au-1	34
3	Au-2	22
4	Au-3	23
5	Au-4	33
6	Au-5	13
7	[Au(OTf)(IPr)]	19
8	[Au(Cl)(IPr)]	38
9	[Au(IPr)(NEt_3)][HF_2]	33

[a] Reaction conditions: **1a** (0.1 mmol), [Au] (5 mol%), Selectfluor (0.2 mmol), toluene (0.3 mL), 80 ºC, 20 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent), using 1-bromo-3-fluorobenzene as internal standard.

At this stage, other transition metal species were tested to further investigate the activity of metal species in the conversion towards **2a** (Table 2.6). Surprisingly, the use of Au is genuinely necessary to maintain the fluorination capacity of the system, with all tested metals displaying a much lower conversion. The studied species ranged from simple Cu(I)/Cu(II) salts (Table 2.6, Entries 1-2) and [Cu(OH)(IPr)] (Table 2.6, Entry 3), to Ag(I) (Table 2.6, Entry 4), Pd(II) (Table 2.6, Entry 5) and Ni(II) (Table 2.6, Entry 6), among many others (for further details about the tested transition metal species and their performance, the Reader is referred to Chapter 7, Table 7.1), obtaining not only lower conversions but also lower selectivities or complete inactivation of fluorination in all tested cases.

Table 2.6. Use of other transition metal-based species.[a]



1a **2a**

Entry	[Au] (mol%)	NMR yield (%)[b]
1	[Au(Cl)(IPr)]	38
2	CuCl	11
3	$CuCl_2 \cdot 2H_2O$	4
4	[Cu(OH)(IPr)]	< 1
5	AgCl	15
6	[Pd(η^3-cinnamyl)(Cl)(IPr)]	0
7	$[Ni(acac)_2]$	0
8	[Ni(Cl)(Cp)(SIPr)]	0

[a] Reaction conditions: **1a** (0.1 mmol), [Au] (5 mol%), Selectfluor (0.2 mmol), toluene (0.3 mL), 80 ºC, 20 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent), using 1-bromo-3-fluorobenzene as internal standard.

The use of Au in this reaction was clearly shown to be essential, although the reaction mechanism is certainly unclear at this point. Since the best NMR yield so far (38%) has been obtained for [Au(Cl)(IPr)], which is a species that theoretically does not present any complexation reactivity towards arylsulfonic acids, a reaction mechanism involving more than simple formation of a modified sulfonato species must be discussed.

Within this context, Au(III) chemistry is now a feasible approach. This proposal is inspired by the utility of Selectfluor not only as an electrophilic fluorine source, but also as an oxidant due to its high oxidation potential. Moreover, the access to reactive Au(III) species from Au(I) precursors in the presence of Selectfluor has been documented in the literature.[14] These considerations encouraged the proposal of Au(III) mediation in the desulfonative fluorination of arylsulfonic acids. A tentative catalytic cycle involving a Au(I)/Au(III) system would be initiated by the oxidation of a given Au(I)-NHC catalyst to its corresponding Au(III) fluoride species in the presence of Selectfluor; this species can promote fluorine transfer to an arylsulfonic acid *via*

desulfonation of the substrate, yielding the desired compound and regenerating the Au(I) species (Figure 2.4).

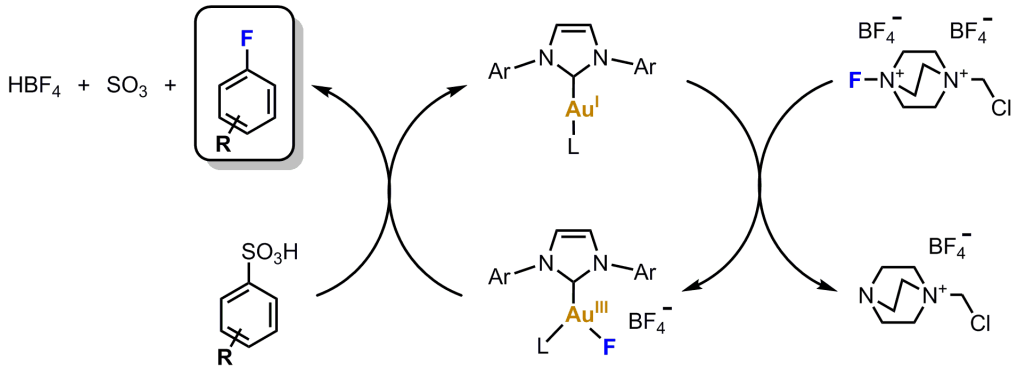
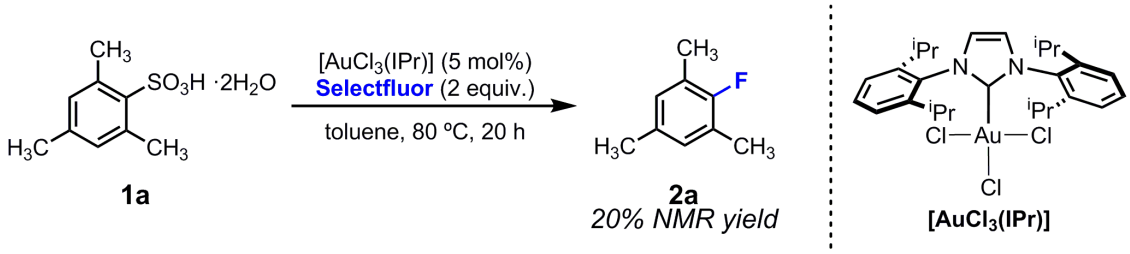


Figure 2.4. General scheme for the newly proposed Au-catalysed synthesis of aryl fluorides from arylsulfonic acids *via* Au(III) species.

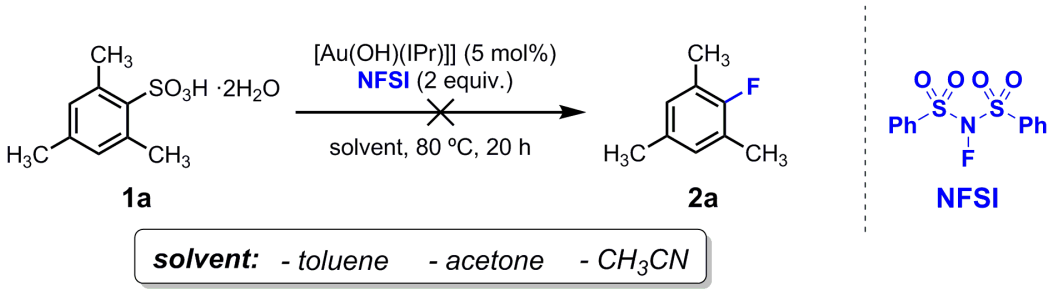
While no clear experimental evidences of this cycle have been yet obtained, the lack of fluorination selectivity observed in all catalytic tests and the impossibility to isolate or characterise most of these species, together with the known long-term instability of Au(III)-NHC species, strongly support such a fluorination pathway. An exhaustive investigation of Au(III) systems has been therefore started within our research group, to further unravel the reactive possibilities of these catalytic systems. Initially, the feasibility of the use of Au(III)-NHC complexes as catalysts was tested. The reaction of **1a** under our standard conditions (two equivalents of Selectfluor in toluene, 80 ºC for 20 h), using 5 mol% of [$AuCl_3$(IPr)] as catalyst, afforded 20% NMR yield of **2a** (Scheme 2.17). This shows that Au(I)/Au(III) oxidation is not a rate-limiting step, and that the use of Au(III) species still allows the formation of **2a**, although in lower NMR yields that the Au(I) homologue [Au(Cl)(IPr)].



Scheme 2.17. Fluorination/desulfonation of **1a** in the presence of a Au(III)-NHC catalyst.

Next, the use of a less oxidising fluorination source was tested. This approach was designed to assess the importance of Selectfluor for the reaction to proceed, which could, in the last instance, be directly related to its oxidising capacity. NFSI was used as

an alternative electrophilic fluorine source in this case, having a lower oxidation potential than that for Selectfluor, yet still being a powerful fluorination source.[17] Using standard test conditions in the absence or presence of 5 mol% of [Au(OH)(IPr)] as catalyst, and using two equivalents of NFSI, no traces of the desired compound **2a** were observed (Scheme 2.18). While a new single fluorinated species could be instead detected, with a peak at -91 ppm by ^{19}F NMR analysis in 81% NMR yield, extensive decomposition after standard extraction techniques in air or under inert atmosphere was obtained, precluding for any characterisation of the new species. The use of other solvents commonly used with NFSI, such as acetone or CH_3CN did not yield any of the expected product either.



Scheme 2.18. Unsuitability of NFSI for the synthesis of **2a.**

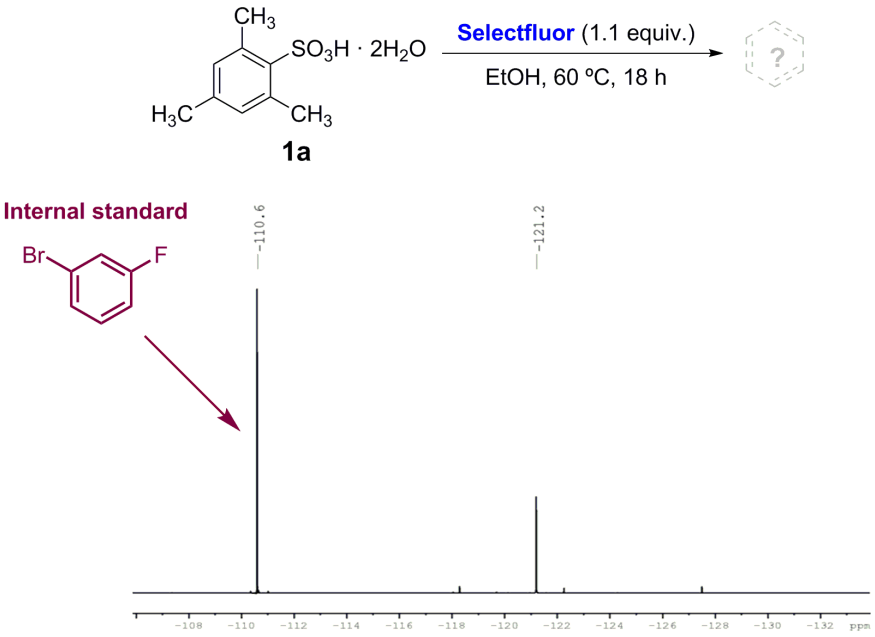
The studies of the Au(III)-catalysed fluorination of arylsulfonic acids are currently in progress, within the interest of our research group to uncover new evidence for the role of Au and Selectfluor in this chemical transformation.

2.2.4.4 Other reactions: C(sp^2)-H fluorination of arylsulfonic acids

During our optimisation studies, many side products were obtained, usually in low amounts and without any possible clean isolation. However, the use of reaction mixtures containing polar protic solvents displayed very good selectivity towards a single fluorinated species according to NMR studies, and therefore our attention was attracted towards the investigation of such reactivity.

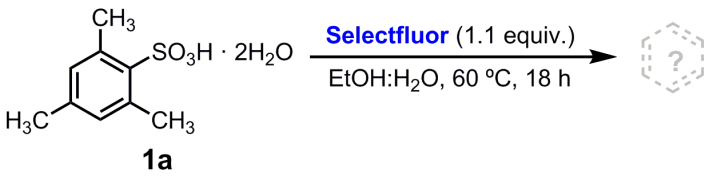
The synthesis of this species in a selective fashion was initially observed when Cu(I) species were being tested as catalysts. Reacting **1a** with 1.1 equivalents of Selectfluor in the presence of catalytic CuCl (5 mol%) and imidazole (10 mol%), afforded 28% NMR yield of a new species, with only trace amounts of other fluorinated side-products. The employed solvent was technical grade EtOH, and the reaction was performed at 60 ºC for 18 h. This strongly contrasted with the common lack of

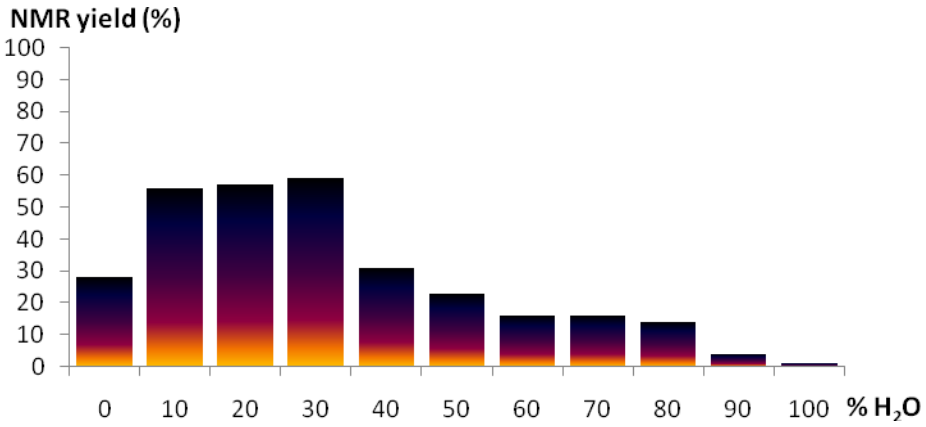
selectivity in our fluorination tests, thus attracting our synthetic efforts to the understanding of such a reaction. Further tests actually showed that the system could be simplified, with the presence of copper and base not being required for the preparation of this compound, which was obtained in 29% NMR yield using Selectfluor in EtOH at 60 ºC (Scheme 2.19).



Scheme 2.19. Preliminary tests for the selective synthesis of a new fluorinated species.

The optimisation of this reaction was next investigated. Aware of the solubility issues related to the use of Selectfluor in organic solvents, the addition of water to the reaction media could increase "F^+" availability in the reaction media. Indeed, EtOH:H_2O mixtures proved very efficient for building up better NMR yields of the new species without reducing or changing the selectivity of the process (Figure 2.5), with a 7:3 ratio of EtOH/H_2O displaying the highest NMR yield (59%).



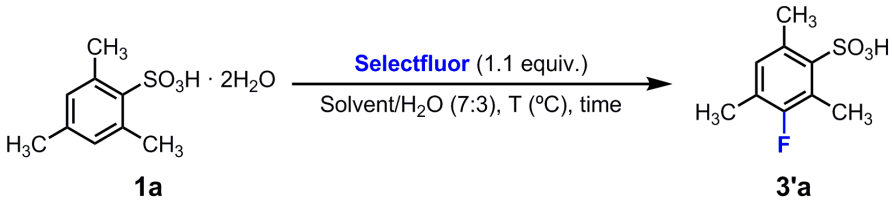


[a] Reaction conditions: **1a** (0.10 mmol), Selectfluor (0.11 mmol), EtOH:H_2O (0.5 mL), 60 ºC, 18 h.

Figure 2.5. Effect of water in the fluorination of **1a** in EtOH as solvent.

Using these conditions, the product could be isolated, although in an impure mixture, with all spectroscopic data matching the monofluorination product **3'a** (Table 2.7). Further optimisation proceeded using an EtOH/H_2O (7:3) solvent mixture. The reduction of the reaction temperature to 40 ºC afforded better NMR yields of the new species (63%) (Table 2.7, Entry 3). Under these conditions, other organic solvents were tested in combination with water. In general, polar protic solvents performed similarly to EtOH, promoting high degrees of selectivity for **3'a** (Table 2.7, Entries 5-11), with the exception of glycerol (most probably due to difficult homogenisation of the reaction mixture; Table 2.7, Entry 7). The use of polar aprotic (Table 2.7, Entries 12-15) or non-polar solvents (Table 2.7, Entries 16) led to very low fluorination of **1a**. Due to its good performance and interest in synthesis as a green solvent,[18] *n*-butanol (Table 2.7, Entry 9) was selected for further optimisation. Using these conditions, an increase in the reaction time to 48 h (Table 2.7, Entry 17) or a higher substrate concentration in the reaction media (Table 2.7, Entries 18) could still not provide quantitative conversion to **3'a**; however, the increase in the amount of Selectfluor (Table 2.7, Entries 19-21) displayed a consistent increase in the observed NMR yield, with two equivalents of Selectfluor being optimal (Table 2.7, Entry 20). Unfortunately, **3'a** could not be isolated in pure form, with minor amounts of impurities or solvent being present in all tests.

Table 2.7. Optimisation of the fluorination of **1a**.

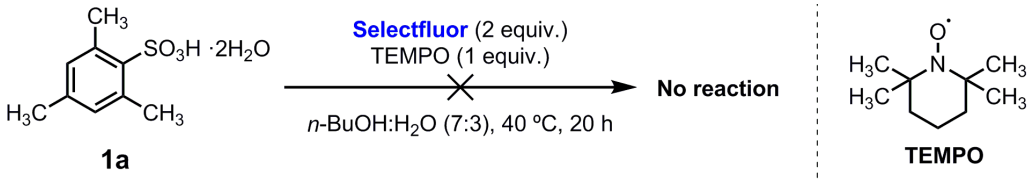


1a **3'a**

Entry	Selectfluor (equiv.)	Solvent	T (ºC)	t (h)	NMR yield (%)[b]
1	1.1	EtOH	60	20	59
2	1.1	EtOH	50	20	60
3	1.1	EtOH	40	20	63
4	1.1	EtOH	30	20	46
5	1.1	^{i}PrOH	40	20	70
6	1.1	2-methoxyethanol	40	20	42
7	1.1	glycerol	40	20	0
8	1.1	*t*-AmOH	40	20	60
9	1.1	*n*-BuOH	40	20	77
10	1.1	Ethanediol	40	20	58
11	1.1	*n*-hexanol	40	20	65
12	1.1	2-Me-THF	40	20	0
13	1.1	CPME	40	20	0
14	1.1	CH_3CN	40	20	3
15	1.1	acetone	40	20	5
16	1.1	toluene	40	20	4
17	1.1	*n*-BuOH	40	48	79
18[c]	1.1	*n*-BuOH	40	48	72
19	1.5	*n*-BuOH	40	20	81
20	2	*n*-BuOH	40	20	91 (90)
21	3	*n*-BuOH	40	20	92

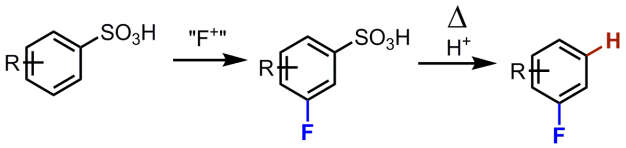
[a] Reaction conditions: **1a** (0.1 mmol), Selectfluor, solvent (0.5 mL). [b] Based on ^{19}F NMR analyses using 1-bromo-3-fluorobenzene as internal standard ($CDCl_3$ as solvent). [c] [**1a**] = 1 M.

Experimental tests in the presence of radical traps were used to define the nature of the fluorine transfer. When TEMPO was used as a radical scavenger under the optimised reaction conditions, no trace of any fluorinated product was observed, therefore suggesting that a more complex mechanism than simple electrophilic fluorination is actually taking place in this reaction (Scheme 2.20). This is not surprising, since ESI-MS studies of systems containing Selectfluor have proven the existence of reaction intermediates that can only be explained by means of single-electron transfer mechanisms.[19]



Scheme 2.20. Radical trapping test for the C(sp^2)-H fluorination using Selectfluor.

The utility of this type of fluorinated arylsulfonic acids was tested in preliminary applications for synthesis. One of the main discussed ideas was the use of these molecules as aryl fluoride surrogates for a fluorination/desulfonation mechanism. In essence, the sulfonic acid group could be used as a *meta* directing group, yielding the corresponding *m*-fluoroarylsulfonic acids which, upon treatment at high temperatures in the presence of catalytic acid, could undergo desulfonation, yielding the related aryl fluoride (Scheme 2.21).

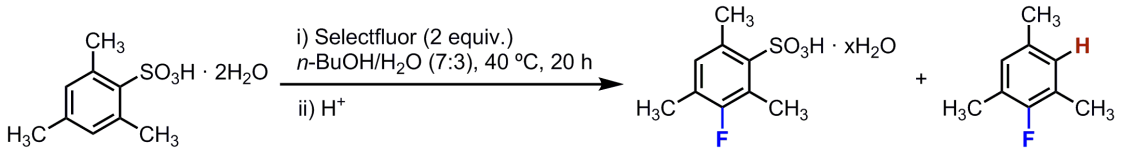


Scheme 2.21. Proposed fluorination-desulfonation sequence of arylsulfonic acids for the synthesis of fluoroarenes.

Different approaches were followed to investigate the accessibility to a one-pot fluorination-desulfonation procedure (Table 2.8). Initially, the use of the optimised conditions together with the addition of catalytic H_2SO_4 led to lower NMR yields for **3'a** while only traces of **2a** were present (Table 2.8, Entry 2), as expected from the known inefficiency of acid-catalysed desulfonation processes at moderate temperatures. To avoid any chemical interference, a sequential treatment of **1a** seemed to be necessary, and was therefore tested. After the use of our optimal conditions for maximum efficiency of the fluorination step, 10 mol% of H_2SO_4 was then added to the

stirred mixture and warmed up to 100 ºC for 5 h. While some consumption of **2'a** was observed, no proportional amount of **2a** was present (Table 2.8, Entry 3). To ascertain any possible reactivity towards our desired compound, forcing conditions were used. Using one equivalent of H_2SO_4 and 120 ºC in this step, full consumption of **3'a** was observed, although only 8% of **2a** was present in the reaction mixture (Table 2.8, Entry 4). Finally, the use of 2.5 equivalents of acid led to a similar consumption of **3'a**, but in this case a very broad signal around -128 ppm was present by ^{19}F NMR analysis, corresponding to the area of **2a**, and therefore suggesting a more extensive conversion towards this species (Table 2.8, Entry 5). This promising observation is currently being investigated by our research group.

Table 2.8. Preliminary studies on the fluorination-desulfonation of **1a.**



1a **3'a** **2a**

Entry	Additional reagents in step i)	Step ii)	NMR yield (%)[b]	
			3'a	2a
1	---	---	91	---
2	H_2SO_4 (10 mol%)	---	59	3
3	---	H_2SO_4 (10 mol%), *n*-BuOH/H_2O (7:3), 100 ºC, 5 h	72	4
4	---	H_2SO_4 (1 equiv.) *n*-BuOH/H_2O (7:3), 120 ºC, 5 h	0	8
5	---	H_2SO_4 (2.5 equiv.) *n*-BuOH/H_2O (7:3), 120 ºC, 5 h	traces	Broad peak

[a] Reaction conditions: i) **1a** (0.1 mmol), Selectfluor (0.2 mmol), solvent (0.5 mL), 40 ºC, 20 h; ii) See Table. [b] Based on ^{19}F NMR analyses using 1-bromo-3-fluorobenzene as internal standard ($CDCl_3$ as solvent).

2.3 Conclusions

In conclusion, the use of arylsulfonic acids as substrates for fluorination chemistry has been explored for the first time in the literature, having led to very

interesting results that will be of great importance for the future development of related synthetic methods.

First, the access to aryl fluorides from the corresponding arylsulfonic acids through a C-F formation/C-S cleavage sequence has been experimentally demonstrated. This approach will definitely provide an interesting alternative to the current fluorination methodologies once our on-going studies are completed. Feasible reaction mechanisms have been proposed and studied by establishing conceptually correct synthetic sequences (in the case of non-catalysed systems) and catalytic cycles (in the case of metal-catalysed systems), with special attention to the application of Au(I)-NHC complexes as catalysts. Sufficient experimental evidences have been gathered to discard a desulfonation/fluorination procedure for NHC-Au-sulfonato species. However, evidences of the important mediation of Selectfluor as an electrophilic fluorinating source and as an oxidant, together with the highly convenient use of Au-NHC catalysts, are now available and being exploited for the development of a fully optimised synthetic methodology. Only partial conversion towards the expected compound has been obtained to date, but the obtained results are encouraging and will soon provide efficient access to aryl fluorides.

Parallel to these studies, the metal-free monofluorination of C(sp^2)-H bonds in arylsulfonic acids for the synthesis of substituted fluoroarylsulfonic acids has been optimised and successfully applied to a highly substituted alkylbenzenesulfonic acid in excellent yield. Although mechanistically simple, this reaction is not available in the synthetic literature, and could represent an important step for the preparation of sulfonic acid derivatives. The applicability of this method is still being studied, in order to expand it to other substituted arylsulfonic acids and to employ these compounds for further synthesis. Preliminary tests have successfully shown the viability of a C-H fluorination/desulfonation sequence, for the synthesis of aryl fluorides through removable directing groups. Although no optimised conditions are yet available, the synthetic concept is very interesting and it is being further explored.

2.4 References

(1) The Reader is referred to the corresponding discussion about the historical inconveniences of fluorination reactions presented in Chapter 1.4.

(2) For other selected references, see: a) A. Koeberg-Telder, A. J. Prinsen and H.

Cerfontain, *J. Chem. Soc. B,* 1969, 1004; b) N. Pellegrini, D. Del Rio, B. Colombi, M. Bianchi and F. Brighenti, *J. Agric. Food Chem.* 2003, **51**, 260; c) B. Rác, M. Nagy, I. Pálinkó and A. Molnár, *Appl. Cat. A,* 2007, **316**, 152; d) A. S. Amarasekara and O. S. Owereh, *Catal. Commun.* 2010, **11**, 1072; e) Acton, W. A.; in: *Arylsulfonic acids - Advances in Research and application,* ScholarlyEditions, **2012;** f) Lindner, O.; Rodefeld, L.; in: *Ullmann's Encyclopedia of industrial chemistry,* Wiley-VCH Verlag GmbH&Co. KGaA, Weinheim, **2012**; g) I. U. Obi, *J. Agric. Biol. Chem.* 2014, 15.

(3) O. G. Lowe, *J. Org. Chem.* 1976, **41**, 2061.

(4) For some selected examples, see: a) F. P. Ballistreri, G. A. Tomaselli and R. M. Toscano, *Tetrahedron Lett.* 2008, **49**, 3291 ; b) L. A. H. van Bergen, G. Roos and F. De Proft, *J. Phys. Chem. A,* 2014, **118**, 6078; K. N. Parida, A. Chandra and J. N. Moorthy, *Chem. Select,* 2016, **1**, 490.

(5) Y. Suzuki, Y. Ishiwata, K. Moriyama and H. Togo, *Tetrahedron Lett.* 2010, **51**, 5950.

(6) For some selected examples, see: a) S. G. Modha, V. P. Mehta and E. V. Van der Eycken, *Chem. Soc. Rev.* 2013, **42**, 5042; b) G. Rajsekhar, C. P. Rao, P. K. Saarenketo, E. Kolehmainen and K. Rissanen, *Inorg. Chem. Commun.* 2002, **5**, 649; c) D. Borah, *Sep. Purif. Technol.* 2005, **43**, 215.

(7) A. A. N. Magro, G. R. Eastham and D. J. Cole-Hamilton, *Dalton Trans.* 2009, 4683.

(8) A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy and T. Ritter, *J. Am. Chem. Soc.* 2013, **135**, 14012.

(9) F. Yin, Z. Wang, Z. Li and C. Li, *J. Am. Chem. Soc.* 2012, **134**, 10401.

(10) N. R. Patel and R. A. Flowers II, *J. Org. Chem.* 2015, **80**, 5834.

(11) S. Dupuy, F. Lazreg, A. M. Z. Slawin, C. S. J. Cazin and S. P. Nolan, *Chem. Commun.* 2011, **47**, 5455.

(12) a) G. I. Borodkin, P. A. Zaikin and V. G. Shubin, *Tetrahedron Lett.* 2006, **47**, 2639; b) G. I. Borodkin, P. A. Zaikin, M. M. Shakirov and V. G. Shubin, *Russ. J. Org. Chem.* 2007, **43**, 1451.

(13) R. V. Andreev, G. I. Borodkin and V. G. Shubin, *Russ. J. Org. Chem.* 2009, **45**, 1483.

(14) For some selected examples, see: a) L. Cui, G. Zhang and L. Zhang, *Bioorg. Med.*

Chem. Lett. 2009, **19**, 3884; b) A. Simonneau, P. Gacia, J.-P. Goddard, V. Mouriès-Mansuy, M. Malacria and L. Fensterbank, *Beilstein J. Org. Chem.* 2011, **7**, 1379; c) A. Leyva-Pérez, A. Doménech-Carbó and A. Corma, *Nature Comm.* 2014, **6**.

(15) P. C. Hydes and H. Middleton, *Gold Bull.* 1979, **12**, 90.

(16) For some selected examples of catalytic cross-coupling reactions involving Au(III) complexes, see: a) M. N. Hopkinson, A. D. Gee and V. Gouverneur, *Chem. Eur. J.* 2011, **17**, 8248; b) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *Science*, 2012, **337**, 1644; c) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *J. Am. Chem. Soc.* 2014, **136**, 254; d) M. D. Levin and F. D. Toste, *Angew. Chem. Int. Ed.* 2014, **53**, 6211.

(17) For a better understanding of the oxidation potentials and other parameters involved in fluorination using N-F reagents see: X.-S. Xue, Y. Wang, M. Li and J.-P. Cheng, *J. Org. Chem.* 2016, **81**, 4280; and references therein.

(18) H. E. Eastman, C. Jamieson and A. J. B. Watson, *Aldrichimica Acta*, 2015, **48**, 51.

(19) X. Zhang, H. Wang and Y. Guo, *Rapid Commun. Mass Spectrom.* 2006, **20**, 1877.

CHAPTER 3

A New Au(I)-NHC Catalytic System for the Efficient Iodination of Terminal Alkynes

3.1 Introduction

The use of polyfunctionalised organic molecules gives synthetic chemists the opportunity to perform rapid and efficient structural diversification, which is of great interest to the synthetic community. Selecting, assembling and applying these structures represents an example of "smart" chemistry, raising the current frontiers of organic synthesis to new levels of chemical accessibility and efficiency, by rendering synthetic routes more practical and cost-efficient.

Among the wide variety of molecules tagged as "polyfunctionalised", 1-haloalkynes are a family of alkyne derivatives that have certainly attracted much attention in the last decade.[1] Due to their unique reactivity, these molecules are versatile building blocks for organic synthesis. Particular attention is to be paid to 1-iodoalkynes, whose mention in the literature is relatively scarce when compared to bromo- or chloroalkynes. The high reactivity of the C-I bond usually represents a "double-edged sword" in synthesis, with more careful handling and storage for organoiodine compounds being required. However, since 1-iodoalkynes are generally used as immediate reactive species, the real impact of this inconvenience is minimal, and we therefore consider that the utility of 1-iodoalkynes has been widely underestimated. Encouraged by the most recent advances in the preparation of these molecules, the present chapter will discuss the optimisation of a new Au(NHC)-based catalytic system for the preparation of 1-iodoalkynes from simple terminal alkynes and a convenient electrophilic iodination source (Figure 3.1).

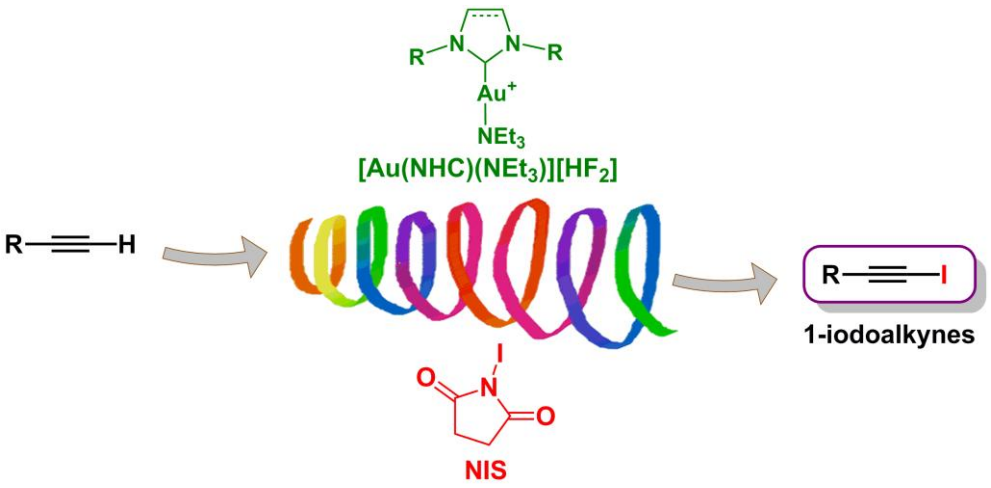


Figure 3.1. General scheme for Au(NHC)-catalysed iodination of terminal alkynes.

3.2 1-Iodoalkynes: state-of-the-art

1-Iodoalkynes constitute a family of terminal alkyne derivatives with an iodinated C-C triple bond, which provides interesting reactive opportunities. First, the well-known π-reactivity of alkynes towards electrophilic addition[2] provides access to functionalised iodoalkenes.[3] On the other hand, the presence of a reactive C-I bond, the common feature in organoiodine compounds,[4] allows metal-mediated cross-coupling chemistry to be accessible, resulting in a useful tool for the synthesis of internal alkynes or for the alkynylation of organic fragments.[5] Both reactive aspects have been exploited, making use of these compounds as versatile intermediates for the preparation of a plethora of organic molecules (Figure 3.2).[6] In addition, the 1-iodoalkyne moiety, in itself, is an important building block that can be found in fungicides[7] and antimicrobial reagents.[8]

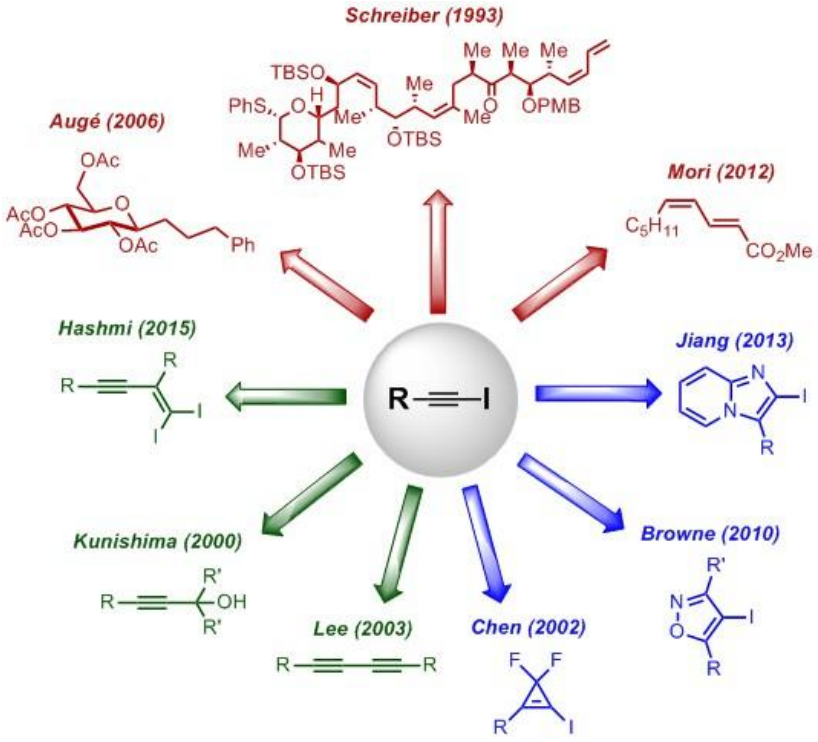
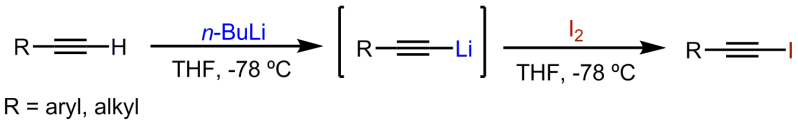


Figure 3.2. Selected uses of 1-iodoalkynes in coupling (**green**) or addition chemistry (**blue**), and iodoalkyne utility as reactive intermediates for the synthesis of complex molecules (**red**).

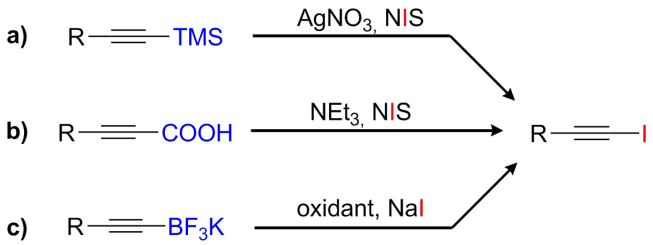
Despite the widespread use of the traditional reaction between a metal acetylide (commonly generated from a terminal alkyne and a strong organometallic base such as *n*-butyllithium)[9] and an electrophilic iodide source (with molecular iodine, I_2, being a widely used source of "I^+") for the iodination of terminal alkynes,[10] the need for stoichiometric amounts of base and the use of restrictive reactions conditions (*e.g.*, low

temperatures and moisture-free conditions) have evidenced a lack of efficiency for more complex systems (Scheme 3.1).



Scheme 3.1. Traditional strategy for the iodination of terminal alkynes.

In order to circumvent the aforementioned inconveniences, the use of end-capped alkyne derivatives as reactive equivalents of terminal alkynes represents a convenient approach. In 1994, Isobe and co-workers reported the use of trimethylsilylacetylenes as substrates for iodination (Scheme 3.2), obtaining moderate to excellent yields for some aliphatic compounds.[11] However, the use of organolithium[12] or organomagnesium intermediates[13] to prepare these molecules constitutes a major hurdle. Later on, the use of propiolic acids provided a very interesting alternative (Scheme 3.2).[14] The excellent isolated yields and the easy iodination procedure at room temperature using catalytic amounts of base in the presence of NIS as electrophilic iodine source was only eclipsed by the very limited scope of commercially available substrates. A base-free protocol with a higher substrate availability was further reported by Kabalka and co-workers in 2004, using alkynyltrifluoroborate substrates (Scheme 3.2).[15] These bench-stable compounds being easily accessed by reaction of the parent boronic acids with KHF_2, provided access to aromatic and aliphatic 1-iodoalkynes at room temperature with excellent performance; however, the use of a specific oxidising reagent (*N*-chloro tosylamide) and the limited scope of substrates have most probably precluded a wider applicability of this method.



Scheme 3.2. Common approaches to the synthesis of 1-iodoalkynes from various terminal alkyne derivatives.

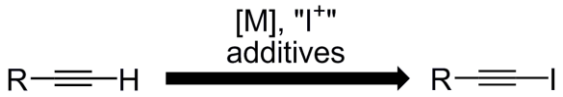
The limited library of commercially available substrates and the moderate atom economy of the protocols described above, as well as other procedures employing terminal alkyne derivatives[16] are of important concern. It is to be noticed that the use of

iodine (I_2) as an electrophilic iodination source has been slowly shifting to other reagents which present improved features for synthesis.[17] Nowadays, the structurally diverse reagents available, including iodide[18] and iodonium salts,[6n,19] iodinated ionic liquids,[20] iodoalkanes,[21] iodinated cyclic nitronates[22] or iodoamino derivatives such as *N*-iodomorpholine hydroiodide[6c,6i,6k,6r] or *N*-iodosuccinimide,[23] can cover a wide range of synthetic necessities. However, despite the great advances within this context, a generally applicable iodination method is still not available, which reaffirms the interest in seeking new alternatives.

The use of transition metals as catalysts for alkyne functionalisation has been extensively reviewed.[24] In that context, the *in situ* generation of metal acetylides under basic conditions has been exploited in-depth, and some examples of metal-catalysed electrophilic iodination of terminal alkynes are available in the literature (Table 3.1). The use of CuI[25] or $AgNO_3$[3f,3h,26] as catalysts has afforded the conversion of a range of alkynes into the corresponding 1-iodoalkynes with good results. Nevertheless, since an excess of base is required for the copper-based system, and due to the fairly high catalyst loading of $AgNO_3$ (10-20 mol%) and sensitivity of the latter catalyst, the search for a better catalytic system for alkyne iodination is still ongoing.

More recently, Sheppard and co-workers have shown the convenience of using Au complexes for this transformation. Inspired by the stoichiometric test from Hashmi and co-workers,[27] they reported the use of a cationic Au(I)-phosphine complex for the iodination of a fairly wide range of aromatic and aliphatic substrates.[28] This report is of great interest, since it removes the requirement for external base or other additives, as well as reducing the toxicity of the catalyst. Inspired by these reports (Table 3.1), the application of transition metal-NHC complexes was suggested as a suitable alternative to phosphine chemistry. Within our interest in the synthesis and catalytic applications of transition metal complexes bearing NHC ligands, we envisaged that the capability of such complexes to activate alkynes could also provide a new expedient access to 1-haloalkynes through electrophilic halogenation.

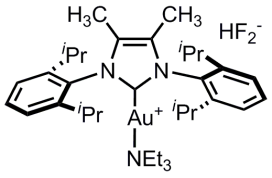
Table 3.1. State-of-the-art for the transition metal-catalysed iodination of terminal alkynes.



Metal	Author (year)	R	Catalyst	Iodination source	Examples and yields
Ag 	Hofmeister (1984)	Alkyl	$AgNO_3$ (10 mol%)	NIS (1.2 equiv.)	8 examples 65-86% yield
	Rowan (2011)	Aryl			2 examples 75-98% yield
	Jiang (2013)	Alkyl Aryl			2 examples No yields provided
	Dichtel (2015)	Aryl			8 examples 71-92% yield
Cu 	Jeffery (1988)	Alkyl Aryl	CuI (5-10 mol%)	I_2 (1 equiv.)	7 examples 77-98% yield
	Yan (2007)	Alkyl Aryl	CuI (5 mol%)	KI (2 equiv.)	10 examples 82-98% yield
	Tsai (2009)	Alkyl Aryl	CuI (1-2 mol%)	I_2 (2 equiv.)	10 examples 41-87% yield
Au 	Sheppard (2012)	Aryl	$[Au(NTf_2)(PPh_3)]$ (1 mol%)	NIS (1 equiv.)	13 examples 29-90% yield

In order to test our hypothesis, a suitable family of catalysts was selected. Au(I)-NHC bifluorides (described in Chapter 1)[29] perfectly match the needs for an active cationic Au(I) species capable of deprotonating a terminal alkyne and further react with electrophiles. Their high tolerance to air, moisture and light makes them suitable for fast and easy screening as catalysts. Increasing the applicability of these species in catalysis is also a very important factor that helped determining the suitability of the presented species for our studies.

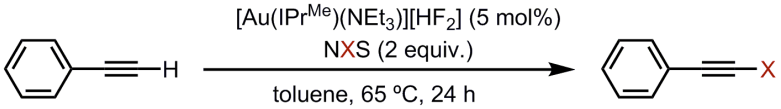
3.3 Results and discussion

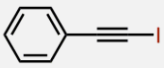
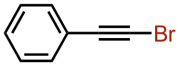
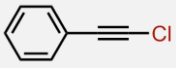


[Au(IPr^{Me})(NEt$_3$)][HF$_2$]

Phenylacetylene (**4a**) was selected as a readily available and simple model substrate for optimisation, while *N*-halosuccinimides (NXS) were chosen as convenient electrophilic halogen sources due to their commercial availability, ease of handling and good reactivity.[30] The first aim was to prove the catalytic activity of Au(I)-NHC bifluorides in the halogenation of terminal alkynes. Gratifyingly, our initial test reacting **4a** with two equivalents of NIS in toluene at 65 ºC for 24 h under nitrogen atmosphere displayed an encouraging 55% conversion towards (iodoethynyl)benzene (**5a**), when 5 mol% of the Au(I) bifluoride catalyst [Au(IPr^{Me})(NEt$_3$)][HF$_2$] was used (Table 3.2, Entry 1). As expected, the reactivity of *N*-bromosuccinimide (Table 3.2, Entry 2) and *N*-chlorosuccinimide (Table 3.2, Entry 3) for the synthesis of the corresponding bromo- and chloro-derivatives, though promising, was significantly lower. These results encouraged us to pursue further optimisation.

Table 3.2. Preliminary tests for the Au-catalysed halogenation of **1a**[a]



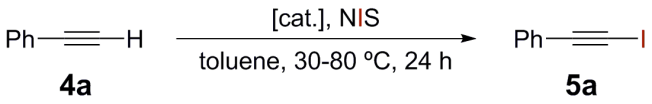
Entry	NXS	Product	Conversion (%)[b]
1	NIS		55
2	NBS		34
3	NCS		15

[a] Reaction conditions: **1a** (0.25 mmol), [Au] (5 mol%), NXS (0.50 mmol), toluene (0.5 mL), 65 ºC, 24 h. [b] Determined by ^{1}H NMR ($CDCl_3$ as solvent).

The importance of the catalyst was first evaluated. In the absence of the gold catalyst, only 6% conversion towards the expected product was observed (Table 3.3, Entry 1). The effect of the temperature was next examined. While the use of 80 ºC (Table 3.3, Entry 3) or 30 ºC (Table 3.3, Entry 5) afforded conversion values lower than 50%, an intermediate value of 50 ºC gave full conversion of the starting material in

favour of the desired species (Table 3.3, Entry 4). This influence is probably due to limited activation of the alkyne at lower temperatures and a higher decomposition rate of NIS at higher temperatures; thus, 50 ºC was selected as the optimal temperature. The stoichiometry of the "I^+" source was next investigated. A clear decrease in the conversion towards **5a** was observed when the number of equivalents was reduced from 2 to 1.5 (Table 3.3, Entry 6). Although the use of a non-polar organic solvent such as toluene presents clear advantages in terms of reactivity, further information about the use of other types of solvents was gathered. A lower performance was evidenced with the use of dichloromethane as a polar aprotic solvent (Table 3.3, Entry 7), with only 36% conversion towards **5a**. When dry EtOH was selected as a polar protic solvent, more complex reactivity was observed, with complete consumption of **4a** and no traces of the expected compound (Table 3.3, Entry 8).[31] It is to be noted that no further solvent testing was performed at this stage, since our studies of the reactivity of 1-iodoalkynes have shown that the use of these three solvents was certainly advantageous.[32] With this information in hand, further optimisation was considered using the experimental conditions detailed in Table 3.3, Entry 4. A decrease in Au loading to 3 mol% was not possible without eroding the reaction conversion (Table 3.3, Entry 9). Refinement of the employed catalyst was explored at this stage. By testing other available Au(I)-NHC bifluorides (Table 3.3, Entries 10-11), a significant improvement could be observed when [Au(SIPr)(NEt_3)][HF_2] was employed; the catalyst loading could now be reduced to 3 mol% without diminishing the iodination reaction performance (Table 3.3, Entry 11). This catalyst also afforded the reduction of the reaction time to 15 h, maintaining full conversion towards **5a** (Table 3.3, Entry 12), and allowing the isolation of the iodinated alkyne in 89% isolated yield.

Table 3.3. Optimisation of the Au(I)-catalysed iodination of **1a**[a]



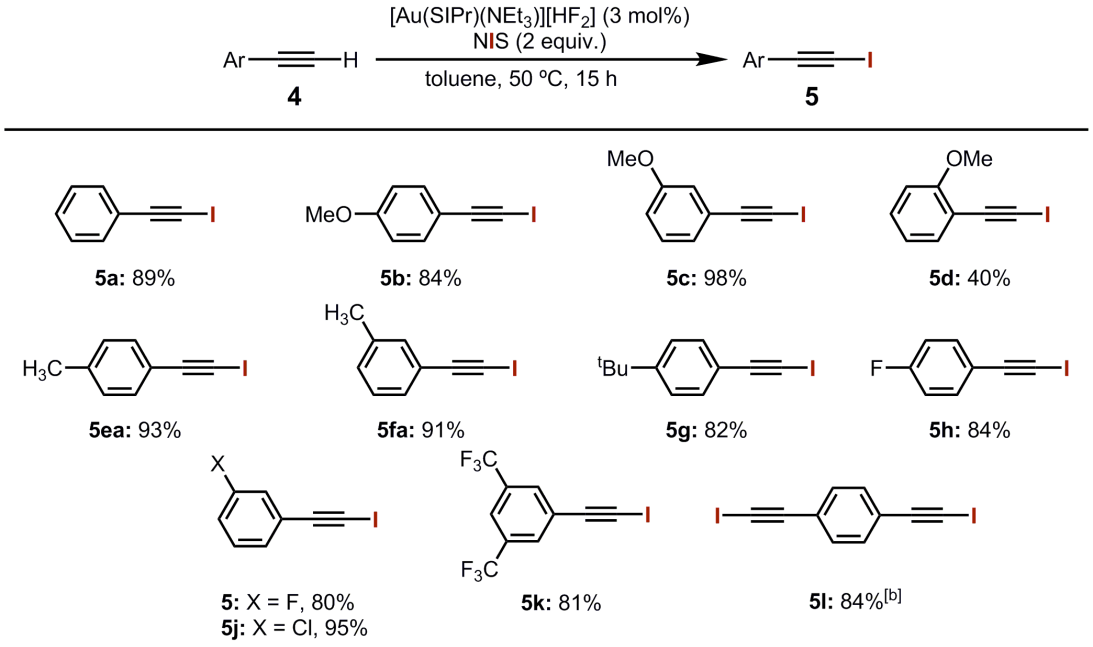
4a **5a**

Entry	[Cat.] (mol%)	T (ºC)	Conversion (%)[b]
1	---	65	6
2	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	65	55
3	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	80	37
4	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	>99
5	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	30	38
6[c]	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	35
7[d]	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	36
8[e]	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	0
9	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (3)	50	43
10	[Au(IPr*)(NEt$_3$)][HF$_2$] (3)	50	76
11	[Au(SIPr)(NEt$_3$)][HF$_2$] (3)	50	>99
12[f]	[Au(SIPr)(NEt$_3$)][HF$_2$] (3)	50	>99 (89)[g]

[a] Reaction conditions: alkyne (0.25 mmol), [Au], NIS (2 equiv.), toluene (0.5 mL), 24 h. [b] Determined by ^{1}H NMR. [c] NIS (1.5 equiv.). [d] CH_2Cl_2 as solvent. [e] Dry EtOH as solvent. [f] 15 h. [g] Isolated yield.

With the optimal conditions in hand, the reactivity of other aromatic terminal alkynes was explored, in order to establish the generality of this iodination procedure. The experimental results are summarised in Scheme 3.3. No significant difference in the reactivity of aromatic alkynes bearing EDG or EWG in the *meta*- or *para* positions was observed. In all cases the corresponding 1-iodoalkynes **5a-5k** were obtained in good to excellent yields. On the other hand, *ortho*-substituted substrates proved to be less compatible, as displayed by the low isolated yield (40%) of the iodinated alkyne **5d**; this is presumably due to the increased steric hindrance in the vicinity of the alkyne, which in turn hampers the coordination of Au to the alkyne moiety. This inconvenience could not be overcome by using a higher catalyst loading or longer reaction times. This limitation is not a new phenomenon in Au-catalysed addition chemistry to alkynes, as it

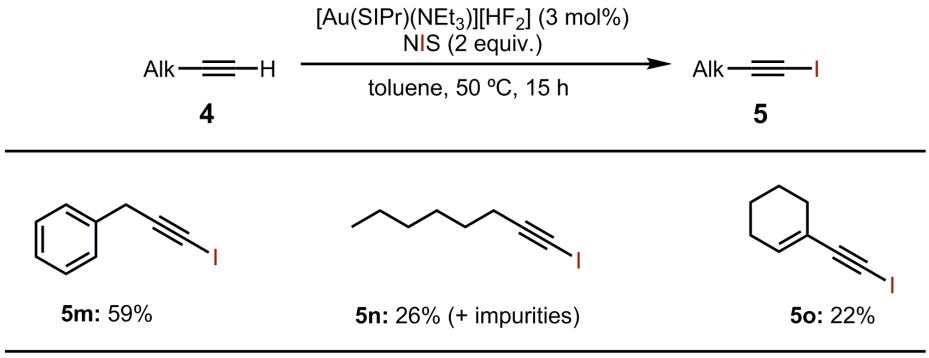
has been observed in other Au-based systems.[33] The general procedure could also be applied to aromatic dialkynes by simply increasing the amount of Au to 6 mol%, with the corresponding double iodination product **5l** being successfully isolated in 84% yield.



[a] Reaction conditions: alkyne (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NIS (1.0 mmol, 2 equiv.), toluene (1 mL), 50 ºC, 15 h. Isolated yields. [b] [Au] 6 mol%.

Scheme 3.3. Scope of the Au(I)-catalysed halogenation of aromatic terminal alkynes[a]

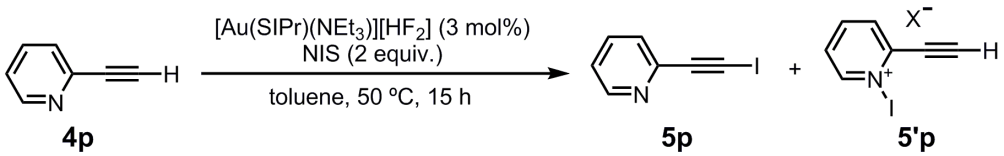
The suitability of aliphatic terminal alkynes was next examined. The benzylic alkyne **1m** could be successfully converted into its related iodoalkyne **5m** in 59% isolated yield (Scheme 3.4). A much more challenging approach was found when reacting 1-octyne or 1-ethynylcyclohexene, for which low conversions (<30%) of the starting material was observed, albeit the products could be isolated and identified in 26% and 22% isolated yields for **5n** and **5o**, respectively (Scheme 3.3). An explanation for this lack of reactivity can be proposed by means of the lower acidity of aliphatic alkynes when compared to the aromatic congeners.



[a]Reaction conditions: alkyne (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NIS (1.0 mmol, 2 equiv.), toluene (1 mL), 50 ºC, 15 h. Isolated yields

Scheme 3.4. Iodination of aliphatic terminal alkynes under the optimised reaction conditions

Heterocyclic substrates were also tested under our optimal conditions, with 2-ethynylpyridine (**4p**) being selected as model substrate. Full consumption of **4p** was observed by ^{1}H NMR, concomitantly with the appearance of two new pyridine-based species, including the expected iodinated alkyne (**5p**) being present as the major species (Scheme 3.5). However, the purification of **5p** proved impossible, due to strong cationic Au-pyridine interactions.[34] In a similar fashion, difficulties associated with the purification of the secondary product hampered the full characterisation of this species. With mass analysis proving the incorporation of iodine in the substrate, the formation of a *N*-iodopyridinium salt (**5'p**) was proposed as a side reaction.

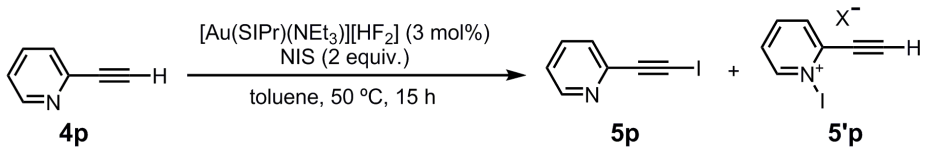


Scheme 3.5. Iodination of 2-ethynylpyridine using optimised conditions.

Further optimisation of the reaction was attempted, and some relevant results are presented in Table 3.4. Increasing or decreasing the catalyst loading diminished the selectivity towards **5p** (Table 3.4, Entries 2-3). The effect of the amount of NIS was also examined. Reducing the amount of NIS from 2 to 1.3 equivalents led to incomplete conversion of the starting material, with a consistent preference for the terminal iodination product (Table 3.4, Entry 4). Further increase to 1.6 equivalents did not follow a trend towards increased selectivity for **5p**, as it could be expected when comparing the results in entries 1 and 4 (Table 3.4). The increase of the reaction time to

24 h was also not effective, with minimum variation in the selectivity being observed (Table 3.4, Entry 6).

Table 3.4. Selectivity optimisation tests for the synthesis of **5p**[a]



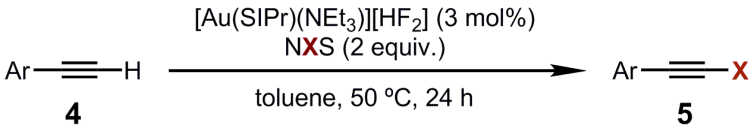
Entry	Experimental conditions	Starting material (%)[b]	Product ratio[b]	
			5p	5'p
1	Optimised conditions	0	85	15
2	5 mol% of [Au]	0	66	34
3	1 mol% of [Au]	0	73	27
4	1.3 equiv. NIS	8	82	18
5	1.6 equiv. NIS	0	56	44
6	24 h of reaction time	0	86	14

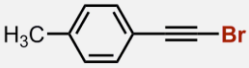
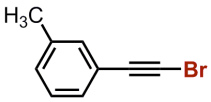
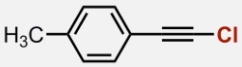
[a] Reaction conditions: **4p** (0.20 mmol), [Au], NIS, toluene (0.4 mL), 50 ºC, 15 h. [b] Based on aromatic signal ratio in ^{1}H NMR ($CDCl_3$).

In view of the difficulties to optimise this catalytic system, the unsuitability of *N*-based heterocycles as substrates for efficient iodination using our optimised procedure was deduced, and the experimental pathway was discarded until further experimental analyses can be performed.

Finally, the versatility of the presented catalytic halogenation procedure was demonstrated by re-testing *N*-halosuccinimides under the optimised conditions, in an attempt to access higher yields of the corresponding 1-bromo- and 1-chloroalkynes. To our delight, total consumption of the starting material was observed by TLC after 24 h when NBS was tested, obtaining the corresponding 1-bromoalkyne for substrates **4e** and **4f** in excellent yields (Table 3.5, Entries 1-2). Unfortunately, the chlorination of **4e** under similar conditions only provided 33% isolated yield of the related chloroalkyne **5ec** (Table 3.5, Entry 3), due to the marked decrease in reactivity of the employed succinimide for electrophilic halogenation, as opposed to the more reactive bromo- and iodo counterparts.

Table 3.5. Bromination and chlorination of aromatic terminal alkynes using the optimised Au-catalysed system.



Entry	Substrate	Product	Yield (%)[b]
1	**4ea**	 **5eb**	91
2	**4fa**	 **5fb**	90
3	**4ea**	 **5ec**	33

[a] Reaction conditions: alkyne (0.50 mmol), [Au] (3 mol%), NXS (1.0 mmol), toluene (1 mL), 50 °C, 24 h. [b] Isolated yields.

3.4 The catalytic system

3.4.1 Reactivity profiling: iodination of 4a

In order to gain further understanding of efficiency of our catalyst for iodination, some reactivity profiles were performed and discussed. First, a more detailed study of the rate of iodination of **4a** *vs* time was carried out**,** as shown in Figure 3.3. The iodination procedure under the optimised conditions (Figure 3.3, **blue**) reached 60% conversion after 5 h, and full conversion could only be obtained after 15 h of reaction time, as previously mentioned in our optimisation discussion. During our experimental work with these profiles, a noticeable acceleration of the conversion could be noticed when the reaction was performed in air instead of under N_2, which was quite surprising and intriguing. Indeed, when a similar conversion profile was run in air for the iodination of **4a** using the optimal conditions (Figure 3.3, **red**), full conversion towards **5a** was observed after only 5 h.

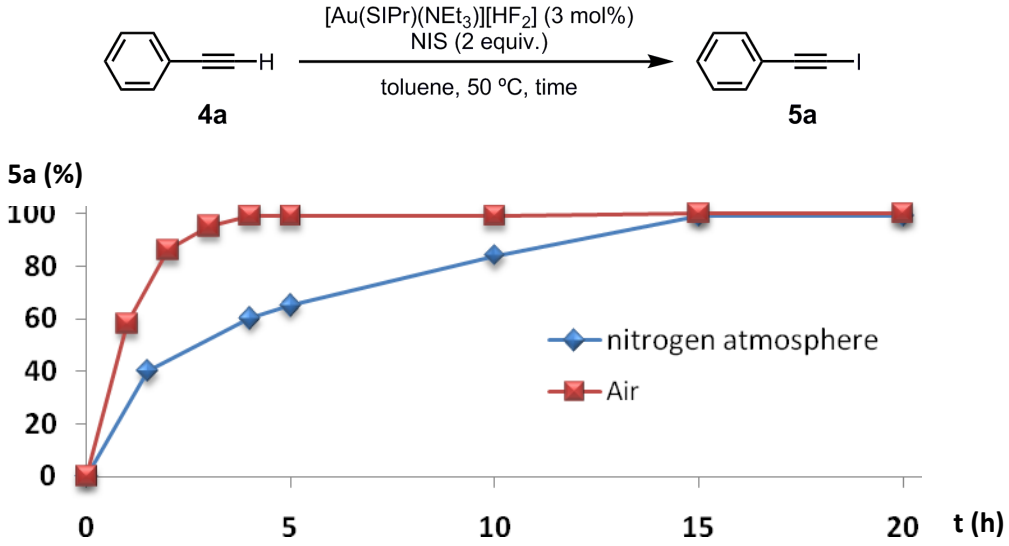


Figure 3.3. Effect of air and N_2 on the conversion of **4a** into **5a.**

In light of these observations, several parameters for this reaction were reassessed, with the amount of NIS being first tested. The use of 1.3 equivalents (Figure 3.4, **red**) displayed a very similar reactivity profile to the use of 2 equivalents (Figure 3.4, **blue**), with full conversion towards **5a** observed after 5 h. Further reduction in the number of equivalents of this reagent led to incomplete consumption of **4a** (Figure 3.4, **green**), and was therefore discarded.

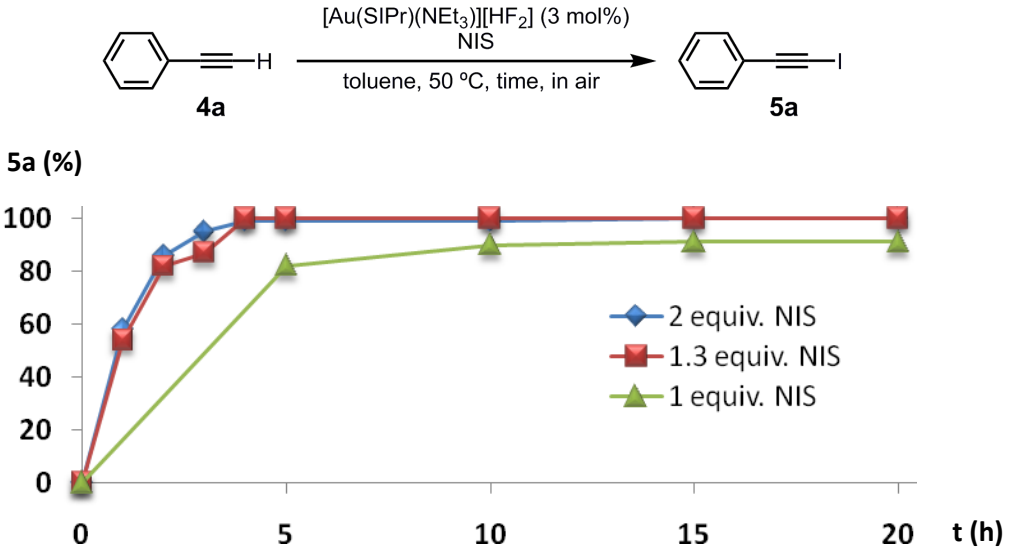
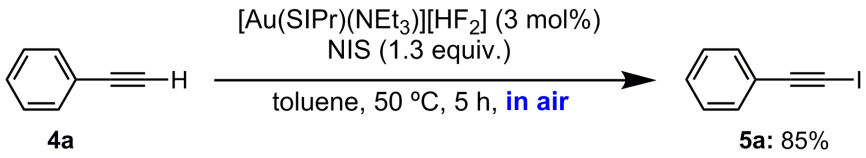


Figure 3.4. Influence of the amount of NIS on the conversion of **4a** into **5a** in air.

In light of this new information, the reaction of **4a** with 1.3 equivalents of NIS using 3 mol% of [Au] in toluene at 50 ºC for 5 h afforded 85% isolated yield of **5a** (Scheme 3.6). This iodination performance is comparable to that presented by our

previous optimised system (89%, see Scheme 3.3), employing a lower loading of NIS and a shorter reaction time. This clearly highlights the great utility of this system for the iodination of alkynes. A very important feature of this final methodology is the need for reaction times comparable to those required for the known Ag-based iodination procedure,[3f,3h,26] rendering the use of Au even more competitive in this area of study.

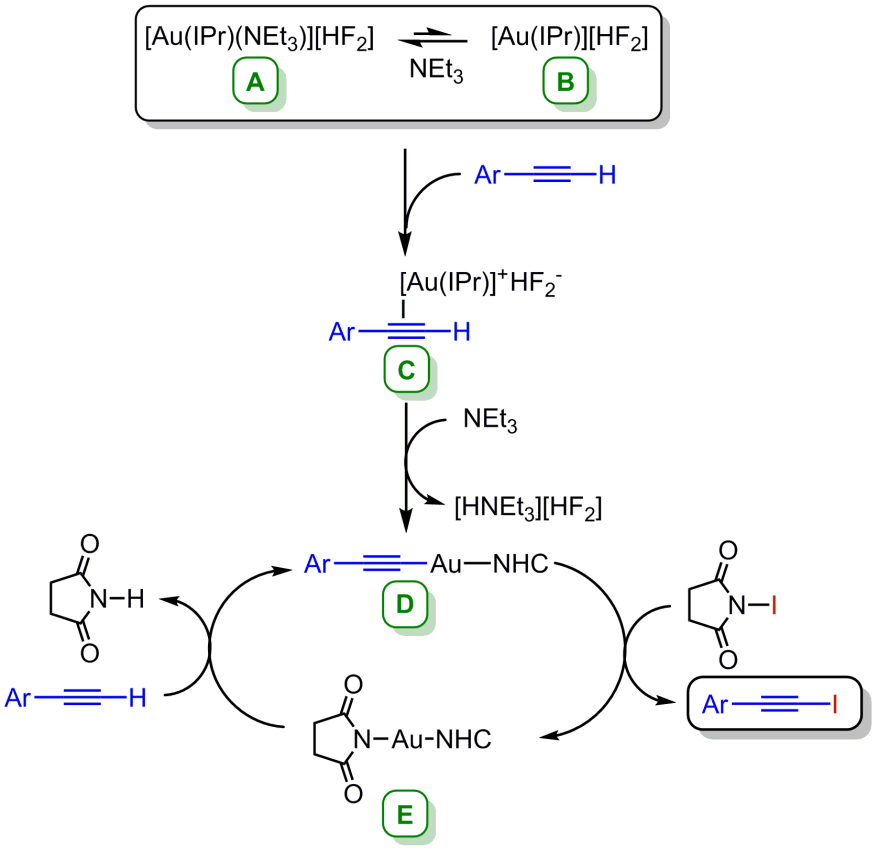


Scheme 3.6. Isolated yield of **5a** using *in-air* optimised iodination conditions.

3.4.2 Mechanistic studies

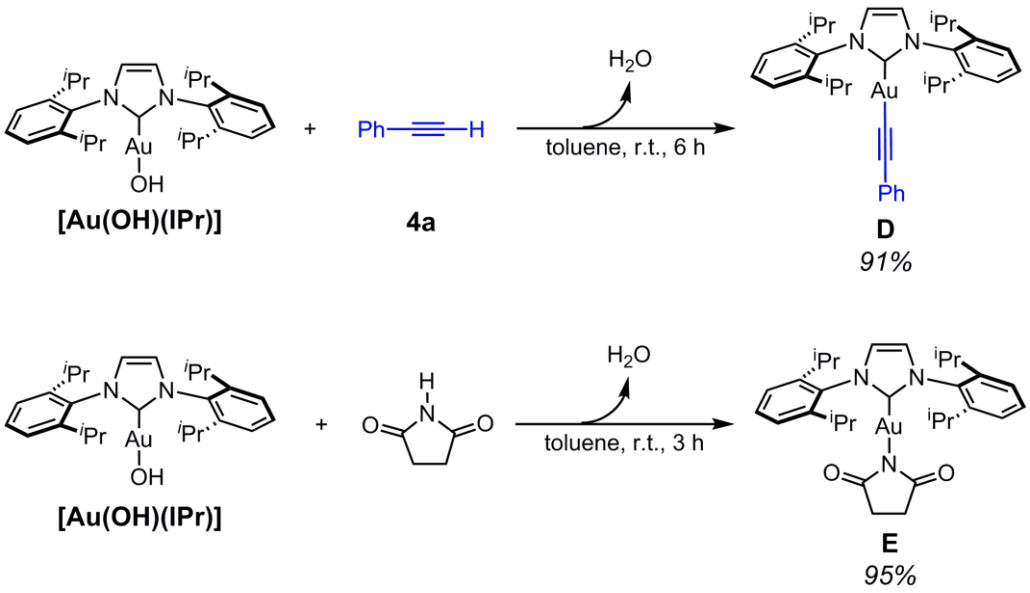
A qualitative mechanistic study of the catalytic iodination of terminal alkynes using Au-NHC bifluorides was conducted, in an attempt to unravel the reaction pathways involved and to support our mechanistic assumptions for this reaction.

A mechanistic proposal can be made (depicted in Scheme 3.7), mainly based on the known reactivity of Au-NHC species and alkynes. Initially, the cationic bifluoride precursor (**A**) is suspected to decoordinate the L-type ligand, generating the cationic $[Au(NHC)]^+$ species (**B**), whose high reactivity displaces the equilibrium back to the amine-ligated form **A** unless a suitable alkyne substrate is present in the reaction mixture to generate the Au-alkyne π complex (**C**). The presence of basic moieties, such as NEt_3, could promote alkyne deprotonation and subsequent π to σ-shift of the gold centre, generating the Au(I) species, Au-acetylide **D**. This species contains an alkyne fragment which can react with electrophiles, such as NIS, leading to a bond metathesis and releasing the expected iodoalkyne **5a,** concomitantly with a Au(I)-succinimide intermediate (**E**). The basic character of the imido fragment could further promote bond metathesis between **E** and another molecule of alkyne to liberate succinimide and to recover the active acetylide **D** in order to close the catalytic cycle.



Scheme 3.7. Proposed catalytic cycle for the Au(I)-catalysed iodination of terminal alkynes.

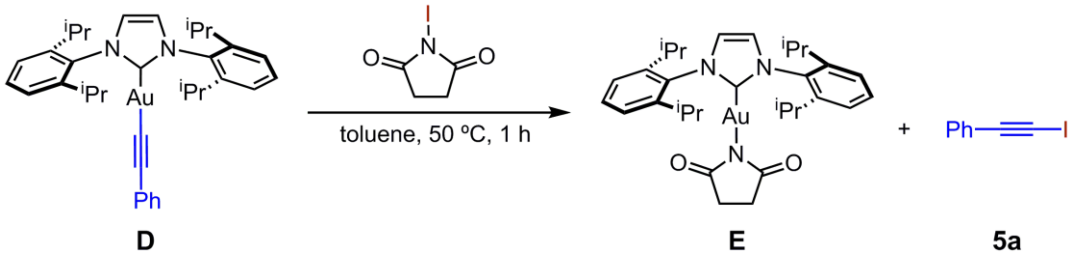
The study of these individual reactive steps was then performed. First, experimental evidence of the mediation of species **D** in the iodination reaction and regeneration of the Au catalyst into the cycle were explored. For such purpose, the advantageous reactivity of the Au complexes with the formula [Au(OH)(NHC)] for the activation of acidic X-H bonds (X = C, O, N) was exploited. Species **D** was easily prepared by following a procedure reported by Nolan and co-workers in 2010, based on mixing equimolar amounts of [Au(OH)(IPr)] and **4a** in toluene for 6 h at room temperature.[35] The expected acetylide complex **D** was isolated in 90% yield as a white solid (Scheme 3.8, top). Substituting **4a** with succinimide and following the same experimental procedure, a white solid, identified as complex **E**, was cleanly isolated in 95% yield after 3 h (Scheme 3.8, bottom).



Scheme 3.8. Synthesis of gold intermediates **D** and **E.**

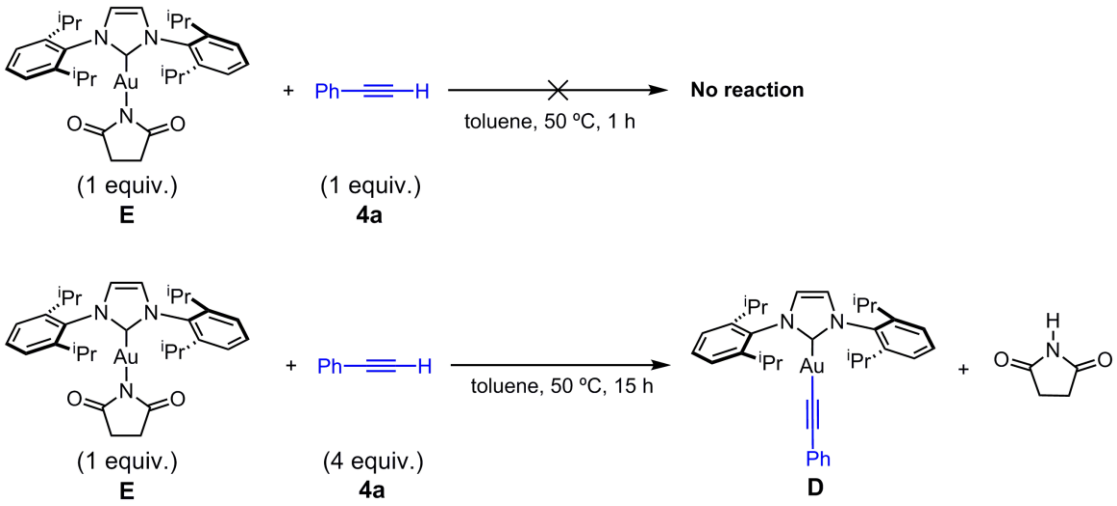
Further stoichiometric reactions were performed with these complexes:

1) When complex **D** was reacted with 1.3 equivalents of *N*-iodosuccinimide in toluene at 50 ºC, clear conversion towards the iodinated alkyne **5a** was detected (Scheme 3.9). ^{1}H NMR analysis clearly showed complete consumption of complex **D** after 1 h of reaction. This supports the feasible role of **D** as the active gold-alkyne species for the electrophilic iodination step, as proposed in the previous catalytic cycle.



Scheme 3.9. Stoichiometric synthesis of **5a** through direct iodination of NHC-Au-acetylide complex **D.**

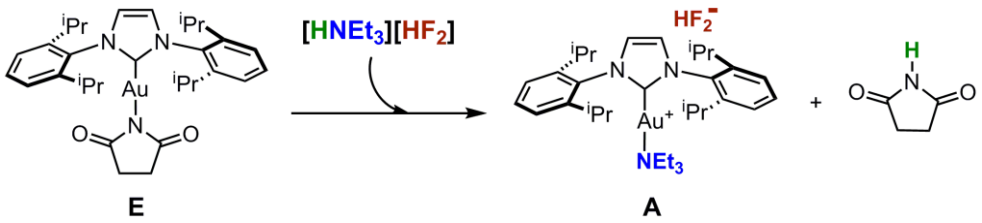
2) In an attempt to test the recyclability of intermediate **E**, this complex was reacted with **4a** in stoichiometric amounts, in toluene at 50 ºC. However, the formation of the acetylide species **D** was not observed after 1 h. Complex **D** could only be detected by NMR analyses when an excess of alkyne was used (four equivalents) and the reaction time was extended to 15 h (Scheme 3.10).



Scheme 3.10. Recyclability test of the Au-succinimide species **C** in the presence of **4a**.

These results clearly evidence the rate-limiting character of the conversion of species **E** into species **D**. This can be explained by the lower availability of "free" base to deprotonate **4a** after complete consumption of triethylamine. The use of an excess of **4a** can push the reaction towards full conversion, based on LeChâtelier's principle, together with longer reaction times.

Another explanation can be given to understand this slow step. The presence of $[HNEt_3][HF_2]$ (generated after the deprotonation of **4a**) could be non-innocent after species **E** is available in the reaction medium, regenerating the highly active bifluoride catalyst **A** (Scheme 3.11), which can indeed react with **4a** at a much faster rate than species **E** following the proposed mechanism in Scheme 3.7. This intermediate step could explain the difficulties for species **E** to be transformed into **D** in the absence of NEt_3 or $[HNEt_3][HF_2]$. However, no further investigation of this pathway was performed.



Scheme 3.11. Proposed regeneration of bifluoride species **A** from species **E** in the presence of $[HNEt_3][HF_2]$.

3.5 Conclusions

In conclusion, a new synthetic approach to 1-iodoalkynes has been designed, providing an alternative to traditional iodination methodologies using strong bases, complex terminal alkyne derivatives or iodination reagents, as well as harsh reaction conditions. This mild methodology has allowed the preparation of aromatic 1-iodoalkynes by using a low catalyst loading of a Au(I) species together with the use of *N*-iodosuccinimide (a commercially available iodination reagent with low toxicity and good reactivity) as electrophilic iodine source. The methodology can be performed either in air or under an inert atmosphere, with minimal modifications required for each approach; in both cases, the methods provide good to excellent yields of aromatic iodoalkynes under mild and practical conditions. While the applicability to aliphatic and heteroaromatic terminal alkynes is restricted, it is firmly believed that future optimisation studies will provide more robust approaches to overcome these inconveniences and adapt the catalytic system to a broader range of substrates.

3.6 References

(1) 1. W. Wu and H. Jiang, *Acc. Chem. Res.* 2014, **47**, 2483.

(2) For some selected information concerning general additions to alkynes, see: a) *Comprehensive Organic Synthesis Vol.4: Additions to and Substitutions at C-C π Bonds,* B. M. Trost, I. Fleming, M. F. Semmelhack, Eds., Pergamon Press, **1991**; b) M. A. Fox, J. K. Whitesell, in: *Organic Chemistry,* Jones and Bartlett Publishers, **2004,** pp. 466-521; c) *Acetylene Chemistry: Chemistry, Biology and Material Science,* F. Diederich, P. J. Stang, R. R. Tykwinski, Eds., Wiley-VCH, **2004**; d) A. Burrows, J. Holman, A. Parsons, G. Pilling, G. Price, in: *Chemistry: Introducing Inorganic, Organic and Physical Chemistry,* Oxford University Press, Oxford, **2013**, pp. 987-991.

(3) For selected examples of alkyne addition reactions using 1-iodoalkynes, see: a) G. Zweifel and H. Arzoumanian, *J. Am. Chem. Soc.* 1967, **89**, 5086; b) W. Xu and Q.-Y. Chen, *J. Org. Chem.* 2002**, 67**, 9421; c) J. E. Hein, J. C. Tripp, L. B. Krasnova, B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.* 2009, **48**, 8018; d) C. Recsei and C. S. P. McErlean, *Tetrahedron: Asymmetry*, 2010, **21**, 149; e) J. A. Crossley and D. L. Browne, *J. Org. Chem.* 2010, **75**, 5414; f) M. Juríček, K. Stout, P. H. J. Kouwer and A. E. Rowan, *Org. Lett.* 2011, **13**, 3494; g) D. Fu, J. Zhang

and S. Cao, *J. Fluorine Chem.* 2013, **156**, 170; h) Y. Gao, M. Yin, W. Wu, H. Huang and H. Jiang, *Adv. Synth. Catal.* 2013, **355**, 2263; i) A. H. Banday and V. J. Hruby, *Synlett*, 2014, **25**, 2463.

(4) a) V. V. Zhdankin, in: *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, John Wiley&Sons, Ltd., Chichester, **2014**; b) L. Wang, X. Zhou, M. Fredimoses, S. Liao and Y. Liu, *RSC Adv.* 2014, **4**, 57350.

(5) For selected examples of coupling reactions using 1-iodoalkynes, see: a) P. L. Southwick and J. R. Kirchner, *J. Org. Chem.* 1962, **27**, 3305; b) K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima and H. Nozaki, *Tetrahedron Lett.* 1985, **26**, 5585; c) R. Takeuchi, Y. Tsuji, M. Fujita, T. Kondo and Y. Watanabe, *J. Org. Chem.* 1989, **54**, 1831; d) J. Barluenga, J. M. González, I. Llorente and P. J. Campos, *Angew. Chem. Int. Ed. Engl.* 1993, **32**, 893; e) M. H. Nantz, D. K. Moss, J. D. Spence and M. M. Olmstead, *Angew. Chem. Int. Ed. Engl.* 1998, **37**, 470; f) S. Yamanoi, T. Matsumoto and K. Suzuki, *Tetrahedron Lett.* 1999**, 40**, 2793; g) M. Kunishima, D. Nakata, S. Tanaka, K. Hioki and S. Tani, *Tetrahedron*, 2000, **56**, 9927; h) M.V. Russo, C. Lo Sterzo, P. Franceschini, G. Biagini and A. Furlani, *J. Organomet. Chem.* 2001, **619**, 49; i) Y. Y. Ku, T. Grieme, P. Sharma, Y.-M. Pu, P. Raje, H. Morton and S. King, *Org, Lett.* 2001, **3**, 4185; j) S. V. Damle, D. Seomoon and P. H. Lee, *J. Org. Chem.* 2003, **68**, 7085; k) A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel and F. Rominger, *Adv. Synth. Catal.* 2010, **352**, 1307; l) D. L. Usanov and H. Yamamoto, *J. Am. Chem. Soc.* 2011, **133**, 1286; m) H. Liu, C. Chen, L. Wang and X. Tong, *Org. Lett.* 2011, **13**, 5072; n) M. Zhu, M. Ning, W. Fu, C. Xu and G. Zou, *Bull. Korean. Chem. Soc.* 2012, **33**, 1325; o) S. Mader, L. Molinari, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. Eur. J.* 2015, **21**, 3910.

(6) For some examples of the synthesis of useful chemicals using 1-iodoalkynes as intermediates, see: a) C. Burgess, G. Cooley, P. Feather and V. Petrow, *Tetrahedron*, 1967, **23**, 4111; b) D. W. Knight and G. Pattenden, *J. Chem. Soc. Perkin Trans. 1*, 1975, 641; c) C. Lüthy, P. Konstantin and K. G. Untch, *J. Am. Chem. Soc.* 1978, **100**, 6211; d) R. Rossi and A. Carpita, *Tetrahedron*, 1983, **39**, 287; e) S. Nishida, M. Murakami, T. Mizuno, T. Tsuji, H. Oda and N. Shimizu, *J. Org. Chem.* 1984, **49**, 3429; f) R. H. Boutin and H. Rapoport, *J. Org. Chem.* 1986,

51, 5320; g) T. D. Aicher and Y. Kishi, *Tetrahedron Lett.* 1987, **28**, 3463; h) Y. Kishi, *Pure and Appl. Chem.* 1992, **64**, 343; i) K. C. Nicolaou, A. Liu, Z. Zeng and S. McComb, *J. Am. Chem. Soc.* 1992, **114**, 9279; j) T. Mandai, T. Matsumoto, M. Kawada and J. Tsuji, *J. Org. Chem*. 1992, **57**, 6090; k) J. B. Nerenberg, D. T. Hung, P. K. Somers and S. L. Schreiber, *J. Am. Chem. Soc.* 1993, **115**, 12621; l) L. M. Antunes and M. G. Organ, *Tetrahedron Lett.* 2003, **44**, 6805; m) J. Picard, N. Lubin-Germain, J. Uziel and J. Augé, *Synthesis*, 2006, **6**, 979; n) N. Joubert, F. Amblard, K. L. Rapp, R. F. Schinazi and L. A. Agrofoglio, *Tetrahedron*, 2008, **64**, 4444; o) S. Dei, T. Shimogaki and A. Matsumoto, *Macromolecules*, 2008**, 41**, 6065; p) D. A. Barancelli, A. C. Mantovani, C. Jesse, C. W. Nogueira and G. Zeni, *J. Nat. Prod.* 2009, **72**, 857; q) R. C. Hoye, G. L. Anderson, S. G. Brown and E. E. Schultz, *J. Org. Chem.* 2010, **75**, 7400; r) K. Mori, *Tetrahedron*, 2012, **68**, 1936; s) M. Ruetz, R. Salchner, K. Wurst, S. Fedosov and B. Kräutler, *Angew. Chem. Int. Ed.* 2013, **52**, 11406; t) K. Okamoto, M. Watanabe, N. Sakata, M. Murai and K. Ohe, *Org. Lett.* 2013, **15**, 5810.

(7) For selected examples, see: a) G. Jaeger, W. Paulus, and H. Genth (A. G. Bayer), Ger. Offen. DE 3122263, 1982 (*Chem. Abstr.* 1983, **98**, 197757); b) G. Jaeger, W. Brandes, and P. E. Frohberger (A. G. Bayer), Eur. Pat. Appl. EP 66771, 1982 (*Chern. Abstr.* 1983, **98**, 197764); c) B. W. Krueger, U. Priesnitz, G. Jaeger, W. Paulus, and H. Genth (A. G. Bayer), Ger. Offen. DE 33058341, 1984 (*Chem. Abstr.* 1984, **101**, 186137); d) W. Singer and C. C. Versfelt (Troy Chemical Corp.), Brit. Pat. Appl. GB 2138292, 1984 (*Chem. Abstr.* 1985, **102**, 057826); e) B. F. Rose (Chevron Research Co.), U.S. Pat. US4639460, 1987 (*Chem. Abstr.* 1987, **106**, 156456).

(8) For selected examples, see: a) W. Gerhardt and R. Lehmann (K. Henkel), Ger. Offen. DE 3216895, 1983 (*Chem. Abstr.* 1984,**100**, 51107); b) W. Gerhardt and R. Lehmann (K. Henkel), Ger. Offen. DE 3224504, 1984 (*Chem. Abstr.* 1984, **100**, 209179); c) G. Schade, W. Paulus, and H. G. Schmitt (A. G. Bayer), Ger. Offen. DE 3526789, 1987 (*Chem. Abstr.* 1987, **106**, 98104).

(9) Diederich, F.; Stang, P.; Tykwinski, R. R. *Acetylene chemistry: chemistry, biology, and material science* Wiley-VCH: Weinheim, 2005.

(10) For some examples using this traditional approach, see: a) T. H. Vaughn and J. A. Nieuwland, *J. Am. Chem. Soc.* 1932, **54**, 787; b) T. H. Vaughn and J. A.

Nieuwland, J. *Am. Chem. Soc.* 1933, **55**, 2150; c) A. F. Kluge, K. G. Untch and J. H. Fried, *J. Am. Chem. Soc.* 1972, **94**, 9256; d) M. Bassetti, B. Floris and G. Illuminati, *Organometallics*, 1985, **4**, 617; e) L. Camici, P. Dembech, A. Ricci, G. Seconi and M. Taddei, *Tetrahedron*, 1988, **44**, 4197; f) J. E. A. Luithle and J. Pietruszka, *Eur. J. Org. Chem.* 2000, 2557; g) H. A. Stefani, R. Cella, F. A. Dörr, C. M. de Pereira, F. P. Gomes and G. Zeni, *Tetrahedron Lett.* 2005, **46**, 2001; h) G.-W. He, F.-W. Liu and X.-H. Xu, *Chin. J. Org. Chem.* 2007, **27**, 663; i) L.-G. Meng, P.-J. Cai, Q.-X. Guo and S. Xue, *Synth. Commun.* 2008, **38**, 225.

(11) T. Nishikawa, S. Shibaya, S. Hosokowa and M. Isobe, *Synlett*, 1994, 485.

(12) a) G. Zweifel and W. Lewis, *J. Org. Chem.* 1978, **43**, 2739; b) H. Hiraoka, K. Furuta, N. Ibeda and H. Yamamoto, *Bull. Chem. Soc. Jpn.* 1984, **57,** 10.

(13) R. B. Miller and T. Reichenbach, *Tetrahedron Lett.* 1974, **6,** 543; R. Ostwald, P.-Y. Chavant, H. Stadtmüller and P. Knochel, *J. Org. Chem.* 1994, **59**, 4143.

(14) a) M. J. Cohen and E. J. McNelis, *J. Org. Chem.* 1984, **49**, 515; b) D. Naskar and S. Roy, *J. Org. Chem.* 1999, **64**, 6896.

(15) a) G. W. Kabalka and A. R. Mereddy, *Tetrahedron Lett.* 2004, **45**, 1417; b) G. W. Kabalka and A. R. Mereddy, *J. Label Compd. Radiopharm.* 2005, **48**, 359.

(16) For other examples of alkyne derivatives, see: a) P. J. Stang and B. W. Surber, *J. Am. Chem. Soc.* 1985, **107**, 1452; b) N. Krause and D. Seebach, *Chem. Ber.* 1987, **120**, 1845; c) M. Ochiai, K. Uemura and Y. Masaki, *J. Am. Chem. Soc.* 1993, **115**, 2528; d) P. Michel and A. Rassat, *Tetrahedron Lett.* 1999, **40**, 8579; e) H. Lahrache, S. Robin and G. Rousseau, *Tetrahedron Lett.* 2005, **46**, 1635.

(17) T. Kaiho, in: *Iodine Chemistry and Applications*, John Wiley&Sons, Ltd., Chichester, **2014,** pp. 249-276.

(18) a) L. J. Hatch and D. J. Mangold, *J. Am. Chem. Soc.* 1955, **77**, 176; b) A. Ricci, M. Taddei, P. Dembech, A. Guerrini and G. Seconi, *Synthesis*, 1989, 461; c) A. Casarini, P. Dembech, G. Reginato, A. Ricci and G. Seconi, *Tetrahedron Lett.* 1991, **32**, 2169; d) I. Nishiguchi, O. Kanbe, K. Itoh and H. Maekawa, *Synlett*, 2000, **1**, 89; e) K. R. Reddy, M. Venkateshwar, C. U. Maheswari and P. S. Kumar, *Tetrahedron Lett.* 2010, **51**, 2170.

(19) a) J. Barluenga, J. M. Gonzalez, M. A. Rodriguez, P. G. Campos and G. Asensio, *Synthesis*, 1987, 661; b) Y. Brunel and G. Rousseau, *Tetrahedron Lett.* 1995, **36**, 2619; c) H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare

and A. Kirschning, *Org. Lett.* 1999, **1**, 2101.

(20) M. Nouzarian, R. Hosseinzadeh and H. Golchoubian, *Synth Commun.* 2013, **43**, 2913.

(21) a) Y. Sasson and O. W. Webster, *J. Chem. Soc. Chem. Commun.* 1992, 1200; b) I. J. Blackmore, A. N. Boa, E. J. Murray, M. Dennis and S. Woodward, *Tetrahedron Lett.* 1999, **40**, 6671; c) E. Abele, M. Fleisher, K. Rubina, R. Abele and E. Lukevics, *J. Mol. Catal. A: Chem.* 2001, **165**, 121.

(22) A. A. Mikhaylov, A. D. Dilman, M. I. Struchkova , Y. A. Khomutova, A. A. Korlyukov, S. L. Ioffe and V. A. Tartakovsky, *Tetrahedron*, 2011, **67**, 458.

(23) L. Bialy and H. Waldmann, *Angew. Chem. Int. Ed.* 2002, **41**, 1748.

(24) For some selected reviews on alkyne activation with transition metals, see: a) S. Aime, L. Milone and D. Osella, *J. Chem. Soc. Chem. Commun.* 1979, 704; b) S. L. Buchwald and R. B. Nielsen, *Chem. Rev.* 1988, **88**, 1047; c) N. E. Schore, *Chem. Rev.* 1988, **88**, 1081; d) P. H. Dixneuf, *Pure Appl. Chem.* 1989, **61**, 1763; e) T. E. Müller and M. Beller, *Chem. Rev.* 1998, **98**, 675; f) I. P. Beletskaya, C. Moberg, *Chem. Rev.* 1999, **99**, 3435; g) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.* 2004, **104**, 3079; h) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.* 2008, **108**, 3795; i) R. Severin and S. Doye, *Chem. Soc. Rev.* 2007, **36**, 1407; j) A. M. Lozano-Vila, S. Monsaert, A. Bajek and F. Verpoort, *Chem. Rev.* 2010, **110**, 4865; k) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.* 2011, **40**, 5084; l) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.* 2011, **111**, 2937; m) R. Chinchilla and C. Nájera, *Chem Rev.* 2014, **114**, 1783; n) R. Dorel and A. M. Echavarren, *Chem. Rev.* 2015, **115**, 9028.

(25) T. Jeffery, *J. Chem. Soc. Chem. Commun.* 1988, **14**, 909; b) J. Yan, J. Li and D. Cheng, *Synlett*, 2007, **15**, 2442; c) S.-N. Chen, T.-T. Hung, T.-C. Lin and F.-Y. Tsai, *J. Chin. Chem Soc.* 2009, **56**, 1078; d) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, B. Pedley and E. Årstad, *J. Am. Chem. Soc.* 2013, **135**, 703.

(26) H. Hofmeister, K. Annen, H. Laurent and R. Wiechert, *Angew. Chem. Int. Ed. Engl.* 1984, **23**, 727; b) T. J. Speed and D. M. Thamattoor, *Tetrahedron Lett.* 2002, **43**, 367; c) D. Lehnherr, J. M. Alzola, E. B. Lobkovsky and W. R. Dichtel, *Chem. Eur. J.* 2015, **21**, 18122.

(27) A. S. K. Hashmi, T. D. Ramamurthi, M. H. Todd, A. S,-K. Tsang and K. Graf,

Aust. J. Chem. 2010, **63**, 1619.

(28) P. Starkov, F. Rota, J. M. D'Oyley and T. D. Sheppard, *Adv. Synth. Catal.* 2012, **354**, 3217.

(29) F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan and S. P. Nolan, *Chem. Cat. Chem.* 2015, **7**, 240.

(30) I. V. Koval, *Russ. J. Org. Chem.* 2002, **38**, 301.

(31) For a more detailed discussion about the use of EtOH with iodoalkynes, the Reader is referred to the experimental results presented in Chapter 4.

(32) For further information, the Reader is referred to Chapter 4.

(33) a) R. Dorel and A. M. Echavarren, *Chem. Rev.* 2015, **115**, 9028; b) L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang and W. He, *J. Org. Chem.* 2013, **78**, 9190.

(34) These interactions are known and have been studied for the preparation of cationic NHC-Au-pyridine complexes. For further information, see: J. Y. Z. Chiou, S. C. Luo, W. C. You, A. Bhattacharyya, C. S. Vasam, C. H. Huang, and I. J. B. Lin, *Eur. J. Inorg. Chem.* 2009, 1950.

(35) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.* 2010, **46**, 2742.

CHAPTER 4

Functionalisation of 1-iodoalkynes: Au(I)-catalysed Hydrofluorination and Hydration

4.1 Introduction

The interest in the synthesis of 1-iodoalkynes for their use as building blocks in organic chemistry was mentioned in the previous chapter, with addition and cross-coupling chemistry representing the main applications for these molecules. With the widespread use of transition metal-NHC catalysts in these two areas of synthesis, the discussion about their use for novel transformations of 1-iodoalkynes was interesting for our research group.

As a result, this chapter will first present the application of Au(I)-NHC bifluorides as catalysts in the hydrofluorination of 1-iodoalkynes, providing selective access to 2-fluoro-1-iodo-2-arylalkenes (Figure 4.1, top). The available methods for the preparation of this fluorinated building block are very limited, and the direct hydrofluorination of these substrates has never been performed, therefore representing a great method for organic synthesis.

On the other hand, the use of Au(I)-NHC catalysts was also explored for a fairly new reaction: the hydration of 1-iodoalkynes for the synthesis of α-iodomethyl ketones (Figure 4.1**,** bottom). Despite some limited number of tests reported in the literature for this route, the reaction conditions have never been optimised. Describing a full methodology will therefore not only facilitate the preparation of these molecules, but also increase their availability and, hence, their presence in the current arsenal of chemical synthesis.

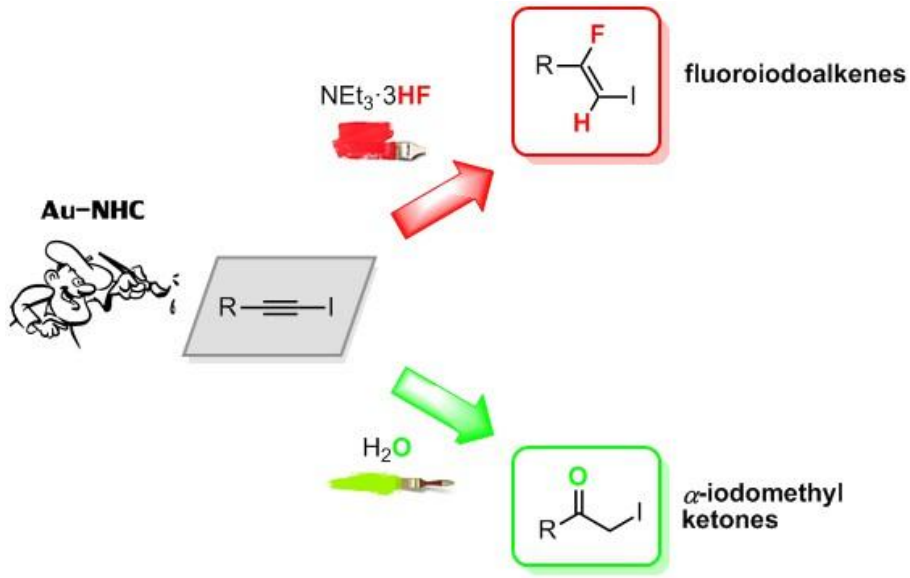


Figure 4.1. General scheme for Au(NHC)-catalysed hydrofluorination (top) and hydration (bottom) of 1-iodoalkynes.

4.2 Hydrofluorination of 1-iodoalkynes

4.2.1 Fluoroiodoalkenes: state-of-the-art

Fluoroiodoalkenes are chemical entities containing both iodo- and fluoro-functionalities on an alkene moiety. This fragment can be found in the literature as a reactive intermediate in a number of organic reactions, exploiting its ability to yield polysubstituted fluorinated alkenes.[1] These molecules exhibit a very rich chemistry that has not been fully explored to date. For example, one can propose the addition of nucleophiles or hydrogen to the fluoroalkene structure, generating complex molecules containing a valuable C(sp^3)-F bond and a controlled substitution pattern that could otherwise be challenging to access (Figure 4.2). Alternatively, coupling chemistry can be employed, being a major application for fast and efficient synthesis of polysubstituted fluoroalkenes. Feasible reactions would be the formation of Grignard reagents for the synthesis of allylic alcohols, or their use in Pd-catalysed cross-coupling chemistry (Figure 4.2). These are only a few proposals of transformations based on fluoroiodoalkene substrates, which would certainly be interesting to explore later on.

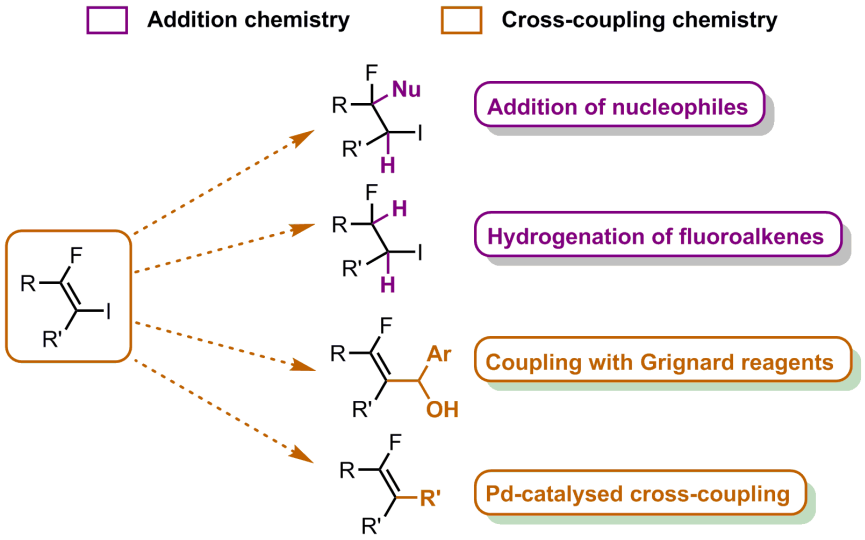


Figure 4.2. Selected feasible concepts of organic functionalisation of fluoroiodoalkenes.

The most common motif in these molecules is a 1,2-dihaloalkene distribution, which results in two C-X bonds with marked reactivity differences (Figure 4.3). While a broader understanding and efficiency on the preparation of tetrasubstituted fluoroiodoalkenes is available in the literature,[2] less is known about the synthesis of the trisubstituted counterparts, therefore attracting our attention.

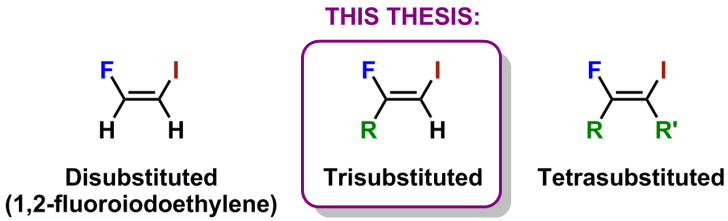


Figure 4.3. Families of fluoroiodoalkenes.

The oldest methodology on the preparation of a fluoroiodoalkene moiety was reported by Nomura in 1986, where these molecules were detected as intermediates in the synthetic pathways to prepare 1-iodoalkynes and iodoalkenyl ethers, utilizing *gem*-difluoro-α-iodoalkanes as substrates (Figure 4.4, **D**).[3] The interest in this chemistry led to later investigation of the use of more accessible precursors to isolate fluoroiodoalkenes. In this context, *gem*-difluoro-α-alcohols have displayed quite a remarkable versatility to yield not only the desired iodoalkane derivatives (Figure 4.4, **A**),[4] but also other precursors to these species, such as the related tosylates (Figure 4.4, **B** and **C**).[5] The direct conversion of *gem*-difluoro-α-iodoalkanes was complemented by other pathways, as studied by Gotoh and co-workers in 1987.[6] The oxidation of these molecules to iodonium salts (Figure 4.4, **E**), followed by controlled elimination of HF (Figure 4.4, **F**), afforded fluoroalkenyl iodonium species that could then be transformed into the corresponding fluoroiodoalkenes (Figure 4.4, **G**).

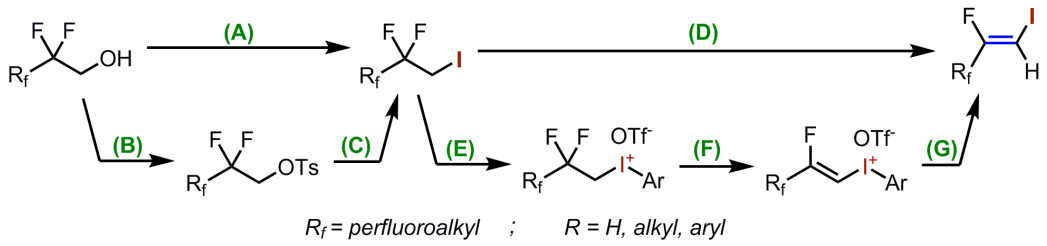
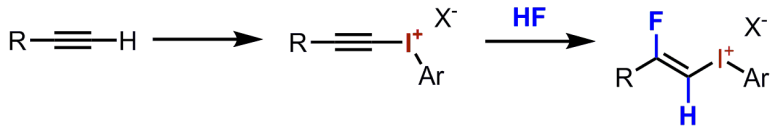


Figure 4.4. Traditional use of *gem*-difluoroalkyl derivatives for the synthesis of fluoroiodoalkenes.[3-6]

While this alternative method adds more complexity to the overall synthesis of fluoroiodoalkenes, this was balanced by a wider substrate scope, now tolerating substrates other than perfluorinated alkanes. With a generally higher overall performance for the synthesis of fluoroiodoalkenes, iodonium salts have overtaken traditional approaches in this field. Since the early examples of this reaction,[6,7] the synthetic access to suitable iodonium species has been significantly facilitated, thanks to new functionalisation methods. Among these advances, the use of terminal alkynes as

substrates for the preparation of fluoroalkenyl iodonium salts is certainly an important discovery. In combination with the versatility of the hydrofluorination of alkynes provided by the newest reported methodologies, this modern concept for the preparation of fluorinated alkenes represents an interesting strategy in synthesis (Scheme 4.1).



Scheme 4.1. Use of terminal alkynes for the synthesis of fluoroalkenyl iodonium salts.

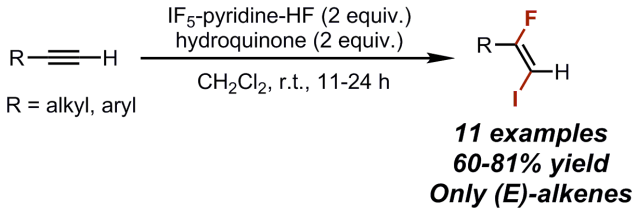
The contributions of Hara and co-workers are significant in this field. Since their earliest work on the electrochemically-generated *p*-iodotoluene difluoride as a reagent to prepare fluoroalkenyl iodonium fluoride salts,[8] this group has explored the utility of these species for the synthesis of different fluoroalkenyl derivatives. This includes species such as α,β-unsaturated fluorinated esters[9] and, for the interest of the discussed chemistry, fluoroiodoalkenes. Various methods for the transformation of terminal alkynes into the related iodonium salts are nowadays available in the literature,[10] and the use of aqueous HF for the hydrofluorination of these intermediates is most commonly considered to access the desired fluoroiodoalkenes. [11] In the case of that last step, a standarised procedure involving CuI as catalyst in the presence of KI is frequently employed for the final conversion of fluoroalkenyl iodonium salts into fluoroidoalkenes (Scheme 4.2).

Scheme 4.2. Cu-catalysed synthesis of fluoroiodoalkenes from fluoroalkenyl iodonium salts.

Iodonium salts can also be used as substrates to prepare other reactive molecules affording fluoroiodoalkenes. This is the case of (fluoroalkenyl)boranes, which can be obtained from the corresponding iodonium salts, and have been shown to be alternative sources of a fluoroalkenyl skeleton leading to the desired fluoroalkenes.[12]

In an attempt to simplify the synthetic procedures, direct iodofluorination of terminal alkynes has been discussed.[2b,13] With precedents in the work from Gregorčič and Zupan from 1987,[13a] this chemistry has been explored in more recent years,

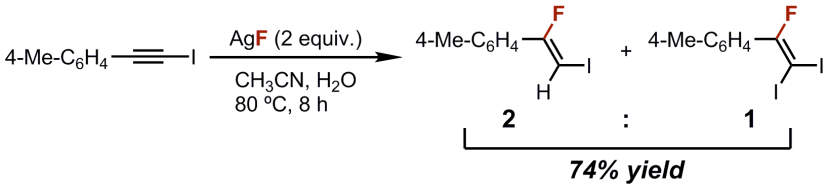
providing interesting results. In fact, the most recent example in fluoroiodoalkene synthesis has been released during this year, with the work from Hara and co-workers on the catalyst-free iodofluorination of terminal alkynes with IF_5-pyridine-HF in the presence of hydroquinone (Scheme 4.3).[2c,14]



Scheme 4.3. Iodofluorination of terminal alkynes using IF_5-pyridine-HF.[14]

While fluoroiodination procedures are interesting, the need for complex reaction systems and the impossible task of obtaining (*Z*)-fluoroiodoalkenes in any reported procedure, are important drawbacks that have not been fully addressed to date.

It is surprising that only one piece of work about direct hydrofluorination of 1-iodoalkynes has been reported in the literature as a suitable approach for the preparation of fluoroiodoalkenes. Analysing the reported methods, it can be seen that the formation of iodonium salts is always performed prior to the hydrofluorination step, thus suggesting that the protection of the C-I is important for the reactions to proceed. Further supporting this proposal, during the studies for the sequential bromination/hydrofluorination of terminal alkynes by Jiang and co-workers, 1-iodoalkynes provided an unselective mixture of the desired fluoroiodoalkene and the corresponding fluorinated *gem*-diiodo species (Scheme 4.4).[15] This represented the first proof of concept of a direct hydrofluorination reaction of 1-iodoalkynes.

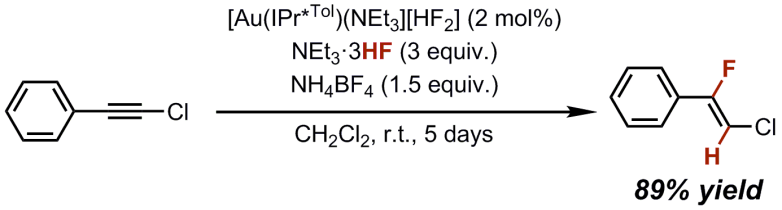


Scheme 4.4. First reported direct hydrofluorination of 1-iodoalkynes for the synthesis of fluoroiodoalkenes.[15]

Although being strong evidence for the interference between addition of HF to multiple bonds and the presence of free C-I moieties, no consistent studies have clearly demonstrated the generality of this incompatibility. Moreover, other terminal alkyne derivatives, such as ynamides, have been hydrofluorinated using modern methodologies without any evidence of side reactivity.[16] Further support can be found in the recent

advances in mild hydrofluorination of alkynes using transition metals, especially gold(I) catalysts (for further details, the Reader is referred to Chapter 1). Considering all aforementioned reasons, the feasibility of the hydrofluorination of 1-iodoalkynes was re-assessed.

The most inspiring report for a direct hydrofluorination of 1-haloalkynes was recently presented by Nolan and co-workers, with the use of a hydrofluorination system catalysed by a Au(I)-NHC bifluoride species.[17] In the presented substrate scope, 1-(chloroethynyl)benzene was used, obtaining 89% isolated yield of 1-chloro-2-fluoro-2-phenylethene (Scheme 4.5).

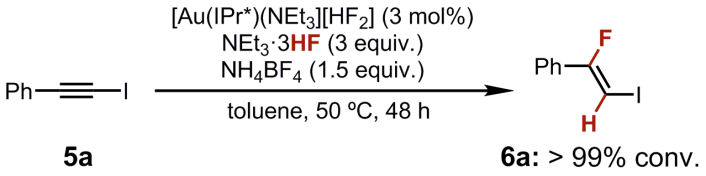


Scheme 4.5. Hydrofluorination of (chloroethynyl)benzene using a Au(I)-NHC bifluoride catalyst.[17]

No further exploration of other 1-haloalkynes was presented in this report, therefore representing a great opportunity to investigate the feasibility of the hydrofluorination of 1-iodoalkynes for the synthesis of fluoroiodoalkenes.

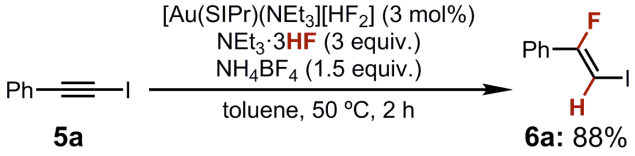
4.2.2 Results and discussion

(Iodoethynyl)benzene (**5a**) was selected as model substrate, due to its simplicity and easy synthetic access through the Au-catalysed method described in Chapter 3. Our initial test was analogous to the catalytic conditions employed by Nolan for the hydrofluorination of internal alkynes. By using 3 mol% of the bifluoride catalyst with the formula [Au(IPr*)(NEt_3)][HF_2], in the presence of three equivalents of NEt_3·3HF and 1.5 equivalents of NH_4BF_4 in toluene, full conversion of the starting material towards a new species was confirmed by TLC and ^{1}H NMR analyses after 48 h at 50 ºC (Scheme 4.6). The product was confirmed as the hydrofluorination compound, 2-fluoro-1-iodo-2-phenylethene (**6a**). Very interestingly, no signs of any side-product was observed in this reaction, completely discarding our concerns about possible chemical incompatibilities, and representing the first reported method for the selective hydrofluorination of 1-iodoalkynes.



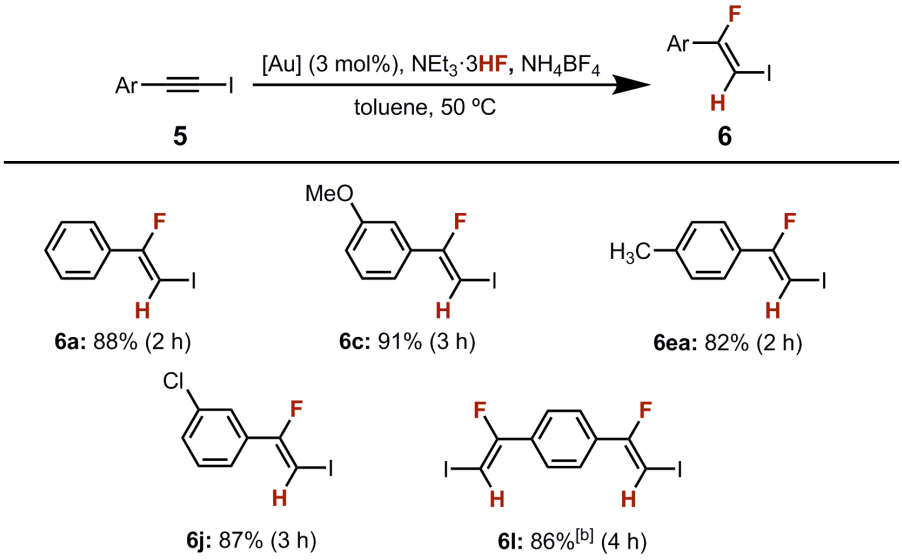
Scheme 4.6. Preliminary test on the Au(I)-catalysed hydrofluorination of **5a**.

Gratified by this result, further optimisation studies were conducted (for the complete experimental data, the Reader is referred to the Supporting Data CD, Experimental Annex - Chapter 4, Table S1). The use of a simpler bifluoride system was desirable, and changing the NHC ligand from IPr* to SIPr still afforded complete consumption of **5a** yielding **6a** as the sole product. This change in the NHC does not only benefit from the relative ease of preparation of SIPr when compared to IPr* (due to the higher molecular complexity of the later), but also to a practical feature that will be exploited in further reactions (for additional information about this, the Reader is referred to Chapter 5). Under these experimental conditions, the SIPr-derived catalyst allowed a decrease of the reaction time to 2 h while still maintaining full conversion towards **6a**. Under these reaction conditions, **6a** was isolated in 88% yield by simple purification through column chromatography, with all spectroscopic data matching with a vicinal (*Z*)-fluoroiodoalkene moiety (Scheme 4.7).



Scheme 4.7. Optimised hydrofluorination conditions for **5a.**

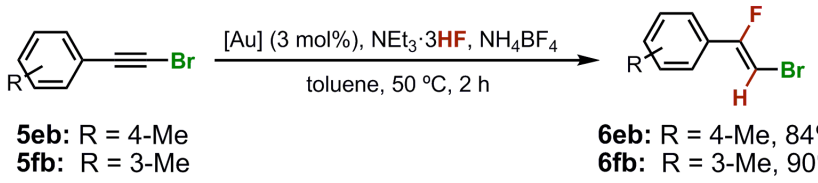
These optimised conditions were applied to various 1-iodoalkynes, in order to investigate the generality of the method (Scheme 4.8). The procedure was successfully applied to various aromatic 1-iodoalkynes, maintaining high reactivity at fairly short reaction times. Interestingly, a challenging substrate such as **5k** afforded the corresponding symmetrical compound (**6k**) as a single product through double hydrofluorination using 6 mol% of the gold catalyst after only 4 h and in an 86% isolated yield.



[a] Reaction conditions: alkyne (0.50 mmol), $NEt_3 \cdot 3HF$ (1.5 mmol), NH_4BF_4 (0.75 mmol), $[Au(SIPr)(NEt_3)][HF_2]$ (3 mol%), toluene (1 mL), 50 ºC. Isolated yields. Reaction times in parenthesis. [b] 6 mol% of [Au].

Scheme 4.8. Scope of the Au(I)-catalysed hydrofluorination of 1-iodoalkynes.[a]

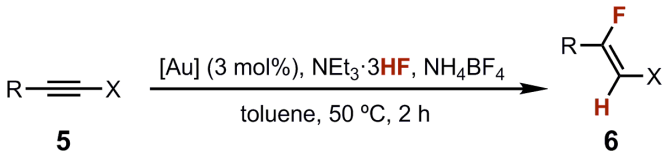
The suitability of this catalytic system for the hydrofluorination of 1-bromoalkynes was also tested. Bromoalkynes **5eb** and **5fb** were reacted under the optimised conditions, and after 2 h, the derived hydrofluorinated products **6eb** and **6fb** were obtained in 84% and 90% yields, respectively (Scheme 4.9).



Scheme 4.9. Hydrofluorination of 1-bromoalkynes using the optimised Au-catalysed system.

The robustness of the methodology was further demonstrated by performing some scale-up reactions. **5a**, **5eb** and **5fb** were tested in quantities of up to 3 mmol, and in all cases the expected products were obtained in comparable yields to those reported in Scheme 4.8, with no changes in the reaction times (Table 4.1).

Table 4.1. Scale-up experiments: hydrofluorination of iodo- and bromoalkenes[a]



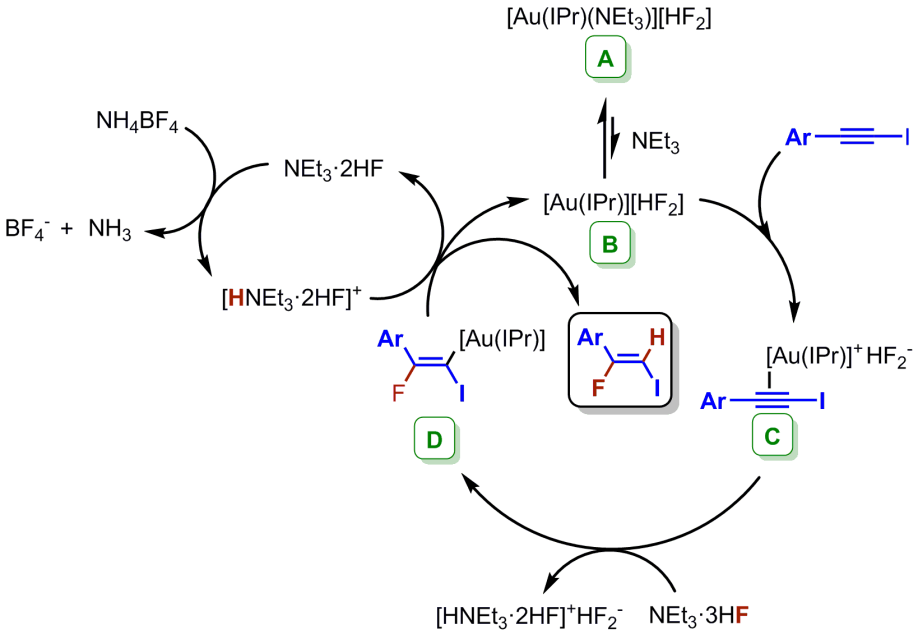
5 **6**

Entry	Substrate	Amount (g)	Product	Amount (g)	Isolated yield (%)
1	**5a**	0.68 g	**6a**	0.67 g	91
2	**5eb**	0.43 g	**6eb**	0.40 g	85
3	**5fb**	0.43 g	**6fb**	0.43 g	90

[a] Reaction conditions: 1-haloalkyne, $NEt_3 \cdot 3HF$ (3 equiv.), NH_4BF_4 (1.5 equiv.), $[Au(SIPr)(NEt_3)][HF_2]$ (3 mol%), toluene, 50 ºC, 2 h.

4.2.3 Mechanistic studies

An in-depth investigation into the mechanism of the Au-catalysed hydrofluorination of 1-iodoalkynes was not conducted within our experimental work; however, a catalytic cycle is tentatively proposed for this reaction, based on the known reactivity of Au complexes with general alkynes (Scheme 4.10). As discussed in Chapter 3, the equilibrium of the employed Au(I) bifluoride precursor between its coordinated (Scheme 4.10, **A**) and its "naked" form (Scheme 4.10, **B**) generates an active species that, upon coordination with the employed 1-iodoalkyne, forms the π-coordinated Au(I)-iodoalkyne species (Scheme 4.10, **C**). The reaction with the nucleophilic fluorine source generates the related 2-fluoro-1-iodoalkenyl gold(I) species (Scheme 4.10, **D**), which released the expected compound upon reaction with H^+, regenerating the active cationic Au(I) species for another catalytic cycle. The regioselectivity of the reaction can be rationalised from the perspective of general addition chemistry of HX reagents to alkynes, following a Markovnikov-type addition.[18]



Scheme 4.10. Proposed catalytic cycle of the Au(I)-catalysed hydrofluorination of 1-iodoalkynes.

4.3 Hydration of 1-iodoalkynes

4.3.1 *α*-Iodomethyl ketones: state-of-the-art

The family of *α*-iodomethyl ketones conforms to a group of molecules with an outstanding performance in synthesis. By being important precursors for the formation of C-C, C-O and C-N bonds, these compounds are excellent substrates for the synthesis of heterocycles[19] or as reactive precursors for *α*-functionalisation of ketones.[20] As a result of this versatility, the use of *α*-iodomethyl ketones in total synthesis is nowadays a valuable approach to increase molecular complexity. For example, the preparation of certain pharmacological substances, such as (-)-trachelanthamidine,[21] dendrobine[22] or cylindricine C,[23] among others,[24] has benefited from the use of iodoketones as key intermediates (Figure 4.5).

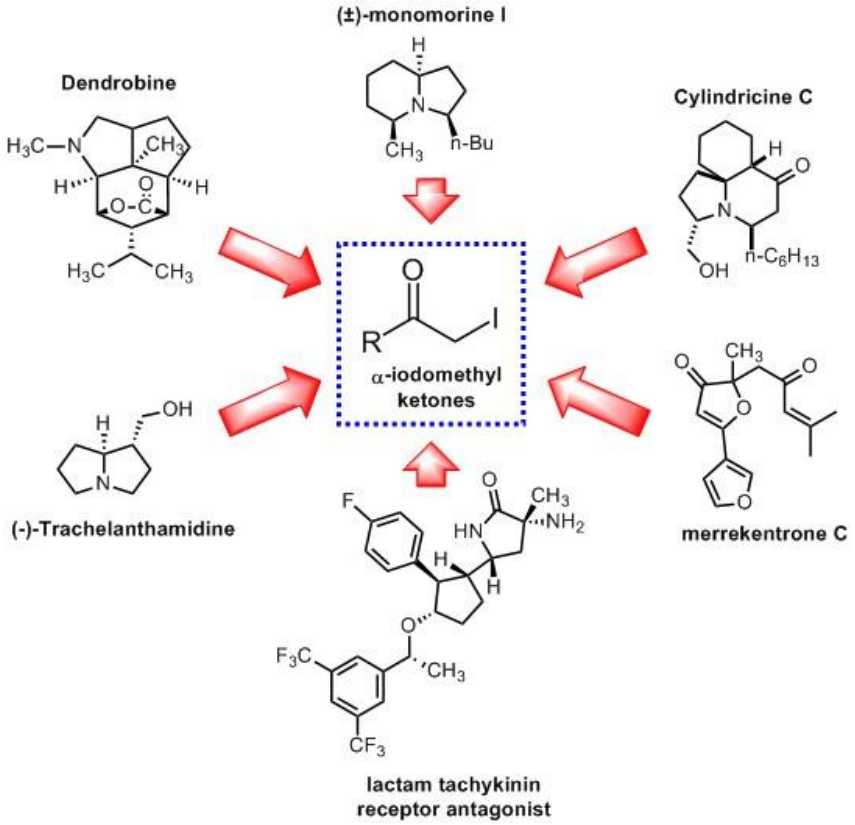
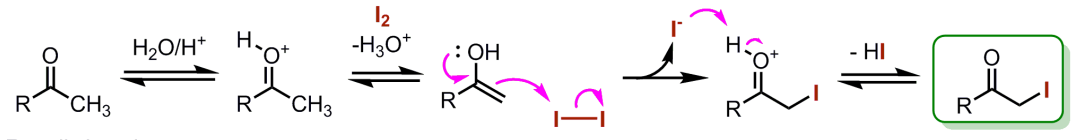


Figure 4.5. Some examples of "*Blockbuster*" drugs prepared *via* α-iodomethyl ketone intermediates.

These molecules can be prepared in different ways, with the direct iodination of methyl ketones still being the most common and direct approach,[25] as a result of the good availability of the corresponding substrates and the high atom economy of the iodination process. This type of acid-promoted iodination proceeds *via* the formation of an enol that readily attacks the electrophilic iodine source (with molecular iodine being the traditional reagent for such purpose). Subsequent regeneration of the ketone moiety affords the desired final product (Scheme 4.11).



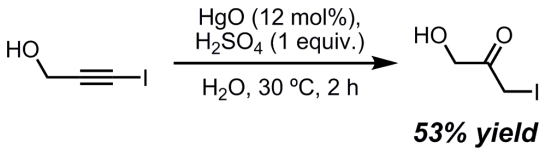
R = alkyl, aryl

Scheme 4.11. Traditional electrophilic iodination of methylketones.

However, direct iodination procedures present a number of drawbacks that have only been partially assessed over the decades, such as undesirable polyhalogenation products and complex solvent/additive combinations required for high efficiency. The use of silyl enol ethers or acetates has been explored as a suitable alternative,[26] but the difficult preparation and purification of the related substrates has precluded a more

extensive application. Some other protocols have taken advantage of the chemistry of different functional groups, such as the oxidation/iodination of alkenes,[27] the oxidation of iodoalcohols[28] or the electrophilic iodination of α-substituted methyl ketone precursors,[26b,29] therefore resulting in a range of synthetic possibilities being nowadays available for the preparation of these species. However, the need for α-substituents as directing groups significantly limit the application of these approaches, and the discovery of simpler approaches is still of interest.

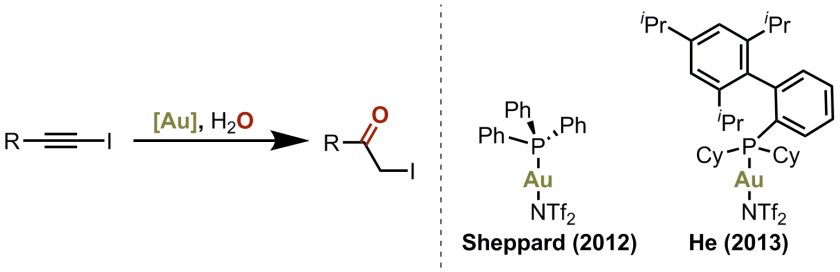
A highly attractive method is based on the hydration of 1-iodoalkynes. This protocol presents important advantages, such as a very high atom economy, the use of water as the only reagent and a generally broader scope of accepted substrates. Surprisingly, this strategy has only been scarcely discussed in the literature. The early work by Nakagawa and co-workers in 1972 represents the first described attempt to hydrate a 1-iodoalkyne moiety.[30] In their report, iodopropargyl alcohol was successfully hydrated to its related ketone in the presence of catalytic HgO under acidic conditions, using H_2O as solvent (Scheme 4.12). Despite this interesting reaction, the use of mercuric oxide as catalyst significantly restricted the interest in this method, and no further hydration attempts for haloalkynes followed for some years



Scheme 4.12. First report of the synthesis of an α-iodomethyl ketone *via* Hg-catalysed hydration of iodopropargyl alcohol.[30]

Later on, and in consonance with the growing success of catalytic hydration of alkynes[31] (specially in the case of gold catalysis),[32] a reborn interest in this reaction was witnessed. In 2012, during the study of the Au(I)-catalyzed iodination of terminal alkyne derivatives using the gold bistriflimide complex [Au(NTf_2)(PPh_3)], Sheppard and co-workers reported the first experimental proof of a mild catalytic system for the hydration of aromatic 1-iodoalkynes, together with two examples of α-iodomethyl ketones isolated in moderate yields (Scheme 4.13).[33] However, very limited experimental data were provided for this system. Encouraged by the performance of Au(I)-phosphine systems, He and co-workers later reported a more general hydration system for 1-haloalkynes (Scheme 4.13).[34] In spite of its optimal application to bromo- and chloroalkyne substrates, very low catalytic activity was observed upon use of the

corresponding iodo derivatives, with the hydration product from (iodoethynyl)benzene (**5a**) being observed in < 20% NMR yield. It was assumed that steric hindrance was limiting the efficiency of the hydration of 1-iodoalkynes, but no further experimental information was provided.



Scheme 4.13. Au-catalysed hydration of 1-iodoalkynes reported by Sheppard[33] and He.[34]

More recently, two new alternatives to gold catalysis have expanded the available protocols for hydration chemistry. While these approaches report the use of simple Ag(I)[35] and Cu(II)[36] salts, important inconveniences can be still witnessed for these methods, such as the use of a non-innocent strongly-acidic solvent (trifluoroacetic acid), or the limited information about their application to 1-iodoalkynes. Four examples of aromatic α-iodomethyl ketones were isolated in $\geq$ 90% yield in the case of the Cu(II) system (Figure 4.6), whereas no iodoalkyne hydration examples were studied with the AgF catalyst. Recently this year, a new method involving the use of 10 mol% $In(OTf)_3$ in AcOH at 100 ºC has been applied to a handful of 1-iodoalkynes,[37] although it presents similar drawbacks to those reported for previous protocols (Figure 4.6).

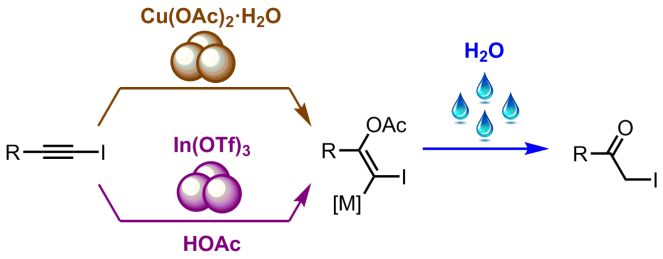


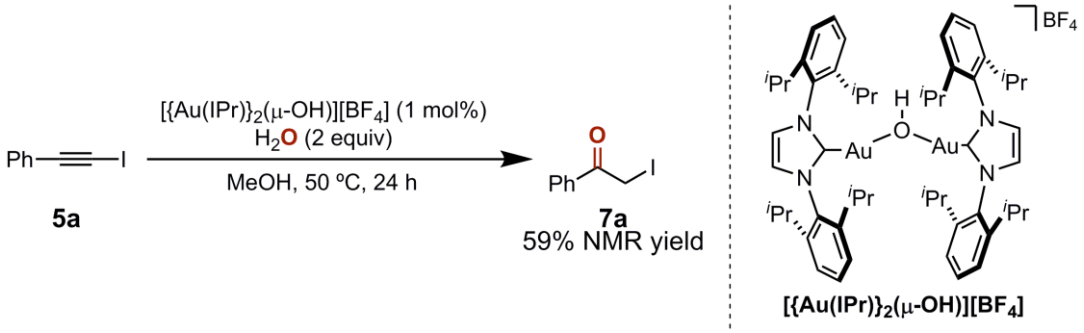
Figure 4.6. Catalytic hydration of 1-iodoalkynes using Cu(II)[36] and In(III) salts.[37]

With all this information at hand, it is noticeable that no general mild system for the synthesis of α-iodomethyl ketones from 1-iodoalkynes is yet available in the literature, thus a more consistent study will be well received by the research community. Our interest in the preparation and application of transition metal-NHC complexes (NHC = N-heterocyclic carbene) was considered as a plausible solution to this problem.

Considering the aforementioned success of gold catalysts, and with the plethora of complexes available for the excellent general hydration of alkynes,[32e-j,32o] the use of Au(I)-NHC catalysts was indeed an interesting choice for examination.

4.3.2 Results and discussion

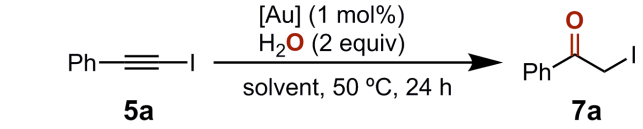
The optimisation of a hydration protocol for (iodoethynyl)benzene (**5a**) as model substrate was discussed. The initial blank test, under metal-free conditions, revealed that stirring **5a** in the presence of two equivalents of water in MeOH at 50 ºC for 24 h affords no conversion towards the expected product, 2-iodo-1-phenylethanone (**7a**). However, when 1 mol% of the digold(I)-NHC complex [{Au(IPr)}$_2$(μ-OH)][BF_4] was introduced, 59% NMR yield of **7a** was observed, using 1-bromo-3-fluorobenzene as internal standard (Scheme 4.14). The selection of this complex for preliminary studies responded to the recent studies presented by Nolan and co-workers about its high efficiency for the hydration of alkynes,[38] providing an excellent starting point for optimisation purposes.

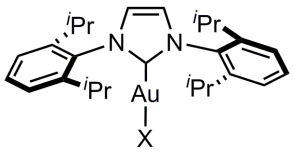


Scheme 4.14. Preliminary test of the hydration of **5a** using Au(I)-NHC catalysts.

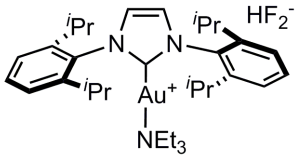
Encouraged by this result, further optimisation was conducted. The nature of the Au catalyst was first studied (Table 4.2). While the chloride, hydroxide and bifluoride species derived from the IPr-Au(I) fragment showed low catalytic activity (Table 4.2, Entries 2, 3 and 5, respectively), an increase in the reactivity was observed when [Au(NTf_2)(IPr)] was used (69% NMR yield; Table 4.2, Entry 4).

Table 4.2. Testing Au(I)-NHC catalysts in the hydration of **5a.**





X = OH **[Au(OH)(IPr)]**
X = Cl **[Au(Cl)(IPr)]**
X = NTf_2 **[Au(NTf$_2$)(IPr)]**



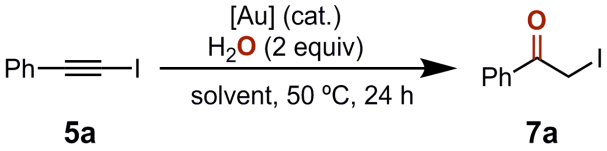
[Au(IPr)(NEt$_3$)][HF$_2$]

Entry	[Au] (mol %)	5a (%)[b]
1	[{Au(IPr)}$_2$(μ-OH)][BF_4]	59
2	[Au(Cl)(IPr)]	10
3	[Au(OH)(IPr)]	0
4	[Au(NTf_2)(IPr)]	69
5	[Au(IPr)(NEt_3)][HF_2]	0

[a] Reaction conditions: **5a** (0.10 mmol), [Au] (1 mol%), H_2O (0.20 mmol), solvent (0.30 mL). [b] ^{1}H NMR yields using 1-bromo-3-fluorobenzene as NMR standard ($CDCl_3$ as solvent).

This complex, first reported by Gagosz and co-workers,[39] was selected for further optimisation. The selection of the solvent was next examined (Table 4.3). Upon testing a variety of solvents, the performance of alcohols (Table 4.3, Entries 1-4) was clearly superior to polar aprotic (Table 4.3, Entries 5-10) and non-polar solvents (Table 4.3, Entries 11-12). While the performance of commercial EtOH as solvent was high (Table 4.3, Entry 2), the use of dry EtOH (commercial EtOH dried over activated 4Å Molecular Sieves for at least 48 h; stored under nitrogen atmosphere) was optimal for this reaction, obtaining 86% NMR yield of **7a** (Table 4.3, Entry 3).

Table 4.3. Effect of the solvent in the Au(I)-catalysed hydration of **5a**[a]

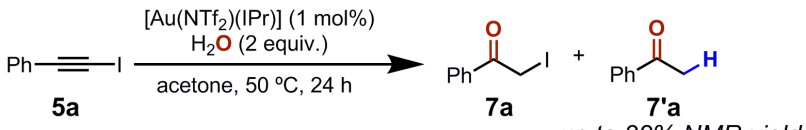


5a **7a**

Entry	[Au] (mol %)	Solvent	7a (%)[b]
1	[Au(NTf$_2$)(IPr)] (1)	MeOH	69
2	[Au(NTf$_2$)(IPr)] (1)	EtOH	76
3	[Au(NTf$_2$)(IPr)] (1)	EtOH (dry)	86
4	[Au(NTf$_2$)(IPr)] (1)	*i*-PrOH	71
5	[Au(NTf$_2$)(IPr)] (1)	*t*-AmOH	29
6	[Au(NTf$_2$)(IPr)] (1)	Acetone	0
7	[Au(NTf$_2$)(IPr)] (1)	CH_3CN	0
8	[Au(NTf$_2$)(IPr)] (1)	THF	47
9	[Au(NTf$_2$)(IPr)] (1)	2-Me-THF	25
10	[Au(NTf$_2$)(IPr)] (1)	DCE	3
11	[Au(NTf$_2$)(IPr)] (1)	CPME	7
12	[Au(NTf$_2$)(IPr)] (1)	Toluene	4
13	[Au(NTf$_2$)(IPr)] (1)	1,4-dioxane	44

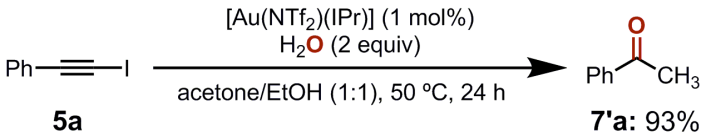
[a] Reaction conditions: **5a** (0.10 mmol), [Au] (cat.), H_2O (0.20 mmol), solvent (0.30 mL), 50 ºC, 24 h. [b] ^{1}H NMR yields using 1-bromo-3-fluorobenzene as NMR standard ($CDCl_3$ as solvent).

At this stage, the recurrent presence of a side product was noticed. Although rarely observed in NMR yields > 15%, the nature of this product did not match any expected species. This species was observed in up to 32% NMR yield when acetone was used as reaction solvent (Table 4.3, Entry 5), and could be identified as the deiodination product of **7a** (acetophenone, **7'a**) (Scheme 4.15).



Scheme 4.15. Side reactivity using acetone as solvent: deiodination of **7a**.

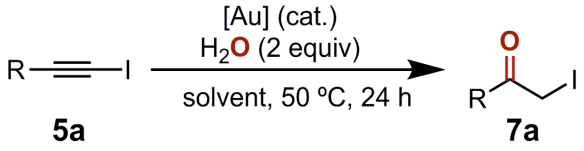
The selectivity of the reaction was completely shifted towards **7'a** when an EtOH/acetone mixture was used under the conditions shown in Table 4.3. The deiodinated species **7'a** was isolated in 93% yield using these catalytic conditions (Scheme 4.16).



Scheme 4.16. Optimised system for the hydration/deiodination of **5a**.

Further refinements to the methodology for the selective conversion of **5a** into **7a** were still required. The optimisation of other reaction parameters is presented in Table 4.4. The adjustment of the reaction temperature was discussed. Both decreasing (Table 4.4, Entry 1) or increasing (Table 4.4, Entry 2) the reaction temperature had a detrimental effect on the optimal conversion towards **7a**. Similar observations were made when the number of equivalents of H_2O were altered (Table 4.4, Entries 3-4), with two equivalents proving to be optimal. The increase of the catalyst loading to 2 mol% finally afforded > 99% NMR yield of **7a** (Table 4.4, Entry 5). Under these conditions, **7a** was isolated in 88% yield after evaporation of the volatiles under reduced pressure and column chromatography. The contrast between the NMR yield and the isolated yield resulted from the difficulty to isolate pure **7a,** as the main side product of this reaction (**7'a**, see Scheme 4.15) could not be efficiently separated from the desired compound by simple purification methods, thus inconveniencing the overall procedure. In order to overcome this problem, further evaluation of the methodology was considered. Since an increase in the amount of [Au] was strictly required to obtain reproducible full consumption of **5a,** it was hypothesised that the reaction conditions could be re-optimised at such catalyst loading. Indeed, after some testing, the reduction of the reaction time to 5 h could not only maintain the full consumption of **5a**, but also reduce the amount of **7'a** to < 3%, with **7a** being isolated in 96% yield (Table 4.4, Entry 6).

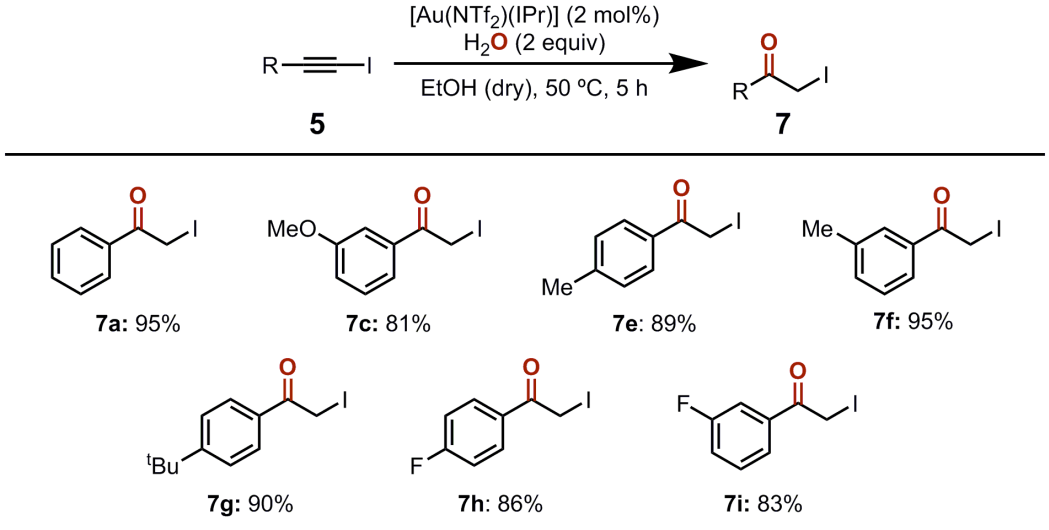
Table 4.4. Optimisation of the Au-catalysed hydration of **5a** into **7a**.[a]



Entry	[Au(NTf$_2$)(IPr)] (mol%)	H$_2$O (equiv.)	T (ºC)	2a (%)[b]
1	1	2	40	68
2	1	2	60	50
3	1	1	50	68
4	1	3	50	68
5	2	2	50	99 (88)[c]
6[d]	2	2	50	99 (96)[c]

[a] Reaction conditions: **5a** (0.10 mmol), [Au] (cat.), H_2O (0.20 mmol), solvent (0.30 mL), 50 ºC, 24 h. [b] ^{1}H NMR yields using 1-bromo-3-fluorobenzene as NMR standard ($CDCl_3$ as solvent). [c] Isolated yield in parenthesis. [d] 5 h.

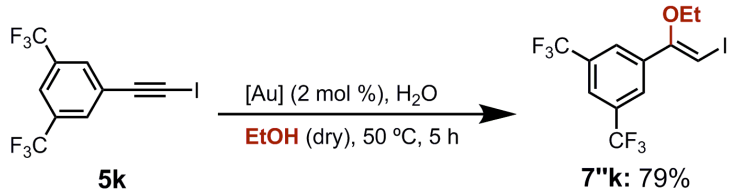
With the optimal conditions at hand, the reaction scope was investigated (Scheme 4.17). The hydration conditions can tolerate different substitutions in *meta*- and *para*-positions of the aromatic ring, and the corresponding products can be isolated in good to excellent yields. Other substrates are currently being tested in our research group to further expand the substrate scope.



Reaction conditions: iodoalkyne (0.50 mmol), H_2O (1.00 mmol), [Au(NTf$_2$)(IPr)] (2 mol%), toluene (0.75 mL), EtOH (0.75 mL), 50 ºC, 24 h. Isolated yields.

Scheme 4.17. Scope of the Au(I)-catalysed hydration of 1-iodoalkynes.[a]

An interesting observation was made when the highly electron-withdrawing 1-(iodoethynyl)-3,5-bis(trifluoromethyl)benzene (**5k**) was used as substrate. The optimised conditions did not afford any trace of the iodoketone; instead, the monoalkoxylation product **7''k** was isolated in 80% yield (Scheme 4.18).

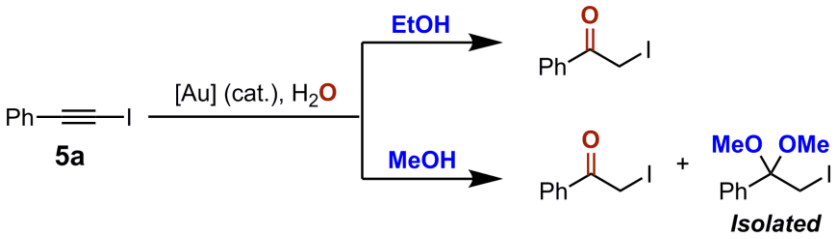


5k **7''k:** 79%

Scheme 4.18. Au-promoted hydroalkoxylation of 1-(iodoethynyl)-3,5-bis(trifluoromethyl)benzene (**5k**).

This species has never been isolated for any other substrate in the presented scope, thus evidencing the presence of a competitive side-reaction, most likely promoted by the electron-poor nature of **5k**. While this type of products have been reported to hydrolyse under acidic conditions to yield the corresponding ketones, our experimental attempts to hydrolyse **7''k** into **7k** were not clean, with substantial side reactivity observed in the process. Current investigations are exploring the hydration of other electron-deficient substrates to establish a possible reactivity trend, as well as more consistent hydrolysis methods for the selective liberation of the desired ketones.

The presence of hydroalkoxylation products was not new in our studies, since during our early optimisation tests for the hydration of **5a,** partial nucleophilic attack of the alcohol solvent (MeOH) to this substrate was observed under certain reaction conditions involving high [Au] loadings. Under these conditions, although monoalkoxylation products were not observed, the dialkoxylation product could be identified and isolated in poor yields (Scheme 4.19). This further supports the crucial importance of the use of EtOH as solvent for the selective hydration of 1-iodoalkynes into the corresponding α-iodomethyl ketones. Some discussion about the effect of the solvent in Au-catalysed hydration of internal alkynes is available in the literature,[40] although no analogous studies for haloalkynes are available.



Scheme 4.19. Selectivity of the Au-catalysed hydration of **5a** in the presence of MeOH or EtOH as solvent.

4.3.3 Mechanistic studies

4.3.3.1 Hydration of 5a

The mechanism for the hydration of 1-iodoalkynes can now be discussed. No mechanism has been presented in the literature for the hydration of these substrates; nevertheless, the structural similarities to general alkynes suggest that similar hydration pathways might be involved. Based on these background studies, and considering our experimental observations, a mechanistic proposal for the Au-catalysed hydration of 1-iodoalkynes in EtOH as solvent can be depicted (Figure 4.7). The neutral Au(I) complex (Figure 4.7, **A**), in equilibrium with its active cationic form (Figure 4.7, **B**), can activate the iodoalkyne *via* π-coordination (Figure 4.7, **C**). The resulting species can then be attacked by a molecule of water (Figure 4.7, **D**), which readily deprotonates to generate the gold(I) enol species (Figure 4.7, **E**). Upon protodeauration, the cationic Au fragment is released back into the catalytic cycle, together with the corresponding iodoenol (Figure 4.7, **F**), which can tautomerise to yield the desired iodoketone.

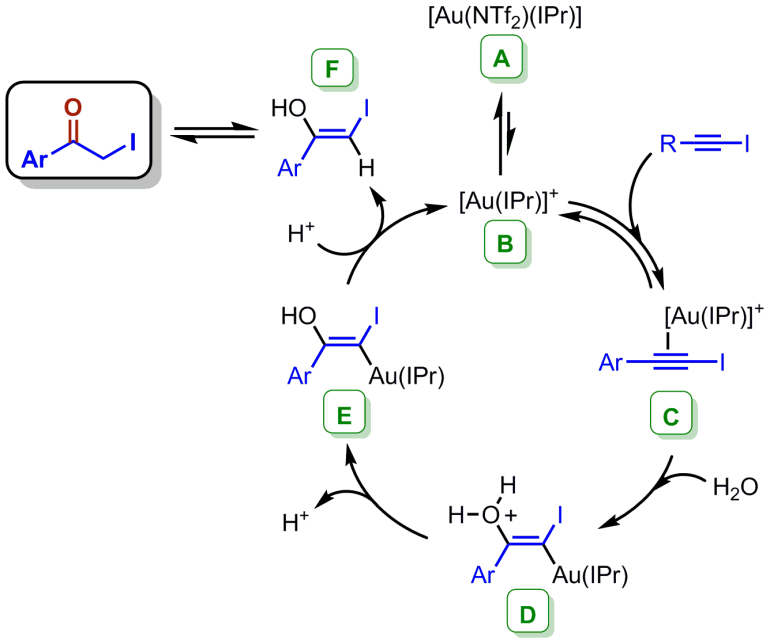


Figure 4.7. Proposed mechanism for the Au-catalysed hydration of 1-iodoalkynes.

This mechanism will compete with the nucleophilic addition of EtOH for the case of **5k**, which will proceed through a similar catalytic cycle where the added nucleophile is an alcohol molecule, and where species **F** will be the final hydroalkoxylation product. The competitiveness of these reactions is being further studied within our research labs.

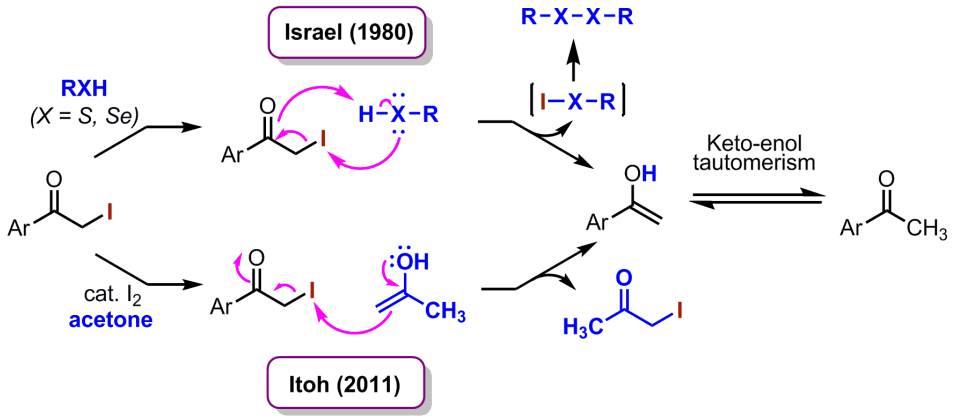
As mentioned before, recent studies on the mechanism of the Au-catalysed hydration of alkynes has shed some light into the effect of the solvent in the involved steps in the hydration reaction.[40] This study has provided consistent proofs of the importance of the solvent for the lowering of reaction barriers and also for proton transfer from water to alkyne substrates (in our case, a concerted transformation of species **D** into species **F**, see Figure 4.7). Another important revised effect is related to the present anions from the initial Au species, which present a non-innocent role to promote efficient hydration of alkynes.[41] Among their conclusions, the positive effect of anions containing an -SO_3 fragment is in accordance with the optimal performance of [Au(NTf_2)(IPr)] as catalyst for the presented hydration of 1-iodoalkynes. Both contributions are nowadays purely speculative for our reaction system, and therefore further evidence is to be gathered for a full comprehension of the hydration mechanism for 1-iodoalkynes.

4.3.3.2 Hydration/deiodination of 5a

The formation of the deiodinated product **7'a** from its corresponding α-iodomethyl ketone **7a** has been reported in the literature, and two different pathways have been proposed to operate in this reaction:

- Israel and co-workers reported the deiodination of α-iodomethyl ketones in the presence of thiols and selenols.[42] The proposed mechanism involves deiodination by the heteroatom, followed by deprotonation of the X-H bonds (X = S or Se), generating the corresponding enol. This molecule can then tautomerise to the desired methylketone. The generated R-X-I intermediates (X = S or Se) are unstable species that will undergo fast homocoupling with excess thiol/selenol to generate disulfides or diselenides, respectively (Scheme 4.20, top). The presence of disulfides was confirmed by vapor-phase chromatography, therefore supporting the validity of this mechanism.

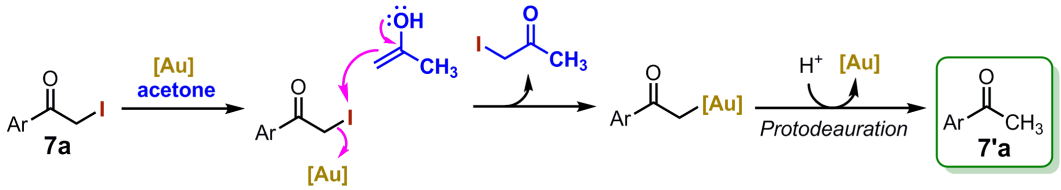
- The combination of acetone and Lewis acids has been recently proposed to promote deiodination of α-iodomethyl ketones. Itoh and co-workers observed this unexpected product, and suggested a reaction pathway for its preparation involving the activation of these substrates by catalytic I_2 (acting as Lewis acid) towards iodine abstraction by the enol of acetone, releasing α-iodoacetone and the corresponding methylketone in the process (Scheme 4.20, bottom).[43]



Scheme 4.20. Mechanistic proposals for the deiodination of α-iodomethyl ketones.

Both mechanisms seemed operative in our system, depending on the employed reaction conditions . The proposed mechanism for the deiodination of **7a** into **7'a** using a [Au]/acetone system is presented in Scheme 4.21. In an initial step, the enol of acetone deiodinates **7a** with concomitant formation of a C-Au bond. The resulting ketoalkyl

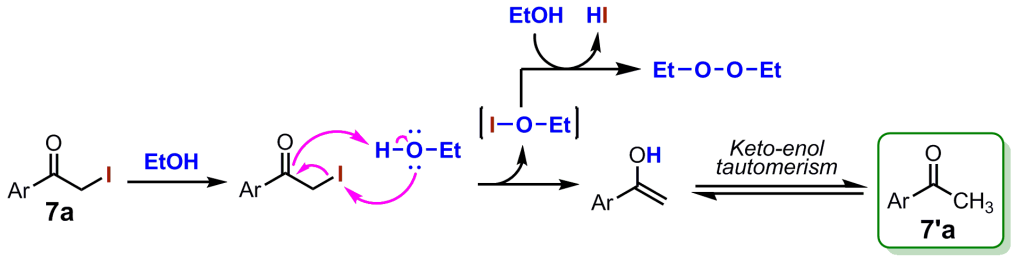
gold(I) species can then undergo protodeauration to generate the expected side product **7'a**.



Scheme 4.21. Proposed mechanism for the deiodination of **7a** in the presence of acetone.

On the other hand, proposing a reaction mechanism to explain the deiodination product observed in an acetone-free system is a more difficult task. This is due to the impossibility to unequivocally detect any involved intermediate during our experiments. As a result, only speculative mechanisms can be proposed to date, which are the object of further studies in our group in the current days.

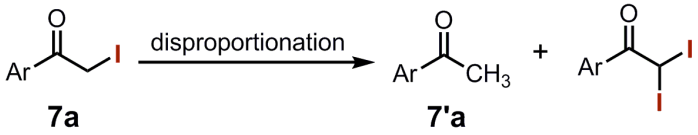
Initially, an analogous pathway to the aforementioned thiol-promoted deiodination proposal could be proposed. In this case, alcohols will promote the deiodination of **7a,** with the resulting enol tautomerising to the methyl ketone **7'a**. Unstable EtOI is formed in the process, and similarly to thiols and selenols, this species could undergo homocoupling with excess EtOH to generate ethyl peroxide as side-product (Scheme 4.22). The presence of the organic hypoiodite in the reaction mixture has not been confirmed to date, with the chemistry literature lacking consistent structural/chemical information to support this route.[44]



Scheme 4.22. Proposed mechanism for the acetone-free deiodination of **7a.**

Alternatively, a disproportionation reaction of the α-iodoketones can be proposed (Scheme 4.23). This reaction will lead to the corresponding methylketone and α,α-diiodoketone. This type of disproportionation has been observed by Voronkov and co-workers, although being performed under inert and photochemical conditions (λ =

254 nm).[45] Again, no experimental evidence about a similar mechanism being operative in our system has been gathered thus far.



Scheme 4.23. Alternative mechanism for the synthesis of **7'a** *via* disproportionation of **7a**.

4.4 Conclusions

In summary, two new Au(I)-catalysed funcionalisation methodologies for 1-iodoalkynes have been designed. The utility of Au(I)-NHC bifluorides as catalysts in hydrofluorination chemistry of internal alkynes has been extended to these terminal alkyne derivatives, obtaining fluoroiodoalkenes with high regio- and stereoselectivity. Moreover, the hydration of 1-iodoalkynes using a Au(I)-NHC catalyst represents the first optimised procedure for the hydration of 1-iodoalkynes, and can now be postulated as a very straightforward synthetic pathway for the preparation of α-iodomethyl ketones, a group of synthetically versatile building blocks. In both cases, good performance of the Au(I)-NHC catalytic systems under fairly mild conditions was observed, with a good number of examples having been prepared and isolated. These methodologies will certainly be interesting synthetic approaches in organic synthesis for the efficient preparation of organic molecules derived from fluoroalkenes and ketones.

4.5 References

(1) These structures can be found as reaction intermediates in various synthetic routes. For a representative example of a concise route employing these building blocks in complex synthesis, see: T. Guan, M. Yoshida, D. Ota, T. Fukuhara and S. Hara, *J. Fluorine Chem.* 2005, **126**, 1185.

(2) For some examples, see: a) D. F. Shellhamer, B. C. Jones, B. J. Pettus, T. L. Pettus, J. M. Stringer and V. L. Heasley, *J. Fluorine Chem.* 1998, **88**, 37; b) P. Conte, B. Panunzi and M. Tingoli, *Tetrahedron Lett.* 2006, **47**, 273; c) H. Ukigai and S. Hara, *Tetrahedron Lett.* 2016, **57,** 1379.

(3) H. Yamanaka, T. Araki, M. Kuwabara, K. Fukunishi and M. Nomura, *Nippon Kagaku Kaishi*, 1986, **10**, 1321.

(4) S. Saito, T. Kawasaki, N. Tsuboya and Y. Yamamoto, *J. Org. Chem.* 2001, **66**, 796.

(5) a) T. Konno, J. Chae, M. Kanda, G. Nagai, K. Tamura, T. Ishihara and H. Yamanaka, *Tetrahedron*, 2003, **59**, 7571; b) T. Konno, M. Kishi, T. Ishihara and S. Yamada, *J. Fluorine Chem.* 2013, **156**, 144.

(6) T. Unemoto and Y. Gotoh, *Bull. Chem. Soc. Jpn.* 1987, **60**, 3307.

(7) M. Ochiai, K Oshima and Y. Masaki, *Chem. Lett.* 1994, 871.

(8) a) S. Hara, M. Yoshida, T. Fukuhara and N. Yoneda, *Chem. Commun.* 1998, 965; b) M. Yoshida, K. Kawakami and S. Hara, *Synthesis*, 2004, **17**, 2821.

(9) M. Yoshida, A. Komata and S. Hara, *J. Fluorine Chem.* 2004, **125**, 527.

(10) For some selected examples, see: a) M. Yoshida, N. Nishimura and S. Hara, *Chem. Commun.* 2002, **9**, 1014; b) L. I. Dixon, M. A. Carrol, T. J. Gregson, G. J. Ellames, R. W. Harrington and W. Clegg, *Eur. J. Org. Chem.* 2013, **12**, 2334; c) T. Kitamura, C. H. Lee, H. Tanigushi, M. Matsumoto and Y. Sano, *J. Org. Chem.* 1994, **59**, 8053.

(11) a) M. Yoshida and S. Hara, *Org. Lett.* 2003, **5**, 573; b) M. Yoshida, A. Komata and S. Hara, *Tetrahedron*, 2006, **62**, 8636.

(12) S. Hara, T. Guan and M. Yoshida, *Org. Lett.* 2006, **8**, 2639.

(13) a) A. Gregorčič and M. Zupan, *Bull. Chem. Soc. Jpn.* 1987, **60**, 3083; b) S. Kobayashi, M. Sawaguchi, S. Ayuba, T. Fukuhara and S. Hara, *Synlett*, 2001, **12**, 1938; c) M. S. Wiehn, S. D. Lindell and S. Bräse, *Angew. Chem. Int. Ed.* 2008, **47**, 8120.

(14) For the original reference of the synthesis of IF_5-pyridine-HF, see: S. Hara, M. Monoi, R. Umemura and C. Fuse, *Tetrahedron*, 2012, **68**, 10145.

(15) Y. Li, X. Liu, D. Ma, B. Liu and H. Jiang, *Adv. Synth. Catal.* 2012, **354**, 2683.

(16) B. Métayer, G. Compain, K. Jouvin, A. Martin-Mingot, C. Bachmann, J. Marrot, G. Evano and S. Thibaudeau, *J. Org. Chem.* 2015, **80**, 3397.

(17) F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan and S. P. Nolan, *ChemCatChem.* 2015, **7**, 240.

(18) W. Markovnikoff, *Ann. Pharm.* 1870, **153**, 228.

(19) For some selected examples, see: a) A. W. Erian, S. M. Sherif and H. M. Gaber, *Molecules*, 2003, **8**, 793; b) Y.-P. Zhu, F.-C. Jia, M.-C. Liu and A.-X. Wu, *Org. Lett.* 2012, **14**, 4414; c) Q.-H. Gao, Z. Fei, Y.-P. Zhu, M. Lian, F.-C. Jia, M.-C.

Liu, N.-F. She and A.-X. Wu, *Tetrahedron*, 2013, **69**, 22; d) K. K. D. R. Viswanadham, M. P. Reddy, P. Sathyanarayana, O. Ravi, R. Kant and S. R. Bathula, *Chem. Commun.* 2014, **50**, 13517; e) Q. Gao, X. Wu, S. Liu and A. Wu, *Org. Lett.* 2014, **16**, 1732; f) W.-J. Xue, K.-L. Zheng, H.-Z. Li, F.-F. Gao and A.-X. Wu, *Tetrahedron Lett.* 2014, **55**, 4212.

(20) For some examples, see: a) G. Yin, B. Zhou, X. Meng, A. Wu and Y. Pan, *Org. Lett.* 2006, **8**, 2245; b) C. De Dobbeleer, J. Pospíšil, F. De Vleeschouwer, F. De Proft and I. E. Markó, *Chem. Commun.* 2009, 2142; c) M. Gao, Y. Yang, Y.-D. Wu, C. Deng, L.-P. Cao, X.-G. Meng and A.-X. Wu, *Org. Lett.* 2010, **12**, 1856; d) Y.-P. Zhu, M.-C. Liu, F.-C. Jia, J.-J. Yuan, Q.-H. Gao, M. Lian and A.-X. Wu, *Org. Lett.* 2012, **14**, 3392; e) F.-C. Jia, Y.-P. Zhu, M.-C. Liu, M. Lian, Q.-H. Gao, Q. Cai and A.-X. Wu, *Tetrahedron*, 2013, **69**, 7038; f) Y.-P. Zhu, Q. Cai, Q.-H. Gao, F.-C. Jia, M.-C. Liu, M. Gao and A.-X. Wu, *Tetrahedron*, 2013, **69**, 6392; g) H.-Z. Li, W.-J. Xue and A.-X. Wu, *Tetrahedron*, 2014, **70**, 4645; h) M. R. Reddy, N. N. Rao, K. Ramakrishna and H. M. Meshram, *Tetrahedron Lett.* 2014, **55**, 1898; i) G. Majji, S. Rajamanickam, N. Khatun, S. K. Santra and B. K. Patel, *J. Org. Chem.* 2015, **80**, 3440.

(21) M. Ikeda, H. Teranishi, K. Nozaki, H. Ishibashi, *J. Chem. Soc. Perkin Trans. 1*, 1998, **10**, 1691.

(22) Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada and Y. Hirata, *Tetrahedron*, 1971, **27**, 5157.

(23) G. Lapointe, K. Schenk and P. Renaud, *Org. Lett.* 2011, **13**, 4774.

(24) For other selected examples, see: a) K. R. Campos, C. Chen, H. Ishibashi, S. Kato, A. Klapars, Y. Kohmura, D. J. Pollard, A. Takezawa, J. H. Waldman, D. Wallace, N. Yasuda, WO 2008021029 A2, **2008**; b) C. Gryparis, I. N. Lykakis, C. Efe, I.-P. Zaravinos, T. Vidali, E. Kladou and M. Stratakis, *Org. Biomol. Chem.* 2011, **9**, 5655; c) G. Lapointe, A. Kapat, K. Weidner and P. Renaud, *Pure. Appl. Chem.* 2012, **84**, 1633.

(25) For selected examples, see: a) B. Šket and M. Zupan, *Tetrahedron*, 1984, **40**, 2865; b) S. Stavber, M. Jereb and M. Zupan, *Chem. Commun.* 2002, 488; c) T. Okamoto, T. Kakinami, T. Nishimura, I.- Hermawan and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.* 1992, **65**, 1731; d) J. C. Lee and Y. H. Bae, *Synlett*, 2003, **4**, 507; e) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros, J. M.

González, *Chem. Commun.* 2004, 2616; f) J. C. Lee, J. Y. Park, S. Y. Yoon, Y. H. Bae, S. J. Lee, *Tetrahedron Lett.* 2004, **45**, 191; g) M. L. N. Rao and D. N. Jadhav, *Tetrahedron Lett.* 2006, **47**, 6883; h) M. A. Khalilzadeh, A. Hosseini, M. Shokrollahzadeh, M. R. Halvagar, D. Ahmadi, F. Mohannazadeh and M. Tajbakhsh, *Tetrahedron Lett.* 2006, **47**, 3525; i) G. Yin, M. Gao, N. She, S. Hu, A. Wu and Y. Pan, *Synthesis*, 2007, **20**, 3113; j) J. Pavlinac, M. Zupan and S. Stavber, *Org. Biomol. Chem.* 2007, **5**, 699; k) J. Iskra, S. Stavber and M. Zupan, *Tetrahedron Lett.* 2008, **49**, 893; l) G. Stavber, J. Iskra, M. Zupan and S. Stavber, *Adv. Synth. Catal.* 2008, **350**, 2921; m) I. Pravst, M. Zupan and S. Stavber, *Tetrahedron*, 2008, **64**, 5191; n) J. S. Yadav, G. Kondaji, M. S. R. Reddy and P. Srihari, *Tetrahedron Lett.* 2008, **49**, 3810; o) G. Stavber, J. Iskra, M. Zupan and S. Stavber, *Green Chem.* 2009, **11**, 1262; p) M. M. Reddy, M. A. Kumar, P. Swamy and N. Narender, *Tetrahedron Lett.* 2011, **52**, 6554; q) R. Prebil and S. Stavber, *Tetrahedron Lett.* 2014, **55**, 5643.

(26) For selected examples, see: a) R. C. Cambie, R. C. Hayward, J. L. Jurlina, P. S. Rutledge and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 1978, 126; b) Y. D. Vankar and G. Kumaravel, *Tetrahedron Lett.* 1984, **25**, 233; c) J. M. Aizpurua, M. Juaristi, B. Lecea and C. Palomo, *Tetrahedron*, 1985, **41**, 2903; d) C.-K. Sha, J.-J. Young and T.-S. Jean, *J. Org. Chem.* 1987, **52**, 3919; e) A. D. Cort, *J. Org. Chem.* 1991, **56**, 6708.

(27) For selected examples, see: a) G. Cardillo and M. Shimizu, *J. Org. Chem.* 1977, **42**, 4268; b) R. D. Evans and J. H. Schauble, *Synthesis*, 1986, 727; c) H. Nakayama and A. Itoh, *Tetrahedron Lett.* 2007, **48**, 1131; d) J. S. Yadav, B. V. S. Reddy, A. P. Singh, A. K. Basak, *Tetrahedron Lett.* 2008, **49**, 5880; e) J. N. Moorthy, K. Senapati and N. Singhal, *Tetrahedron Lett.* 2009**,** **50**, 2493; f) T. Nobuta, S.-I. Hirashima, N. Tada, T. Miura and A. Itoh, *Synlett*, 2010, **15**, 2335; g) H. P. Kalmode, K. S. Vadagaonkar and A. C. Chaskar, *RSC Adv.* 2014, **4**, 60316; h) P. Klahn, H. Erhardt, A. Kotthaus and S. F. Kirsch, *Angew. Chem. Int. Ed.* 2014, **53**, 7913; i) T. K. Achar, S. Maiti and P. Mal, *RSC Adv.* 2014, **4**, 12834; j) K. S. Vadagaonkar, H. P. Kalmode, K. Murugan and A. C. Chaskar, *RSC Adv.* 2015, **5**, 5580; k) S. Dutta, S. S. Kotha and G. Sekar, *RSC Adv.* 2015, **5**, 47265.

(28) a) M. Shimizu, H. Okimura, N. Manabe and I. Hachiya, *Chem. Lett.* 2008, **37**, 28; b) S. L. Bartlett and C. M. Beaudry, *J. Org. Chem.* 2011, **76**, 9852; c) M.

Takahashi, N. Suzuki and T. Ishikawa, *J. Org. Chem.* 2013, **78**, 3250; d) M. M. Reddy, P. Swamy, M. Naresh, K. Srujana, C. Durgaiah, T. V. Rao and N. Narender, *RCS Adv.* 2015, **5**, 12186.

(29) For some selected examples, see: a) J. C. Lee and Y. S. Jin, *Synth. Commun.* 1999, **29**, 2769; c) A. R. Kiasat and S. Sayyahi, *Mol Divers.* 2010, **14**, 155; d) S. Sayyahi and J. Saghanezhad, *Chin. Chem. Lett.* 2011, **22**, 300.

(30) T. Ando, S. Shioi and M. Nakagawa, *Bull. Chem. Soc. Jpn.* 1972, **45**, 2611.

(31) For selected reviews, see: a) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem. Int. Ed.* 2004, **43**, 3368; b) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev*. 2004, **104**, 3079; c) L. Hintermann and A. Labonne, *Synthesis*, 2007, **8**, 1121.

(32) For some selected examples, see: a) E. Mizushima, K. Sato, T. Hayashi and M. Tanaka, *Angew. Chem. Int. Ed.* 2002, **41**, 4563; b) R. Casado, M. Contel, M. Laguna, P. Romero and S. Sanz, *J. Am. Chem. Soc.* 2003, **125**, 11925; c) S. Sanz, L. A. Jones, F. Mohr and M. Laguna, *Organometallics*, 2007, **26**, 952; d) A. Leyva and A. Corma, *J. Org. Chem.* 2009, **74**, 2067; e) A. Almassy, C. E. Nagy, A. C. Benyei and F. Joo, *Organometallics*, 2010, **29**, 2484; f) P. Nun, S. Dupuy, S. Gaillard, A. Poater, L. Cavallo and S. P. Nolan, *Catal. Sci. Technol.* 2011, **1**, 58; g) P. Nun, R. S. Ramon, S. Gaillard and S. P. Nolan, *J. Organomet. Chem.* 2011, **696**, 7; h) M. Bouhrara, E. Jeanneau, L. Veyre, C. Copéret and C. Thieuleux, *Dalton Trans.* 2011, **40**, 2995; i) C. Tubaro, M. Baron, A. Biffis and M. Basato, *Beilstein J. Org. Chem.* 2013, 9, 246; j) X. Xu, S. H. Kim, X. Zhang, A. K. Das, H. Hirao and S. H. Hong, 2013, **32**, 164; k) N. Ghosh, S. Nayak, B. K. Prabagar and A. Sahoo, *J. Org. Chem.* 2014, **79**, 2453; l) J. Cordón, J. Jiménez-Osés, J. López-de-Luzuriaga, M. Monge, M. E. Olmos and D. Pascual, *Organometallics*, 2014, **33**, 3823; m) T. R. Pradhan, K. L. Mendhekar and D. K. Mohapatra, *J. Org. Chem.* 2015, **80**, 5517; n) T. Chen and C. Cai, *Catal. Commun.* 2015, **65**, 102; o) F. Li, N. Wang, L. Lu and G. Zhu, *J. Org. Chem.* 2015, **80**, 3538.

(33) P. Starkov, F. Rota, J. M. D'Oyley and T. D. Sheppard, *Adv. Synth. Catal.* 2012, **354**, 3217.

(34) L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang and W. He, *J. Org. Chem.* 2013, **78**, 9190.

(35) Z.-W. Chen, D.-N. Ye, M. Ye, Z.-G. Zhou, S.-H. Li and L.-X. Liu, *Tetrahedron Lett.* 2014, **55**, 1373.

(36) H. Zou, W. He, Q. Dong, R. Wang, N. Yi, J. Jiang, D. Pen and W. He, *Eur. J. Org.*

Chem. 2016, 116.

(37) M. Zeng, R.-X. Huang, W.-Y. Li, X.-W. Liu, F.-L. He, Y.-Y. Zhang and F. Xiao, *Tetrahedron*, 2016, **72**, 3818.

(38) A. Gómez-Suárez, Y. Oonishi, S. Meiries and S. P. Nolan, *Organometallics*, 2013, **32**, 1106.

(39) L. Ricard and F. Gagosz, *Organometallics*, 2007**, 26**, 4704.

(40) C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, *ChemCatChem*. 2010, **2**, 1226

(41) a) M. Trinchillo, P. Belanzoni, L. Belpassi, L. Biasiolo, V. Busico, A. D'Amora, L. D'Amore, A. Del Zotto, F. Tarantelli, A. Tuzi and D. Zuccaccia, *Organometallics*, 2016, **35**, 641; b) L. Biasiolo, M. Trinchillo, P. Belanzoni, L. Belpassi, V. Busico, G. Ciancaleoni, A. D'Amora, A. Macchioni, F. Tarantelli and D. Zuccaccia, *Chem. Eur. J.* 2016, **20**, 14594.

(42) R. Seshadri, W. J. Pegg and M. Israel, *J. Org. Chem.* 1981, **46**, 2596.

(43) T. Nobuta, S.-I. Hirashima, N. Tada, T. Miura and A. Itoh, *Org. Lett.* 2011, **13**, 2576.

(44) a) K. Baum and C. D. Beard, *J. Org. Chem.* 1975, **40**, 2536; b) R. J. H. Clark and J. R. Dann, *J. Phys. Chem.* 1996, **100**, 532.

(45) L. G. Shagun, I. A. Dorofeev, L. V. Klyba, I. A. Tokareva and M. G. Voronkov, *Russ. J. Org. Chem.* 2008, **44**, 1549.

CHAPTER 5

Functionalised 1-Iodoalkyne Derivatives: Reactivity and Application in Sequential Synthesis

5.1 Introduction

In the previous chapter, the preparation of fluoroiodoalkenes and α-iodomethyl ketones using Au(I)-NHC complexes has provided new and very interesting methods for synthesis. Taking a closer look at these products, the presence of a C-I bond still represents an opportunity into further functionalisation of these scaffolds. The exploitation of this remaining reactivity of the prepared molecules is detailed within this chapter. First, the studies on the cross-coupling chemistry using fluoroiodoalkenes as substrates, involving either boronic acids or terminal alkynes as coupling partners, will be disscused. The invaluable utility of Pd(II)-NHC catalysts in cross-coupling reactions, a known application for such complexes, can now be expanded to these particular coupling partners, further highlighting its versatility in modern coupling chemistry. On the other hand, the reactivity of α-iodomethyl ketones towards a variety of new species has been acknowledged by reproducing several reports available in the literature.

Finally, a very interesting synthetic approach will be discussed: the use of sequential chemistry involving our catalytic systems. By performing suitable combinations of the presented reactions in a sequential manner, terminal alkynes could be easily converted to a wide range of new organic molecules, without the need for the costly and time-consuming isolation of each intermediate. Our success in this line of study is represented in this chapter by extensive optimisation studies, which have led to a succesful integration of sequential synthetic methods employing Au(I)- and Pd(II)-NHC catalysts (Figure 5.1).

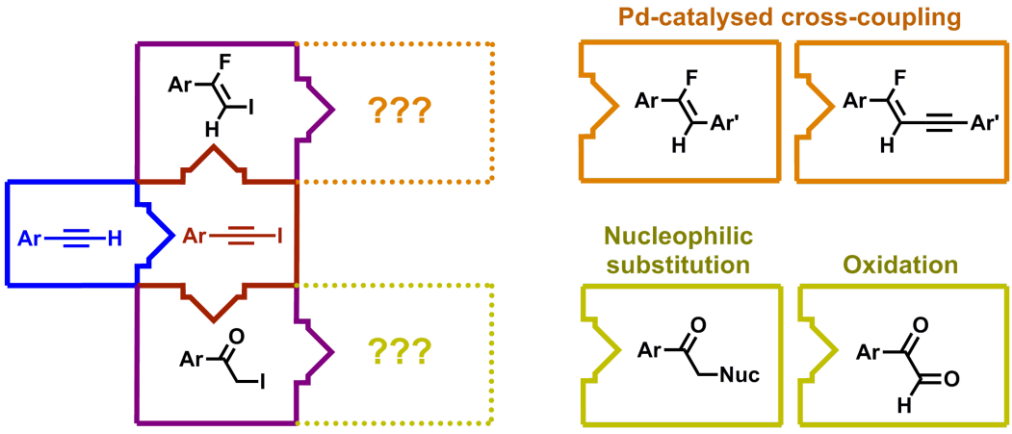


Figure 5.1 Proposed synthesis applications of fluoroiodoalkenes and α-iodomethyl ketones for stepwise or sequential organic synthesis.

5.2 Fluoroiodoalkenes: reactivity studies

5.2.1 Introduction

In organic synthesis, the traditional reactivity of carbon-halogen bonds towards substitution reactions with nucleophiles is well documented. While this type of nucleophilic substitution reactions (S_N) has been used for the synthesis of a wide range of molecules, the attractiveness of the original concept of these reactions has diminished in recent times. This is due to the strict control of the reaction conditions for optimal selectivity, the presence of competing mechanisms (S_N1 vs S_N2) and the low performance of these reactions in more complex systems, reducing the range of useful applications for these reactions.

However, the use of the electrophilicity of the carbon atom in C-X bonds (X = Cl, Br, I) has not been rejected in synthesis. In fact, a new generation of reactions, employing new types of formal nucleophilic substitution of organic halides, has become one of the most admired and powerful family of protocols. This is particularly important in the field of C-C bond formation, where these novel coupling approaches have stood out.

The fluorinated haloalkenes, prepared as described in Chapter 4, conform to a family of molecules that could be used in cross-coupling chemistry. By activating C-I or C-Br bonds towards nucleophilic attack, the fluorohaloalkene moiety could be transformed into trisubstituted fluoroalkenes, a complex and very interesting molecular fragment in organic chemistry.

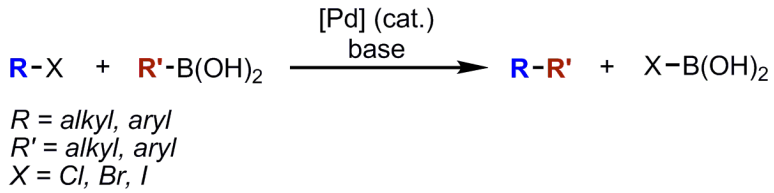
In view of this, the exploration of the reactivity of fluorohaloalkenes towards the addition of carbon-based nucleophiles was discussed within our research group. The results of our experimental work will be discussed in the following sections.

5.2.2 Suzuki-Miyaura cross-coupling with boronic acids

5.2.2.1 Trisubstituted fluoroalkenes: state-of-the-art

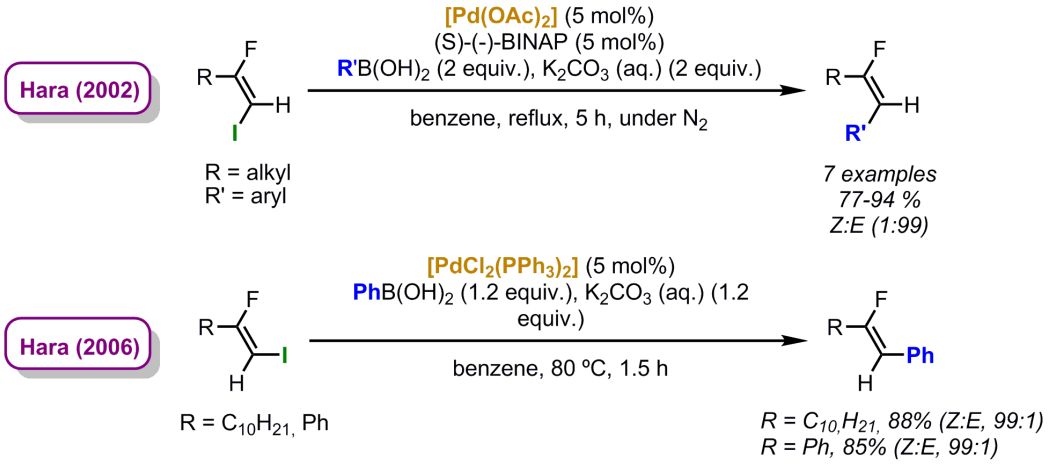
The Suzuki-Miyaura cross-coupling is one of the most well-known cross-coupling transformations within the organic synthesis community. The immense bibliography on this reaction can set up a perfect background for the understanding of this reaction,[1,2] which consists on the coupling of organic halides with boronic acids,

promoting C-C bond formation. The reaction requires the presence of a palladium catalyst and a base to proceed efficiently (Scheme 5.1).



Scheme 5.1. General scheme of the Suzuki-Miyaura cross-coupling reaction.

Since the compounds prepared during the course of our studies contain C-X bonds (X = Cl, Br, I), their use in cross-coupling chemistry was considered. Our attention was attracted towards the reactivity of fluoroiodoalkenes towards coupling with boronic acids. This is not a new synthetic concept, as Hara and co-workers have already detailed two procedures involving Pd(II) catalysts and phosphine ligands for the transformation of fluoroiodoalkenes into the corresponding trisubstituted fluoroalkenes (Scheme 5.2).[3] Both (*Z*)- and (*E*)-fluoroiodoalkenes could be efficiently converted to their corresponding cross-coupled products, maintaining high stereoselectivity (99:1) based on the starting configuration of the substrate.



Scheme 5.2. State-of-the-art in cross-coupling of fluorohaloalkenes with boronic acids using Pd-phosphine catalysts.

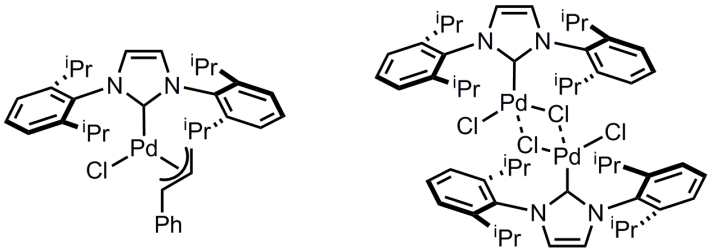
This approach towards cross-coupling of fluoroiodoalkenes is interesting for the synthesis of more complex molecules, as shown in a number of reported examples,[4] thus highlighting the interest of the synthetic community in such protocols.

It is however surprising that no other catalytic system based on palladium has been explored so far for this transformation, especially considering the intensive study of coupling chemistry using other families of Pd(II) complexes. Among those, our

interest in the use of Pd-NHC species was in line with the research aims in our group. With an abundant application of these complexes in general cross-coupling,[5] their application for this particular transformation certainly deserved some attention, as it could provide an alternative to phosphine-based methods and, eventually, a step forward into more efficient coupling chemistry. Circumventing the drawbacks of the reported procedures (such as fairly high Pd loadings, use of benzene as non-green solvent, or a reduced number of reported examples, among others) was also an important reason to further investigate this reaction.

As mentioned before, the use of Pd(II)-NHC catalysts in general Suzuki-Miyaura cross-coupling chemistry is nowadays well documented, with a wide variety of protocols being deeply studied and the involved mechanisms being profoundly analysed and discussed. The most common structure in active palladium catalysts for Suzuki-Miyaura coupling is based on an NHC-Pd(II)-allyl skeleton. These Pd(II) species are generally air- and moisture-stable precursors that have outstanding catalytic properties. In view of this, the feasibility of cross-coupling chemistry to further increment the complexity and the value of fluoroiodoalkenes as building blocks was experimentally tested. The optimisation studies for the Pd(II)-catalysed Suzuki-Miyaura cross-coupling reaction with fluoroiodoalkenes as substrates will next be presented.

5.2.2.2 Results and discussion



Pd-1
[Pd(η^3-cinnamyl)(Cl)(IPr)]

Pd-2
[Pd(μ-Cl)(Cl)(IPr)]$_2$

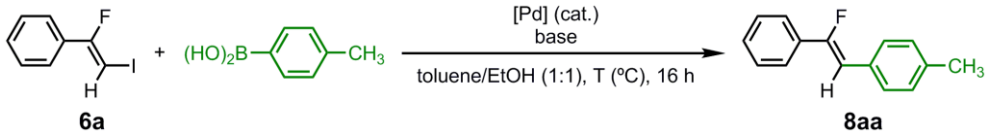
Figure 5.2. Proposed Pd(II)-NHC catalysts for the Suzuki-Miyaura cross-coupling reaction of fluoroiodoalkenes and boronic acids.

Our optimisation started with the use of 2-fluoro-1-iodo-2-phenylethene (**6a**) as a model halide substrate, readily accessible through our previously described hydrofluorination procedure of (iodoethynyl)benzene (**5a**) (see Chapter 4). *p*-Tolylboronic acid was selected as coupling partner, due to its commercial availability and relative structural simplicity for preliminary analyses. [Pd(η^3-cinnamyl)(Cl)(IPr)]

(**Pd-1**) and [Pd(μ-Cl)Cl(IPr)]$_2$ (**Pd-2**) were selected as well-defined Pd(II)-NHC complexes for testing in these studies. Their availability as commercial products and their widespread presence in modern Suzuki-Miyaura coupling reactions in the literature,[6,7] made them a robust choice for testing purposes (Figure 5.2).

The results of the optimisation of this reaction are shown in Table 5.1. The use of both Pd(II) catalysts at 1 mol% in the presence of 1.1 equivalents of the corresponding bases according to the optimal literature procedures,[6d] proved adequate for the reaction between **6a** and *p*-tolylboronic acid in a toluene/EtOH (1:1) mixture at room temperature (Table 5.1, Entries 1-2). The inclusion of toluene in this mixture responds to a characteristic of this system that will be exploited by further experiments, presented later on in this chapter (see Chapter 5.4.2). The use of Pd/C as a simpler and cheaper catalyst did not provide optimal results under these conditions (Table 5.1, Entry 3), therefore highlighting the particularly efficient use of Pd(II)-NHC systems as catalysts. [Pd(η^3-cinnamyl)(Cl)(IPr)] was selected for further optimisation, due to its better performance in the coupling reaction. The increase of the reaction temperature to 50 ºC did not provide significantly better conversion by itself, according to ^{19}F NMR analysis (Table 5.1, Entry 4); however, when combined with a 2 mol% loading of Pd and an increase in the amount of base to two equivalents, full conversion towards the desired cross-coupled **8aa** product was obtained (Table 5.1, Entry 5). This system provided only *Z* isomers of the corresponding trisubstituted fluoroalkenes, thus displaying a stereoselectivity controlled by the substrate. This reaction could also be performed with EtOH as the sole solvent if beneficial for synthetic purposes (Table 5.1, Entry 6). Whereas toluene was unable to convert **6a** optimally (Table 5.1, Entry 6), as expected from the more favorable activation of the Pd(II) catalyst upon usage of alcohols, as previously discussed.[8] Using the conditions reported in Table 5.1, Entry 5, 86% isolated yield for this compound was obtained after simple purification by column chromatography on silica gel.

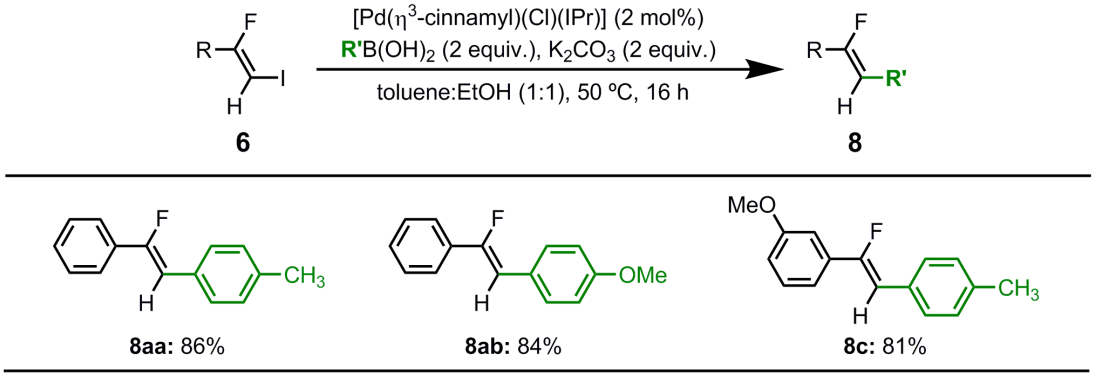
Table 5.1. Optimisation of the Pd-catalysed cross-coupling of **6a** with phenylboronic acid.[a]



Entry	[Pd] (mol%)	Base (equiv.)	T (ºC)	Conversion of 6a (%)[b]
1	Pd-1 (1)	K_2CO_3 (1.1)	25	73
2	Pd-2 (0.5)	NaOMe (1.1)	25	31
3	Pd/C (1)	Na_2CO_3 (2)	25	2
4	Pd-1 (1)	K_2CO_3 (1.1)	50	76
5	**Pd-1 (2)**	**K_2CO_3 (2)**	**50**	**> 99 (86)[e]**
6[c]	Pd-1 (2)	K_2CO_3 (2)	50	54
7[d]	Pd-1 (2)	K_2CO_3 (2)	50	> 99

[a] Reaction conditions: **6a** (0.1 mmol), *p*-tolylboronic acid (0.2 mmol), [Pd] (cat.), solvent (0.2 mL), 16 h. [b] Determined by ^{19}F NMR analysis ($CDCl_3$ as solvent). [c] Toluene as solvent. [d] EtOH as solvent. [e] Isolated yield in parenthesis.

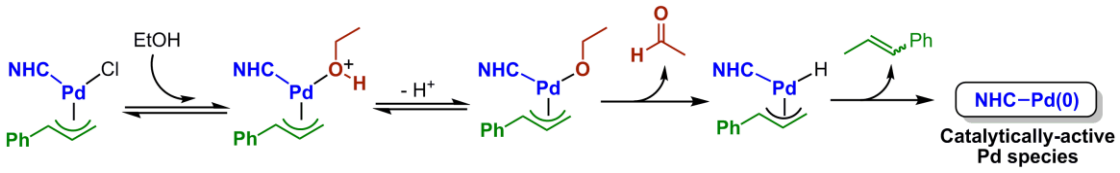
With these conditions in hand, a brief examplification of the reaction was performed (Scheme 5.3). The generality of the system was showcased by obtaining equally good isolated yields when either the boronic acid (**8ab**) or the starting iodoalkene (**8c**) was changed. The obtained products were isolated as pure (*Z*)-alkenes, with no traces of other stereoisomers being detected. The outstanding control over the regio- and stereoselectivity of the final compound must be outlined as the highest attraction of this methodology, as opposed to other available methodologies (such as the hydrofluorination of internal alkynes). As a result of this, the described methodology represents one of the most interesting and competitive approaches towards the synthesis of trisubstituted (*Z*)-fluoroalkenes, and a genuinely good application of fluoroiodoalkenes for the synthesis of complex fluoroalkenes.



[a] Reaction conditions: iodoalkene (0.50 mmol), R'B(OH)$_2$ (1.0 mmol), [Pd(η^3-cinnamyl)(Cl)(IPr)] (2 mol%), K_2CO_3 (1.0 mmol), toluene:EtOH (1:1) (1.0 mL), 50 ºC, 16 h. Isolated yields.

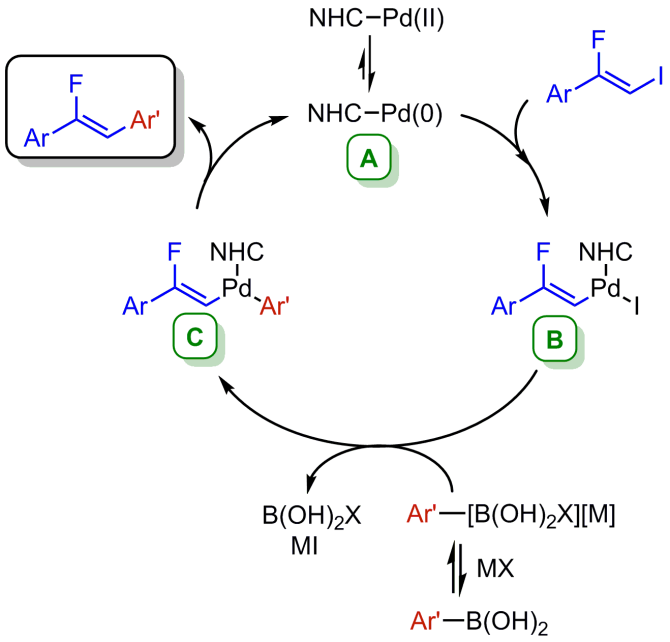
Scheme 5.3. Scope of the Pd-catalysed Suzuki-Miyaura cross-coupling of fluoroiodoalkenes with arylboronic acids.[a]

The proposed mechanism for this reaction is based on the use of Pd(0) species as active catalytic species, using a traditional oxidative addition/reductive elimination sequence. The activation pattern for Pd(II)-NHC to Pd(0)-NHC species in alcohol media is shown in Scheme 5.4. Full computational studies have supported this pathway for Pd(II) reduction to Pd(0) prior to the incorporation of the metal into the catalytic cycle.[8]



Scheme 5.4. Proposed activation pathway for Pd(II)-NHC catalysts in alcohol solvents.[8]

Afterwards, these Pd species (Scheme 5.5, **A**) promotes the oxidative addition of the fluoroiodoalkene, generating the fluoroalkenyl Pd(II) iodide intermediate (Scheme 5.5, **B**). This intermediate reacts with the activated boronic acid, providing the trisubstituted Pd(II) center bearing the required fluoroalkenyl and aryl fragments (Scheme 5.5, **C**). This species can finally undergo reductive elimination, releasing the desired trisubstituted fluoroalkene and regenerating the Pd(0)-NHC species back into the catalytic cycle.

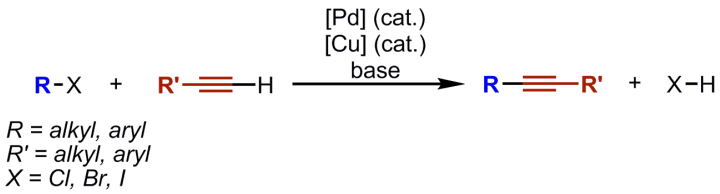


Scheme 5.5. Proposed catalytic cycle for the cross-coupling reaction of fluoroiodoalkenes with arylboronic acids using Pd(II)-NHC catalysts.

5.2.3 Cu(I)-free Sonogashira cross-coupling with terminal alkynes

5.2.3.1 Fluorinated enynes: state-of-the-art

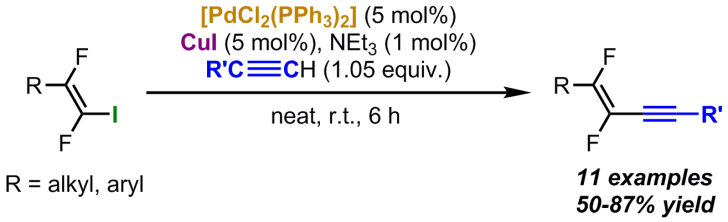
The Sonogashira coupling is another Pd-catalysed transformation for which a lot of attention has been dedicated in the last decades. This reaction consists of the coupling of aryl or vinyl halides with terminal alkynes, yielding the corresponding arylalkynes or enynes, respectively (Scheme 5.6).[9]



Scheme 5.6. General scheme of the Sonogashira cross-coupling reaction.

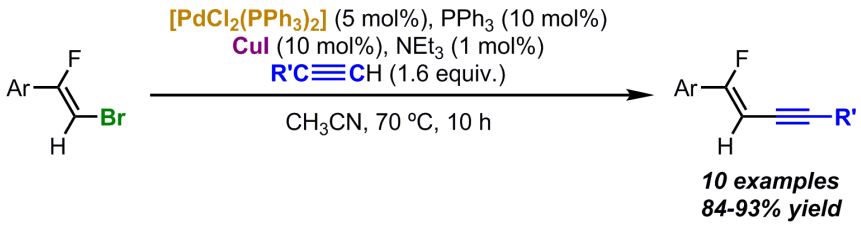
The Sonogashira coupling reaction has also been extensively studied in the literature, with a variety of reports and reviews discussing the conditions, mechanisms and applications of this versatile reaction.[10] As in the case of the Suzuki-Miyaura coupling, fluoroiodoalkenes contain a vinyl halide that could be suitable for Sonogashira-type reactions, in order to access fluorinated enynes starting from fluorohaloalkenes. The concept of this reaction also has limited presence in the

literature. The earliest report on a similar transformation comes from the cross-coupling of difluoroiodoalkenes with terminal alkynes using $[PdCl_2(PPh_3)_2]$ and CuI as dual catalytic system (Scheme 5.7).[11]



Scheme 5.7. First reported Sonogashira coupling of fluorinated iodoalkenes.[11]

This early report from Yang and Burton makes use of a very standarised set of conditions in the Sonogashira coupling, yet it is the only example in the literature where fluorinated iodoalkenes have been used as substrates. The use of bromoalkene derivatives for this type of chemistry has been more commonly reported. Jiang and co-workers explored the utility of a series of bromofluoroalkenes by reacting these substrates with terminal alkynes under Sonogashira conditions. The use of the conventional Pd(II)/Cu(I) mixture reported by Burton, combined with the presence of catalytic PPh_3 and the use of CH_3CN as solvent, permitted the synthesis of 10 examples of TMS-capped fluoroenynes in good to excellent yields (Scheme 5.8).[12]

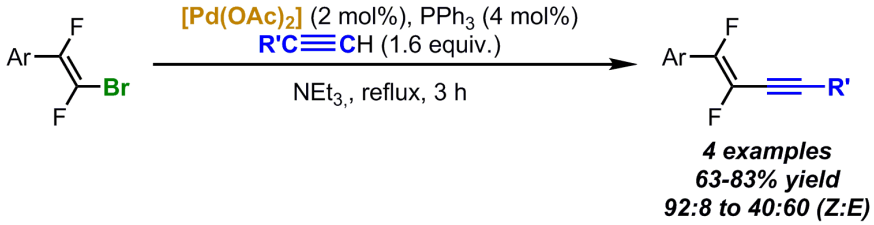


Scheme 5.8. Use of bromofluoroalkenes for Sonogashira coupling.[12]

However, using a simpler catalytic system is greatly desirable. Not only the simplification of the reaction conditions, but also the prevention of side reactivity, was an important concern. The use of Cu(I) as co-catalyst provides the most significant reduction of the system operativity: although it promotes the generation of active acetylide species from the deprotonation of terminal alkynes, the increased activity of such compounds also leads to homocoupling chemistry, releasing 1,3-diynes in the process and neglecting the alkyne source for the Sonogashira coupling.[13]

To overcome this main inconvenience, other approaches have been followed, such as the substitution of Cu by other co-catalysts[14] or the complete removal of such secondary metal source.[15] The latter one retains a much higher importance since it

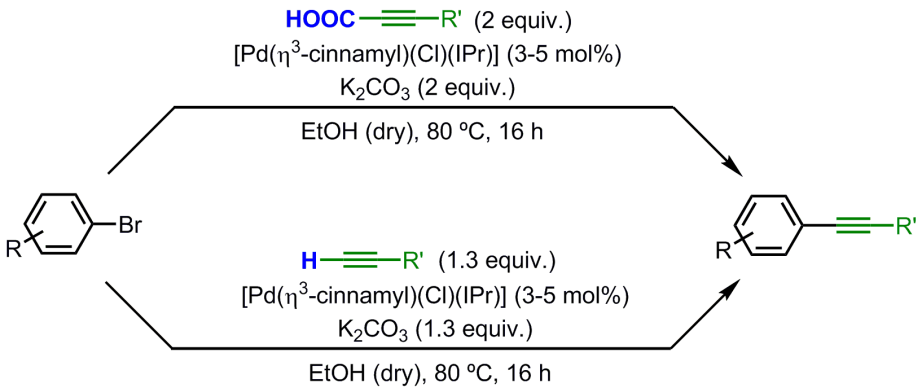
simplifies the required catalytic system and diminishes the operational costs of the reaction. Among the studied approaches, the use of Pd(II) catalyst as the sole pre-catalyst is undoubtedly one of the most powerful synthetic tools within the field; with the catalyst acting as both alkyne activator and cross-coupling mediator. This concept has also been applied to the coupling of fluorohaloalkenes with successful results. Rolando and co-workers used palladium(II) acetate, in conjunction with PPh_3 and NEt_3, for the transformation of mixtures of bromofluoroalkenes and terminal alkynes into the corresponding fluorinated enynes (Scheme 5.9). These forcing conditions (represented by the use of the base as solvent) could still not allow an efficient synthesis of the final compounds, with yields up to 83% and very substrate-dependent stereoselectity of the isolated products.[16]



Scheme 5.9. Copper-free Sonogashira coupling of bromofluoroalkenes.[16]

However, this report is the only reference in the copper-free Sonogashira reaction using fluorohaloalkenes as substrates. Due to this, it represented our starting point for the discussion of a more efficient catalytic system for the synthesis of fluorinated enynes.

Within our research group, and in paralel to our discussions about the utility of fluorohaloalkenes, a new copper-free Sonogashira methodology was developed during this past year. This protocol consisted of the coupling of aryl bromides with propiolic acids, for the generation of internal arylalkynes (Scheme 5.10, top).[16] After the optimisation of the reaction conditions, employing **Pd-1** (see Figure 5.2) as catalyst, it was discovered that not only decarboxylative coupling of propiolic acids could be performed, but also the deprotonative coupling of terminal alkynes could be achieved to provide the corresponding arylalkynes. The later allowed the use of a much more commercially available family of acetylide precursors, while still affording equally good performance towards the desired internal alkynes (Scheme 5.10, bottom).[17]



Scheme 5.10. Pd(II)-catalysed decarboxylative and deprotonative coupling of terminal alkyne derivatives with bromoarenes.[17]

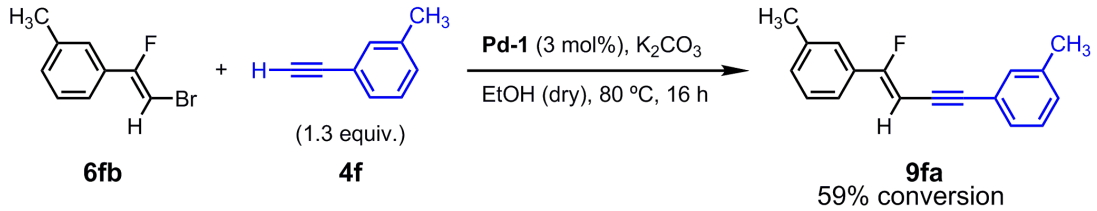
The use of a relatively low amount of base (when compared to other standard copper-free couplings based on Pd), the outstanding reactivity using challenging aryl bromides, and the good performance of a very common Pd(II)-NHC catalyst in our laboratories, encouraged further extension of this reaction to include fluorohaloalkenes. Based on these speculations, bromofluoroalkenes were proposed as suitable starting materials for the Pd-catalysed reaction following an analogous mechanism to that reported in the previously mentioned system. By combining the simplicity of a single catalyst with the utility of bromofluoroalkenes, this procedure could represent a great acquisition to the reduced set of reactions for the synthesis of fluorinated enynes.

5.2.3.2 Results and discussion

1-Bromo-2-fluoro-2-(3-methylphenyl)ethene (**6fb**) was selected as a suitable substrate for optimisation purposes. The preparation of **6fb** from terminal alkynes has been fully described in previous chapters (see Chapter 3.3 and Chapter 4.2.2), *via* bromination of 3-ethynyltoluene (**4f**) followed by hydrofluorination of the resulting 1-bromo alkyne (**5fb**). **4f** was also chosen as the terminal alkyne for the coupling optimisation studies.

The reaction conditions optimised for the coupling of aryl bromides as substrates were directly tested on **6fb**, in order to ascertain the reactive nature of these substrates towards a similar type of coupling. Indeed, when **6fb** was reacted with 1.3 equivalents of the terminal alkyne **4f** in the presence of 3 mol% of [Pd(η^3-cinnamyl)(Cl)(IPr)] (**Pd-1**) and two equivalents of K_2CO_3, a new fluorinated species was obtained in 59%

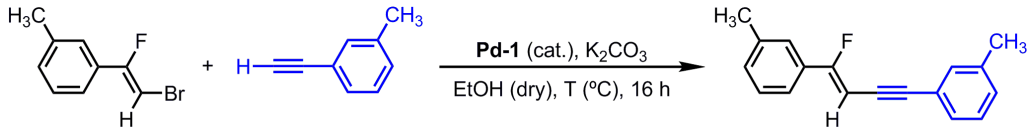
conversion, according to ^{19}F NMR analyses. The species was later confirmed as the expected *Z*-fluoroenyne (Scheme 5.11).



Scheme 5.11. Preliminary test for the Pd-catalysed coupling of bromofluoroalkene **5fb** and terminal alkyne **4f**.

This reaction mixture also showed the presence of a secondary fluorinated compound as a major side product, which was not identified during our optimisation tests. Despite this observation, the promising reactivity of the system (Table 5.2, Entry 1) encouraged further optimisation. Increasing the amount of **4f** to two equivalents afforded full consumption of the starting material, with a slightly higher proportion of **9fa** observed in the reaction mixture (Table 5.2, Entry 2). The increase of the base proved inefficient to promote better selectivity towards **9fa** (Table 5.2, Entry 3), not even when lower temperatures were used to avoid promoting side reactions (Table 5.2, Entry 4). Lastly, the increment of [Pd] to 5 mol% using two equivalents of alkyne and 1.3 equivalents of base could afford full conversion of **6fb** into the corresponding expected compound **9fa** (Table 5.2, Entry 5).

Table 5.2. Optimisation of the Pd-catalysed cross-coupling of **5fb** with **4f**.[a]

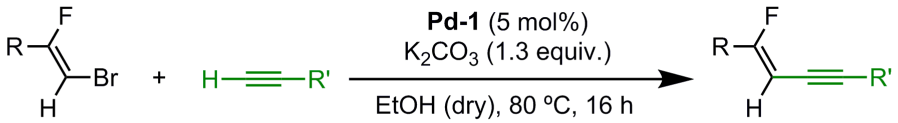


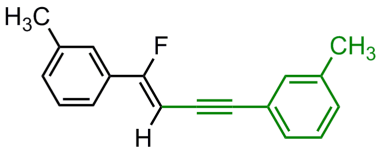
6fb **4f** **9fa**

Entry	[Pd] (mol %)	4f (equiv.)	T (ºC)	K_2CO_3 (equiv.)	Ratio (%)[b]		
					SM	9fa	Others
1	3	1.3	80	1.3	5	59	36
2	3	2	80	1.3	0	67	33
3	3	2	80	2	0	60	40
4	5	2	70	2	0	61	39
5	5	2	80	1.3	0	> 99	< 1

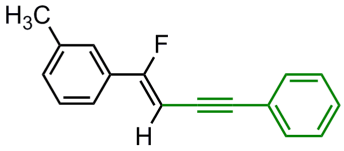
[a]Reaction conditions: **6fb** (0.1 mmol), **4f**, [Pd] (cat.), K_2CO_3, dry EtOH (0.5 mL), 16 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent).

With the optimal conditions on hand, a representative scope of substrates was tested for this transformation (Scheme 5.12). Good to excellent isolated yields and stereoselectivity were obtained in all cases, favoring (*Z*)-alkenes.

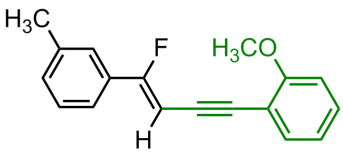




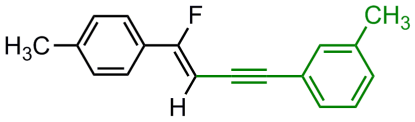
9fa: 90% (98:2, *Z:E*)



9fb: 85% (95:5, *Z:E*)



9fc: 69% (94:6, *Z:E*)

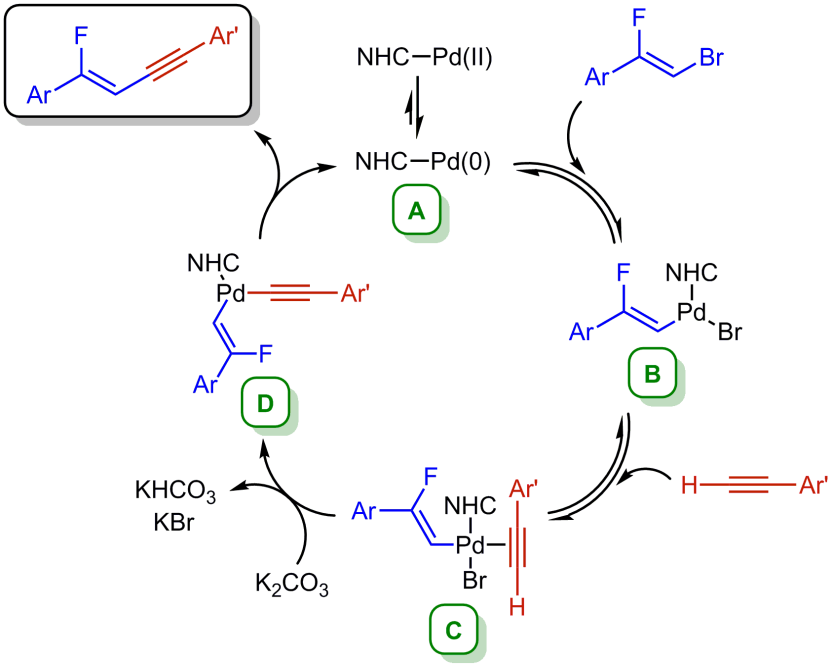


9ea: 91% (96:4, *Z:E*)

[a] Reaction conditions: **6** (0.50 mmol), alkyne (1.0 mmol), [Pd(η^3-cinnamyl)(Cl)(IPr)] (5 mol%), K_2CO_3 (0.65 mmol), EtOH (dry) (1 mL), 80 ºC, 16 h. Isolated yields.

Scheme 5.12. Scope of the Pd-catalysed cross-coupling of terminal alkynes with 1-bromo-2-fluoro-2-arylalkenes [a]

A mechanistic proposal for this reaction can be drawn, which is depicted in Scheme 5.13. First, the generation of a Pd(0) species from the Pd(II) precursor will proceed as described in Scheme 5.4, which will then react with the bromofluoroalkene *via* oxidative addition, generating the fluoroalkenyl-Pd(II) bromide complex (Scheme 5.13, **B**). This species can then coordinate a molecule of terminal alkyne through π-interaction, generation a tetracoordinated Pd(II) species (Scheme 5.13, **C**). In the presence of a suitable base (in this case, K_2CO_3), the alkyne can be deprotonated, inducing σ-coordination in the Pd center and Br^- extrusion in the form of a potassium salt (Scheme 5.13, **D**), with the resulting tricoordinated Pd(II) species having a suitable fragment arrangement for reductive elimination to take place, liberating the corresponding fluoroenyne in the process, and inducing the turnover of Pd(0) species in the catalytic cycle.



Scheme 5.13. Proposed catalytic cycle for the Pd-catalysed copper-free Sonogashira coupling of bromofluoroalkenes.

5.3 *α*-Iodomethyl ketones: reactivity studies

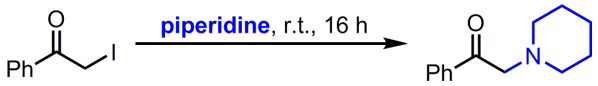
5.3.1 Introduction

The use of α-iodomethyl ketones displays alternative synthetic approaches to the chemistry discussed for fluorohaloalkenes. In the case of these molecules, the study of S_N-type reactions is highly interesting and could be very useful for synthetic purposes. As a result, the use of nucleophiles to functionalise *α*-iodomethyl ketones *via*

nucleophilic substitution mechanisms is commonly used within the scientific community. Moreover, the use of C(sp^3)-I bonds open new synthetic possibilities that are unavailable for alkenyl iodides. The literature has covered a wide range of reactions involving new types of transformations of these substrates, with some examples being definitely attrative for synthetic chemists.

5.3.2 Nucleophilic substitution: synthesis of α-substituted ketones

The main utility of α-iodomethyl ketones is related to their use as organic halides that can react with nucleophiles through displacement of "I". Very much has been investigated in this field, with no new contributions being discussed in this thesis within the field. However, highlighting the feasibility of this reaction was important to acknowledge the interest in preparing these building blocks as discussed in Chapter 4. To achieve this aim, a simple nucleophilic substitution using piperidine as nucleophile was tested. This methodology, reported by Wang and co-workers,[17] was reproduced to obtain the respective α-aminoketone derivative **10a** in excellent yield at room temperature (Scheme 5.14).



7a **10a:** 93%

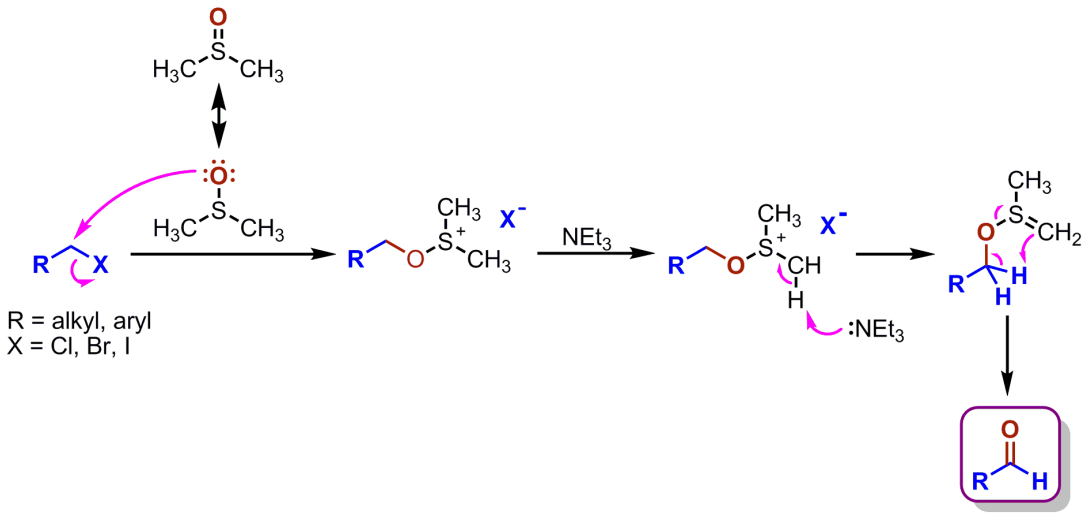
Scheme 5.14. Nucleophilic substitution reaction of **7a** with piperidine.[18]

This reaction is, in fact, a line of study that really interests our research group due to the various synthetic possibilities of α-aminoketones, and current on-going work is being focused on studying this family of substrates and their integration in complex synthetic routes involving the transformation of terminal alkynes using metal-NHC catalysts.

5.3.3 Oxidation chemistry: synthesis and reactivity of α-ketoaldehydes

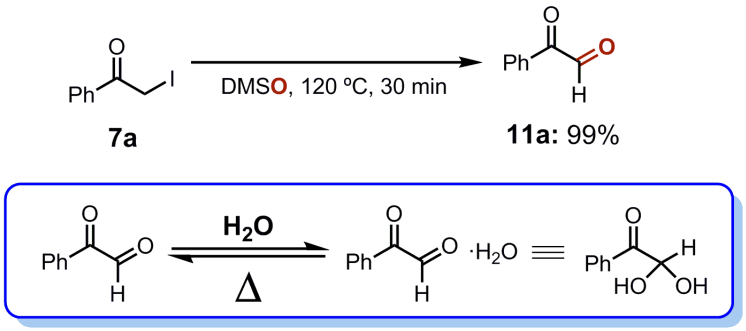
Apart from direct nucleophilic substitution reactions in α-iodomethyl ketones, other synthetic possibilities are accessible for these substrates. Among a variety of examples, their oxidation to 1,2-dicarbonyl species can be cited as one of the most common transformations of these and other α-halomethyl ketones present in the literature. This reaction proceeds through the so-called *Kornblum oxidation*, first

reported by Kornblum and co-workers in 1957.[19,20] The general reaction consists of the transformation of primary organic halides into the corresponding aldehydes, in the presence of DMSO and a base (commonly NEt_3) (Scheme 5.15).



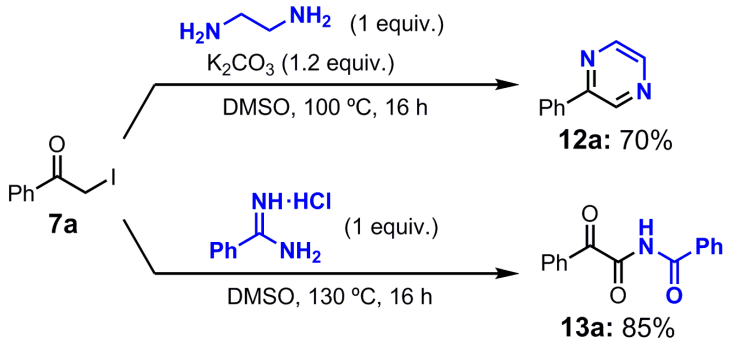
Scheme 5.15. Mechanism of the Kornblum oxidation of organic halides.

In the case of α-iodomethyl ketones, the acidity of the α-protons is sufficient for the oxidation reaction to proceed without the presence of an external base, as reported by different groups in the course of their oxidation studies.[21-23] As a result, α-ketoaldehydes can be prepared following this procedure. Indeed, this reactivity has been acknowledged within our experimental studies by following the method employed by Chaskar and co-workers in 2015,[21] using 1-iodo-2-phenylethanone (**7a**) as substrate; upon stirring this compound in DMSO at 110 ºC for 30 minutes, almost quantitative conversion was observed towards phenylglyoxal (**11a**) (Scheme 5.16). **11a** is a yellow liquid that solidifies upon standing in air, due to the formation of its hydrate. This compound is less prone to polymerisation or decomposition, and represents the usual form of handling for this compound. The hydrate can regenerate the 1,2-dicarbonyl species upon heating, with the hydrated molecule thus acting as sort of a protecting group (Scheme 5.16).



Scheme 5.16. Kornblum oxidation of **7a** for the synthesis of **11a,**[21] and equilibrium between its anhydrous and hydrated form.

Phenylglyoxal and other similar derivatives are useful building blocks in synthesis, further increasing the versatility of α-iodomethyl ketones for the production of complex organic molecules. For example, 1,2-dicarbonylic compounds are excellent intermediates for cyclisation chemistry using appropriate 1,2-disubstituted species with nucleophilic functional groups. A wide variety of transformations using this scaffold are available in the literature, and it was demonstrated that the efficiency of some of these reactions is certainly interesting for the preparation of useful organic compounds. First, **7a** was reacted with ethylenediamine in the presence of DMSO, promoting cyclisation to yield the corresponding substituted pyrazine in 70% isolated yield (Scheme 5.17, top), as reported by Bathula and co-workers in 2014.[22] The use of other similar species, such as aminoalcohols, aminothiols or others, can most certainly provide similar reactive approaches for the preparation of 6-membered-ring heterocycles. Next, monofunctionalisation reactions at the more reactive aldehyde position were explored. Interestingly, the literature accounts for some interesting methodologies allowing the selective derivatisation of the aldehyde group. For example, benzamidine hydrochloride was used, as reported by Wu and co-workers in 2014, for the expedient access to α-ketoimides (Scheme 5.17, bottom).[23] An example of this reaction was performed in our laboratories, successfully transforming **7a** into the corresponding α-ketoimide derivative **13a** in 85% isoalted yield.



Scheme 5.17. Applications of phenylglyoxal in synthesis: direct preparation of substituted pyrazines and α-ketoimides from **7a**.[22,23]

All presented methodologies are straightforward procedures, providing clean products after using traditional extraction/washing techniques and purification by column chromatography. These examples have served to ascertain the interest in preparing α-iodomethyl ketones as valuable building blocks for the synthesis of different families of ketone derivatives, further highlighting the efficient methodology presented in Chapter 4 for their easy preparation from 1-iodoalkynes.

5.4 Sequential chemistry

5.4.1 From terminal alkynes

5.4.1.1 Introduction

With the completed optimisation of several individual reactions using terminal alkynes as substrates, a valuable approach was discussed to provide further utility to this work: the inclusion of these reactions in one-pot protocols. This approach basically represents the integration of each single reaction step into a one-pot procedure allowing to speed up the synthetic process, minimising the required purification steps and simplifying the overall synthesis of the involved intermediates for any synthetic purpose. The various methods presented in this thesis are susceptible to be integrated in one-pot procedures, and therefore some efforts were dedicated to the study of this synthetic consideration, with the results presented in the following subchapters.

5.4.1.2 Iodination/hydrofluorination chemistry: optimisation studies

Our first line of study concentrated on the optimisation of an iodination/hydrofluorination/cross-coupling sequence for terminal alkynes, in order to access trisubstituted (*Z*)-fluoroalkenes (Figure 5.3). The optimisation of the individual

steps has been thoroughly described in this thesis (for further details, the Reader is referred to Chapter 3.3, 4.2.2 and 5.2.2, respectively), with these methods being preliminarily used in the study of each possible sequence before a three-step protocol could be studied in-depth.

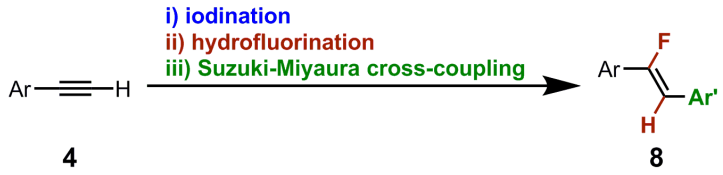
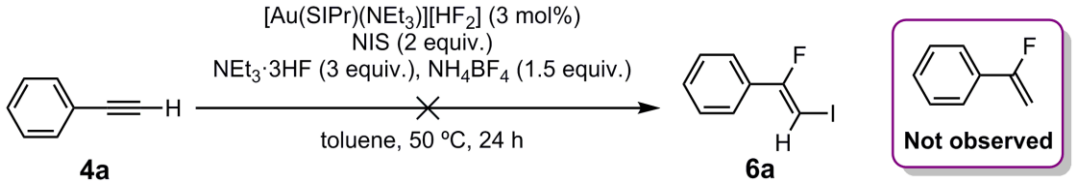


Figure 5.3. Proposed transformation of terminal alkynes (**4**) into trisubstituted (*Z*)-fluoroalkenes (**8**) using sequential iodination/hydrofluorination/Suzuki-Miyaura cross coupling reactions.

Initially, the optimisation of an iodination/hydrofluorination protocol was discussed. The one-pot tandem iodination/hydrofluorination reaction was tested using phenylacetylene (**4a**) as substrate, using both optimised reaction setups in a single vessel. It was hypothesised that this approach could still provide a single stereo- and regioisomer, since the only clear side product (the product of the direct hydrofluorination of **4a** prior to its iodination) could not be observed in control tests reacting **4a** under the optimised hydrofluorination conditions. Despite this encouraging obsertvation, after combining all reagents in a single vial and reacting the mixture at 50 ºC for 24 h, no expected iodofluoroalkene **6a** could be observed, with only partial conversion to iodoalkyne **5a** being witnessed (Scheme 5.18).

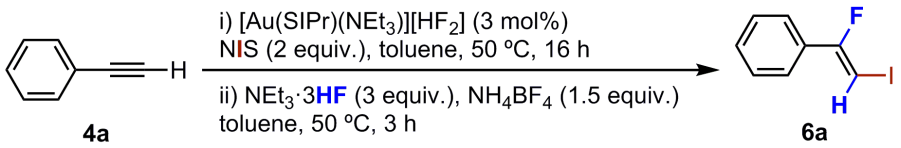


Scheme 5.18. Preliminary test for the one-pot iodination/hydrofluorination of **4a**.

Nevertheless, this discouraging result did not negate our interest in combining the individual steps for a faster, cleaner and easier overall synthetic route. Our focus changed from a one-pot tandem reaction to a one-pot sequential reaction, in which each reactive step could be performed in the same reaction vessel after complete consumption of the involved starting material was acknoweledged. Using this approach, the chances of hampering the involved reactions are lower, thus facilitating a better overall reactivity. Indeed, after some optimisation, the iodination/hydrofluorination sequence could be finally used to access **6a** from **4a** without any intermediate isolation

of **5a**, and the optimisation studies performed to unravel this protocol are summarised in Table 5.3. **4a** was first reacted under the optimised iodination conditions before $NEt_3 \cdot 3HF$ and NH_4BF_4 were added to the reaction mixture. Unfortunately, using this reaction setup did not afford any conversion to **6a**, either in the absence (Table 5.3, Entry 1) or the presence of a fresh charge of the Au(I) catalyst for the second reaction step (Table 5.3, Entry 2). These observations strongly points to a negative interaction of NIS with the hydrofluorination system, and therefore a new approach was followed. Based on the low solubility of this reagent in toluene, a filtration through a small plug of cotton after the first reaction step allowed an easy removal of most of the excess of NIS and the related released product (succinimide, see Scheme 3.7). The supernatant could be then transferred to a clean reaction vessel to perform the hydrofluorination step. Under these conditions, low conversion towards **6a** could finally be obsered (Table 5.3, Entry 3)**.** The filtration step presented an inconvenience: the retention of the gold catalyst in the cotton, due to its also low solubility in toluene, which was most probably causing a low catalytic performance of the hydrofluorination step. To overcome this, a new charge of $[Au(SIPr)(NEt_3)][HF_2]$ was re-introduced in the reaction mixture, obtaining 21% conversion towards **6a** (Table 5.3, Entry 4). The requirement for an excess of NIS in the first reaction step was re-assessed, in order to find another alternative better fitting with sequential conditions. Satisfyingly, it was found that an increase of the reaction time to 24 h in step i) allowed the amount of NIS to be reduced to 1.3 equivalents, maintaining full conversion towards **5a** and providing also full conversion towards **6a** when hydrofluorination conditions were thereafter used (Table 5.3, Entry 5).

Table 5.3. Optimisation of the sequential approach for the conversion of **4a** into **6a**.



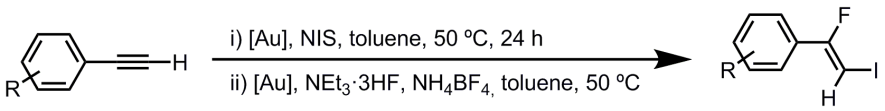
4a **6a**

Entry	Reaction conditions	Conversion (%)[b]
1	Optimised conditions	0
2	**Step ii: + 3 mol% [Au]**	0
3	**After step i: + filtration through cotton**	7
4	After step i: + filtration through cotton **Step ii: + 3 mol% [Au]**	21
5	**Step i: NIS (1.3 equiv.)** **Step i: 24 h of reaction time** After step i: + filtration through cotton Step ii: + 3 mol% [Au]	> 99

[a] Reaction conditions: i) **4a** (0.20 mmol), [Au] (3 mol%), NIS (0.40 mmol), toluene (0.4 mL), 50 ºC, 16 h; ii) $NEt_3 \cdot 3HF$ (0.60 mmol), NH_4BF_4 (0.30 mmol), toluene (0.5 mL), 50 ºC, 3 h. [b] Determined by ^1H NMR ($CDCl_3$ as solvent).

Although the filtration step and the reintroduction of the gold catalyst were still necessary, an excellent 82% isolated yield (based on the starting alkyne) of **6a** could be obtained using these optimised conditions. This value is slightly higher than that obtained in a stepwise transformation of **4a** into **6a** (78% over two individual steps), which certainly shows the great utility of our optimised conditions for fast and efficient synthesis. In addition, the sequential reaction was scaled up to 5 mmol (starting from **4a**), while maintaining a good performance after only increasing the time of step ii) to 4 h (88%, Table 5.4, Entry 1). Other substrates were tested, such as the methoxy- (Table 5.4, Entry 2) or the chloro-derivative (Table 5.4, Entry 3), obtaining equally good results also after increasing the reaction time by one hour from their respective optimised times. This showcases the generality of this straightforward sequential iodination/hydrofluorination procedure, representing a great synthetic step.

Table 5.4. Examples of sequential iodination/hydrofluorination of terminal alkynes (**4**) for the synthesis of fluoroiodoalkenes (**6**).



4 **6**

Entry	R	Product	Time ii)	Conversion of 6a (%)[b]
1	H	**3a**	3 h (4 h)[c]	82 (88%)[c]
2	*m*-OMe	**3c**	4 h	88
3	*m*-Cl	**3j**	4 h	78

[a] Reaction conditions: i) alkyne (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NIS (0.65 mmol), toluene (1 mL); ii) [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NH_4BF_4 (0.75 mmol), NEt$_3$·3HF (1.5 mmol), toluene (1 mL), 50 ºC. [b] Isolated yields. [c] 5 mmol scale in parenthesis.

5.4.1.3 Iodination/hydration/functionalisation chemistry: optimisation studies

The use of α-iodomethyl ketones as intermediates for further functionalisation has some precedent in the literature,[21-24] and therefore the application of sequential chemistry protocols to this field is not as innovative as in the case of fluoroiodoalkenes. However, since our hydration protocol is new, no application in reaction sequences for that particular reaction is available. To the best of our knowledge, all reported examples transforming terminal alkynes to functionalised ketones *via* iodoketone intermediates require the use of oxidants to promote C-O formation; on the other hand, in the previously described hydration methodology for 1-iodoalkynes, the reaction conditions for the formation of such bonds are much milder.

It was therefore straightforward to propose the analysis of reaction sequences including this hydration protocol, which could render ketone synthesis from terminal alkynes much simpler while requiring less harsh conditions. The preparation of functionalised ketones/heterocycles/1,2-dicarbonylic compounds using further expansion of the sequence was proposed as a final aim that could have a huge impact in synthesis (Figure 5.4).

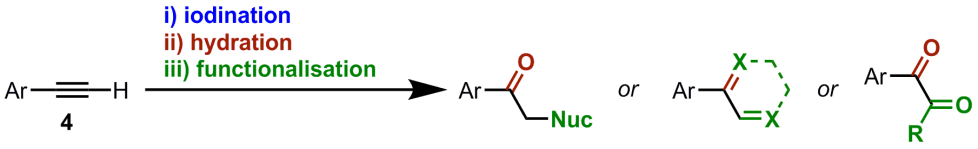
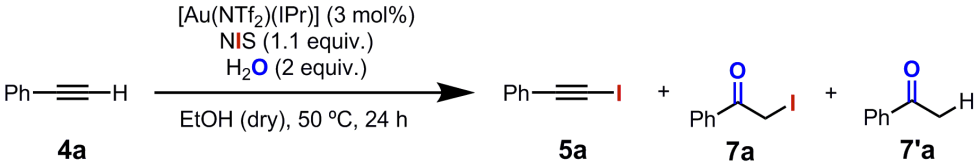


Figure 5.4. Proposed transformation of terminal alkynes (**4**) into ketone derivatives using sequential iodination/hydration/functionalisation reactions.

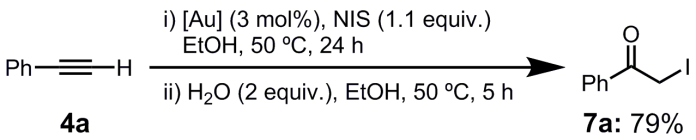
Phenylacetylene (**4a**) and its derivatives were used for the study of the sequential approaches. First, the discussion of a one-pot iodination hydration required some attention; however, this setup was disregarded as a suitable strategy, since Au(I) catalysis is known for also promoting hydration in terminal alkynes, which would eventually lead to complex mixtures of products. Indeed, when 3 mol% of [Au(NTf_2)(IPr)] was used as catalyst in the presence of 1.1 equivalents of NIS and two equivalents of H_2O, **4a** was unselectively converted to a mixture of the hydration product derived from **4a** (acetophenone, **7'a**), (iodoethynyl)benzene (**5a**) and the desired product (1-iodo-2-phenylethanone, **7a**) (Scheme 5.19).



Scheme 5.19. One-pot iodination/hydration of **4a** using [Au(NTf_2)(IPr)] as catalyst.

Although no detailed investigation of this approach was performed, the obtained results suggested a strong influence of the order of addition of the reagents, with a later addition of water providing a better selectivity towards **7a**. This is in accordance with a fast iodination taking place in water-free conditions, thus favoring a higher proportion of **5a** for its conversion into **7a**. These results clearly pointed to a sequential procedure being the most optimal approach for this reaction.

In view of this, sequential transformations were considered. This approach provided a much better approach, since it afforded maximum conversion of **4a** into **5a** prior to the hydration step. First, it was discovered that, by simply stirring a reaction mixture containing **4a**, 3 mol% of [Au(NTf_2)(IPr)] and 1.1 equivalent of NIS in dry EtOH at 50 ºC, full conversion towards **5a** was observed by ^{1}H NMR analysis after 24 h. The addition of two equivalents of H_2O to this reaction mixture, with stirring at 50 ºC for further 5 h, afforded full conversion towards **7a**, which could be isolated *via* column chromatography in 79% yield (with respect to the starting alkyne) (Scheme 5.20).



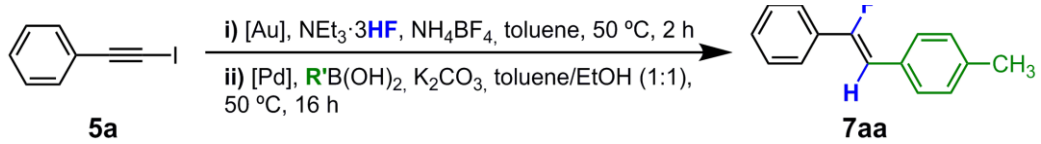
Scheme 5.20. Sequential Au-catalysed iodination/hydration of **4a.**

5.4.2 From 1-iodoalkynes

5.4.2.1 Hydrofluorination/cross-coupling chemistry: optimisation studies

The feasibility of a hydrofluorination/cross-coupling sequence was studied. Due to various incompatibilities between the reactivity of the present compounds (for example, acids and bases), the one-pot reaction was directly discarded. The feasibility of a sequential reaction was also rejected after our preliminary test acknowledged the lack of reactivity of the second step under these conditions (Table 5.5, Entry 1) due to the expected complete neutralisation of the base during the cross-coupling stage by the remaining $NEt_3 \cdot x$HF. An efficient sequential transformation for **5a** into **7aa** would therefore require full neutralisation of $NEt_3 \cdot x$HF species prior to the cross-coupling step. Gratifyingly, a very favorable physical characteristic of the reaction mixture in the hydrofluorination step was key to keep high interest in this reaction: the separation of the acidic compounds in a secondary organic layer. This allowed the easy separation of the toluene layer (containing the hydrofluorination product) into a different reaction vessel for the cross-coupling reaction to be performed. While this approach afforded some conversion towards the expected species **7aa** (Table 5.5, Entry 2), the incomplete conversion of **6a** was most probably due to the presence of some remaining acid in the toluene phase. Stirring this phase with an excess of K_2CO_3 provided the best alternative towards the elimination of any inconvenient species. Although the use of H_2O as co-solvent in this system did still not afford any conversion towards the final product (Table 5.5, Entry 3), EtOH was a better selection for this step, providing full conversion of **5a** into **7aa** in the ulterior cross-coupling step (Table 5.5, Entry 4).

Table 5.5. Optimisation of the sequential approach for the conversion of **5a** into **7aa**.

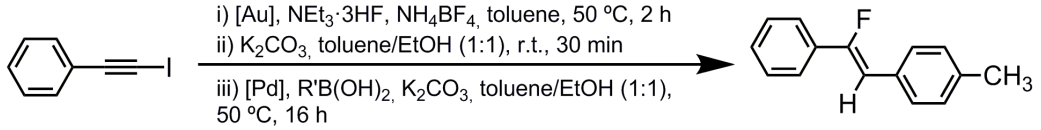


5a **7aa**

Entry	Handling between step i) and ii)	Conversion of 6a (%)[b]
1	None	0
2	+ separation from the acidic layer	11
3	+ separation from the acidic layer **+ stirring with K_2CO_3 (5 equiv.), toluene/H_2O (1:1), r.t., 30 minutes**	0
4	+ separation from the acidic layer + stirring with K_2CO_3 (5 equiv.), **toluene/EtOH (1:1)**, r.t., 30 minutes	> 99

[a] Reaction conditions: i) **5a** (0.20 mmol), NEt_3·3HF (0.60 mmol), NH_4BF_4 (0.30 mmol), toluene (0.4 mL), 50 °C, 3 h; ii) *p*-tolylboronic acid (0.40 mmol), [Pd] (2 mol%), K_2CO_3 (0.40 mmol), toluene/EtOH (0.8 mL), 50 °C, 16 h. [b] Determined by ^{19}F NMR ($CDCl_3$ as solvent).

These conditions granted access to **7aa** in 84% isolated yield after purification by column chromatography on silica gel (Scheme 5.21). Such as in the previously discussed sequence, the obtained final yield of **7aa** is higher than that obtained through the two individual steps (76%), again proving the utility of the sequential use of functionalisation reactions based on transition metal-NHC complexes.



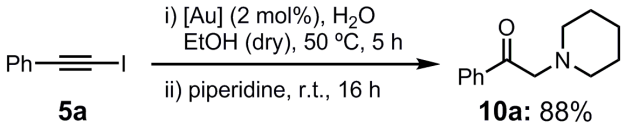
5a **7aa:** 84%

Scheme 5.21. Sequential hydrofluorination/cross-coupling reaction of **5a** iodination/hydrofluorination reactions of terminal alkynes (**4**).

5.4.2.2 Hydration/functionalisation chemistry: optimisation studies

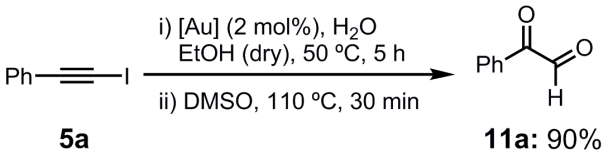
The next step was to investigate if the hydration reaction could integrate any of the previously tested functionalisation reactions. Gratifyingly, removal of EtOH under reduced pressure, after the hydration step, afforded a crude reaction mixture, pure enough to be used for sequential reactivity. For example, piperidine could be added to

this reaction mixture; and after stirring at room temperature for 16 h, 88% isolated yield of the α-aminoketone **10a** was obtained (Scheme 5.23).



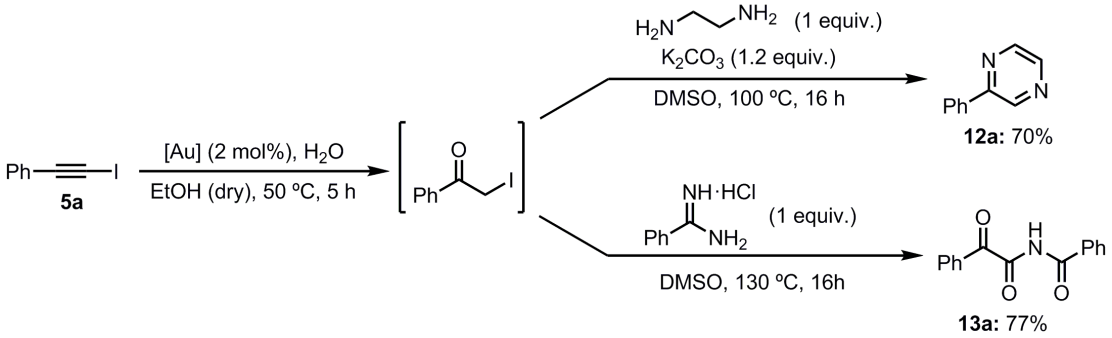
Scheme 5.22. Sequential hydration/nucleophilic substitution of **5a** in the presence of piperidine for the synthesis of α-aminoketone **10a**.

Similarly, addition of DMSO to the previously mentioned mixture and stirring at 120 ºC for 30 minutes also afforded sequential hydration/oxidation chemistry to take place, obtaining 90% yield of phenylglyoxal (**11a**) (Scheme 5.23).



Scheme 5.23. Sequential hydration/Kornblum oxidation of **5a** for the synthesis of phenylglyoxal (**11a**).

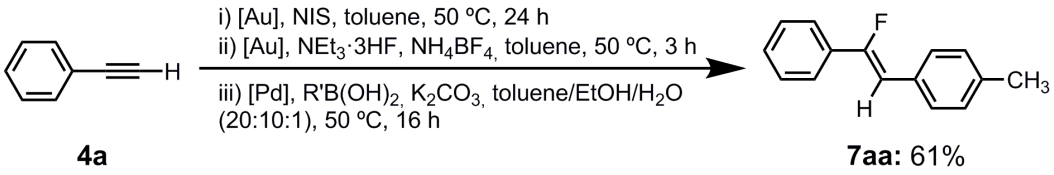
With the sequential access to **11a** having being established, the incorporation of further reactivity was straightfoward. Stirring the reaction crude under the corresponding reaction conditions used for the individual steps described before (see Chapter 5.3.3) afforded good to excellent isolated yields for the related products without any change in the reaction parameters or workup being required. The isolated yields were in all cases comparable to those of the combined individual steps, reinforcing the utility of sequential chemistry for this chemistry (Scheme 5.24).



Scheme 5.24. Sequential hydration/functionalisation of (iodoethynyl)benzene (**5a**) to produce ketone derivatives.

5.4.3 Other reaction sequences: iodination/hydrofluorination/cross-coupling sequence for terminal alkynes

Finally, we attempted to combine several sequential procedures into one. This approach was successful for the preparation of **7aa** starting directly from **4a**. While the combination of both optimised procedures afforded some conversion towards the final species, some unreacted intermediate **6a** could still be observed. During the experimental work, a much more turbid organic phase was observed in this three-step sequence when compared to the previously optimised two-step one, and we therefore proposed that traces of organic species, salts and others were saturating our organic phase, reducing the final neutralisation and cross-coupling steps. To circumvent this problem, the addition of a small amount of water during the neutralisation step proved an excellent solution for the solubilisation of water-soluble products (salts, acids...) from the crowded organic phase, and the coupling step could finally be performed obtaining full conversion towards **7aa**, and isolating this product in 61% yield (Scheme 5.25).



Scheme 5.25. Sequential Au/Pd-catalysed iodination/hydrofluorination/cross-coupling reaction of **4a.**

With only one purification step to afford the end-product, and obtaining a comparable yield to that obtained *via* three individual steps (67%) and with no selectivity decrease upon using more complex systems, this final sequential reaction proves its robustness and synthetic value for the chemistry community.

5.5 Conclusions

The preparation of fluorohaloalkenes and α-iodomethyl ketones has opened new synthetic pathways that have been successfully exploited for the preparation of a "second generation" of 1-iodoalkyne derivatives. First, a Pd(II)-NHC complex, [Pd(η^3-cinnamyl)(Cl)(IPr)], has been successfully used to optimise two new synthetic methods to derivatise fluorohaloalkenes. A Suzuki-Miyaura cross-coupling reaction has given access to stereo- and regiocontrolled trisubstituted (*Z*)-fluoroalkenes starting from

fluoroiodoalkenes; on the other hand, a copper-free Sonogashira cross-coupling was found very useful for the preparation of fluorinated enynes starting from bromofluoroalkenes, with the family of final compounds having no representative in the literature until now.

On the other hand, the use of α-iodomethyl ketones for further transformation into useful chemicals has been reproduced for several reported examples. These tests provided a hint about the reactivity these molecules can access, therefore demonstrating the high remaining interest in the preparation of such compounds.

Finally, several studies of the combination of all presented and individually optimised reactions throughout this thesis have been discussed, obtaining new great sequential methodologies for the preparation of complex fluoroalkene and ketone derivatives starting from simple and commercially available terminal alkynes. The sequential transformation of alkynes has only been scarcely explored in the literature, and only a limited number of reactions have actually been considered within this context. This observation highlights all this presented work as one of the most extensive investigations into the development of new sequential methodologies for the fast functionalisation of terminal alkynes. The utility of transition metal-NHC catalysts for the coupling of the different sequences without any loss in performance and selectivity is an outstanding point that should be mentioned. These catalysts have allowed the use of more simple starting materials, easy between-step handling and good scalability, excellent reactivity and straightforward isolation of the products.This work goes to show the outstanding qualities of these sequential procedures. We hope that this work will help the scientific community in the modern and highly important search for cost-efficient synthetic protocols.

5.6 References

(1) For the original description of this reaction, see: N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.* 1979, **20**, 3437.

(2) For some selected examples of Suzuki-Miyaura cross-coupling reactions, see: a) N. Miyaura, T. Yanagi and A. Suzuki, *Synthesis*, 1981, 513; b) N. Miyaura and A. Suzuki, *Chem. Rev.* 1995, **95**, 2457; c) L. Botella and C. Najera, *Angew. Chem. Int. Ed.* 2002, **41**, 179; d) N. Miyaura, *Top. Curr. Chem.* 2002, **219**, 11; e) Suzuki,

A.; Brown, H. C.; in: *Organic Synthesis via Boranes*, Aldrich, Milwaukee, **2003**, vol. 3; f) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Greeser, J. Garner and M. Breuning, *Angew. Chem. Int. Ed.* 2005, **44**, 5384; g) F.-X. Felpin, T. Ayad and S. Mitra, *Eur. J. Org. Chem.* 2006, 2679; h) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, *J. Am. Chem. Soc.* 2006, **128**, 4101; i) B. Saito and G. C. Fu, *J. Am. Chem. Soc.* 2008, **130**, 6694; j) C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem. Int. Ed.* 2008, **47**, 8059; k) K. L. Billingsley and S. L. Buchwald, *Angew. Chem. Int. Ed.* 2008, **47**, 4695; l) M. G. Organ, G. A. Chass, D. C. Fang, A. C. Hopkinson and C. Valente, *Synthesis*, 2008, 2776; m) T. Fujihara, S. Yoshida, H. Ohta and Y. Tsuji, *Angew. Chem. Int. Ed.* 2008, **47**, 8310; n) M. Tobisu and N. Chatani, *Angew. Chem. Int. Ed.* 2009, **48**, 3565; o) T. S. Jo, S. H. Kim, J. Shin and C. Bae, *J. Am. Chem. Soc.* 2009, **131**, 1656; p) J. Han, Y. Liu and R. Guo, *J. Am. Chem. Soc.* 2009, **131**, 2060; q) Y. Uozumi, Y. Matsuura, T. Arakawa and Y. M. A. Yamada, *Angew. Chem. Int. Ed.* 2009, **48**, 2708; r) H. Li, C. C. C. J. Seechurn and T. J. Colacot, *ACS Catal.* 2012, **2**, 1147; s) C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.* 2012, **51**, 5062; t) R. P. Aravinda, R. A. Babul, R. G. Ramachandra and R. N. Subbarami, *J. Heterocycl. Chem.* 2013, **50**, 1451; u) P. R. Melvin, A. Nova, D. Balcells, W. Dai, N. Hazari, D. P. Hruszkewycz, H. P. Shah and M. T. Tudge, *ACS Catal.* 2015, **5,** 3680; v) P. R. Boruah, A. A. Ali, M. Chetia, B. Saikia and D. Sarma, *Chem. Commun.* 2015, **51**, 11489.

(3) a) M. Yoshida, D. Ota, T. Fukuhara, N. Yoneda and S. Hara, *J. Chem. Soc. Perkin Trans.* 1, 2002, 384; b) M. Yoshida, A. Komata and S. Hara, *Tetrahedron*, 2006, **62**, 8636.

(4) a) T. Guan, M. Yoshida, D. Ota, T. Fukuhara and S. Hara, *J. Fluorine Chem.* 2005, **126**, 1185; b) M. Sakai, T. Guan and S. Hara, *J. Fluorine Chem.* 2007, **128**, 1444.

(5) a) E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem. Int. Ed.* 2007, **46**, 2768; b) G. C. Fortman and S. P. Nolan, *Chem. Soc. Rev.* **2011**, 40, 5151.

(6) For selected applications of Pd-NHC cinnamyl species as coupling catalysts, see: a). O. Navarro, N. Marion, J. Mei and S. P. Nolan, *Chem. Eur. J.* 2006, **12**, 5142; b) N. Marion, O. Navarro, J. Mei, R. D. Stevens, N. M. Scott and S. P. Nolan, *J.*

Am. Chem. Soc. 2006, **128**, 4101; c) A. R. Martin, A. Chartoire, A. M. Z. Slawin and S. P. Nolan, *Beilstein J. Org. Chem.* 2012, **8**, 1637; d) F. Izquierdo, M. Corpet and S. P. Nolan, *Eur. J. Org. Chem.* 2015, 1920.

(7) For selected applications of Pd-NHC dimers as coupling catalysts, see: a) M. S. Viciu, R. M. Kissling, E. D. Stevens and S. P. Nolan, *Org. Lett.* 2002, **4**, 2229; b) O. Diebolt, P. Braunstein, S. P. Nolan and C. S. J. Cazin, *Chem. Commun.* 2008, 3190; c) C. E. Hartmann, S. P. Nolan and C. S. J. Cazin, *Organometallics*, 2009, **28**, 2915.

(8) P. R. Melvin, D. Balcells, N. Hazari and A. Nova, *ACS Catal.* 2015, **5**, 5596.

(9) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.* 1975, **16**, 4467.

(10) For some selected reviews of the Sonogashira coupling reaction, see: a) R. Chinchilla and C. Nájera, *Chem. Rev.* 2007, **107**, 874; b) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.* 2011, **40**, 5084; c) M. Schilz and H. Plenio, *J. Org. Chem.* 2012, **77**, 2798; d) M. Bakherad, *Appl. Organomet. Chem.* 2013, **27**, 125.

(11) Z.-Y. Yang and d. J. Burton, *Tetrahedron Lett.* 1990, **31**, 1369.

(12) Y. Li, X. Liu, D. Ma, B. Liu and H. Jiang, *Adv. Synth. Catal.* 2012, **354,** 2683.

(13) For some recent examples of coupling chemistry of terminal alkynes for the synthesis of 1,3-diynes, see: a) K. Balaraman and V. Kesavan, *Synthesis*, 2010, 3461; b) S. Wang, L. Yu, P. Li, L. Meng and L. Wang, *Synthesis*, 2011, 1541; c) D. Saha, T. Chatterjee, M. Mukherjee and B. C. Ranu, *J. Org. Chem.* 2012, **77**, 9379; d) Z. Huang, R. Shang, Z.-R. Zhang, X.-D. Tan, X. Xiao and Y. Fu, *J. Org. Chem.* 2013, **78**, 4551; e) S. Ahammed, D. Kundu and B. C. Ranu, *J. Org. Chem.* 2014, **79**, 7391.

(14) For some reviews about alternative cross-coupling reactions with alkynes, see: a) K. J. Sonogashira, *J. Organomet. Chem.* 2002, **653**, 46; R. R. Tykwinski, *Angew. Chem. Int. Ed.* 2003, **42**, 1566; c) E. Negishi and L. Anastasia, *Chem. Rev.* 2003, **103**, 1979; d) A. Mori, J. Kawashima, T. shimada, M. Suguro, K. Hirabayashi and Y. Nishihara, *Org. Lett.* 2000, **2**, 2935; Y. Liao, R. Fathi and Z. Yang, *Org. Lett.* 2003, **5**, 909.

(15) For some reviews about metal-free Sonogashira-type cross-coupling reactions with alkynes, see: a) N. E. Leadbeater, M. Marco and B. J. Tominack, *Org. Lett.* 2003, **5**, 3919; b) J. Cheng, Y. Sun, F. Wang, M. Guo, J. Xu, Y. Pan and Z. Zhang, *J. Org. Chem.* 2004, **69**, 5428; c) S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*

2004, **69**, 5752.

(16) S. Eddarir, H. Mestdagh and C. Rolando, *Tetrahedron Lett.* 1991, **32**, 69.

(17) A. Gómez-Herrera, F. Nahra, M. Brill, J. Wu, C. S. J. Cazin and S. P. Nolan, *manuscript in preparation*.

(18) X. Zhang and L. Wang, L. *Green. Chem.* 2012**, 14**, 2141.

(19) For the original description of the reaction, see: N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Am. Chem. Soc.* 1957, **79,** 6562.

(20) For later studies of the Kornblum reaction, see: a) N. Kornblum, W. J. Jones and G. J. Anderson, *J. Am. Chem. Soc.* 1959, **81**, 4113; b) P. Dave, H. S. Byun and R. Engel, *Synth. Commun.* 1986, **16**, 1343.

(21) H. P. Kalmode, K. S. Vadagaonkar and A. C. Chaskar, *RSC Adv.* 2014, **4**, 60316.

(22) K. K. D. R. Viswanadham, M. P. Reddy, P. Sathyanarayana, O. Ravi, R. Kant and S. R. Bathula, *Chem. Commun.* 2014, **50**, 13517.

(23) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.* 2014**, 16**, 2888.

(24) For other selected examples, see: a) J. S. Yadav, B. V. S. Reddy, A. P. Singh and A. K. Basak, *Tetrahedron Lett.* 2008, **49**, 5880; b) Y.-P. Zhu, F.-C. Jia, M.-C. Liu and A.-X. Wu, *Org. Lett.* 2012, **14**, 4414; c) T. J. Donohoe, M. A. Kabeshov, A. H. Rathi and I. E. D. Smith, *Org. Biomol. Chem.* 2012, **10**, 1093; d) K. S. Vadagaonkar, H. P. Kalmode, K. Murugan and A. C. Chaskar, *RSC Adv.* 2015, **5**, 5580; e) S. Imai, H. Kikui, K. Moriyama and H. Togo, *Tetrahedron,* 2015, 71, 5267; f) J. Zhang, Q. Gao, X. Wu, X. Geng, Y.-D. Wu and A. Wu, *Org. Lett.* 2016, **18**, 1686.

CHAPTER 6

Perspectives and Future Work

The reactions presented in this thesis certainly represent new opportunities for the synthetic community to functionalise simple building blocks, and it is hoped that the knowledge discussed hereby can result of great importance for a more extensive application of transition metal-NHC catalysis in sequential chemistry.

The optimisation of a fluorination protocol for arylsulfonic acids through C-S cleavage is being continued within our research group. With the latest results showing an important role of Selectfluor and Au(I) catalysts, our next approaches will be based in the exploration of suitable oxidation conditions for Au(I) to ascertain the importance of oxidative/reductive processes. A broader screening of electrophilic fluorinating sources will be also carried out, in order to further assess its role in the presented reaction. Testing F-TEDA derivatives, *N*-fluoropyridinium salts and others, such as 4-iodotoluene difluoride, will be our next step towards further optimisation of this reaction (Figure 6.1).

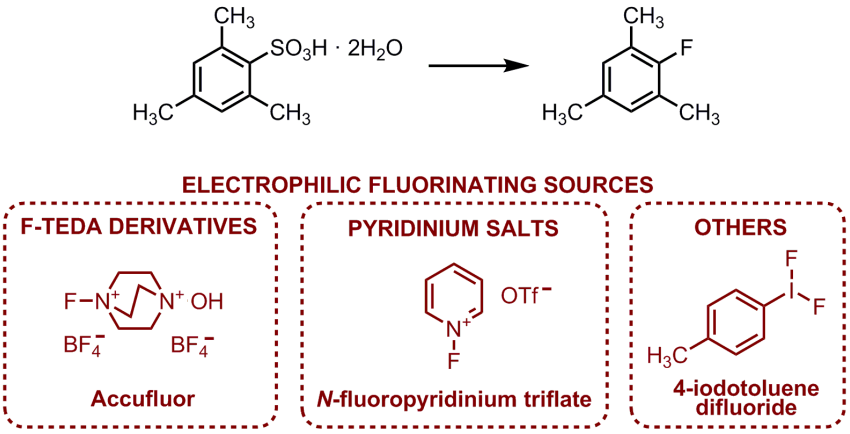


Figure 6.1. Next approaches to be tested in the fluorination of arylsulfonic acids through C-S cleavage: scope of electrophilic iodinating sources and oxidants.

The utility of the C(sp^2)-H fluorination of arylsulfonic acids is also being investigated. Our preliminary studies of this reaction in other substrates have shown low to moderate NMR yields, which indicates that the selection of the substrate is crucial for an optimal performance of this transformation. Variations of the optimised system and the use of other substrates are currently being tested in our lab to further expand the applicability of this method.

The use of 1-iodoalkynes, fluoroiodoketones and α-iodomethyl ketones as building blocks is naturally not restricted to the reactions that have been presented in

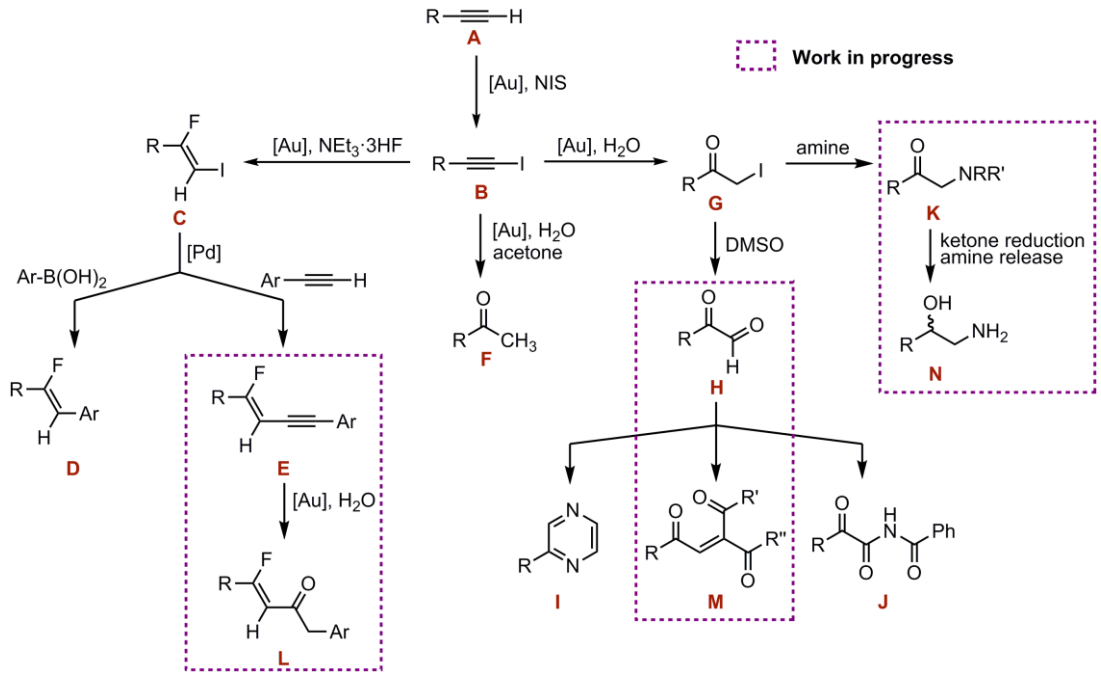
this thesis (Scheme 6.1). Inspired by this fact, our group is currently discussing three new synthetic approaches integrating our optimised protocols:

1) The Au-catalysed hydration of fluorinated enynes for the synthesis of fluorinated α,β-unsaturated ketones (Scheme 6.1, **E** to **L**).

2) The synthesis of α,β-unsaturated tricarbonylic compounds from phenylglyoxal derivatives (Scheme 6.1, **H** to **M**).

3) The enantioselective synthesis of α-aminoalcohols using α-iodomethyl ketones (Scheme 6.1, **K** to **N**).

These methodologies will definitely be important acquisitions for synthesis as individual reactions, and integrating these reactions in sequential synthesis will certainly be considered.



Scheme 6.1. Summary of functionalisation reactions of terminal alkynes studied throughout this thesis, and perspectives for new reactions being currently studied within our research group.

CHAPTER 7

Experimental Section

7.1 General information

Only the most relevant experimental information is described in this session. The supporting information contained in the Supporting Data CD provided with this thesis contains more extensive experimental data, including extra experiments, NMR, IR and HRMS spectra, as well as other source data of interest.

All glassware was dried overnight in an oven at 80 °C before use. Dry solvents were obtained from a PureSolv SPS-400-5 solvent purification system. All other solvents were purchased from commercial sources and used as received. [Au(NHC)(NEt_3)][HF_2],[1] [Au(NTf_2)(NHC)],[2] [{Au(IPr)}$_2$(μ-OH)][BF_4],[3] [Au(Cl)(NHC)],[4] [Au(OH)(NHC)],[5] [Pd(η^3-cinnamyl)(Cl)(IPr)][6] and [Pd(μ-Cl)Cl(IPr)]$_2$[7] were prepared according to reported procedures, with the spectroscopic data in accordance with the literature. All other substrates and reagents were purchased from commercial sources and used as received, unless otherwise stated.

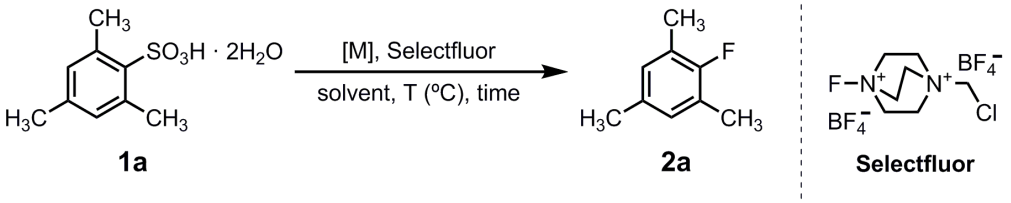
Purification by flash column chromatography was performed using silica gel 60 (230-400 mesh). ^{1}H, ^{13}C-{^{1}H}, ^{19}F-{^{1}H}, COSY, HSQC and HMBC Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AC300 or on a Bruker Avance 400 Ultrashield spectrometer using the residual solvent peak as reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm) at 298K. Elemental analyses were performed at London Metropolitan University 166-220, Holloway Road, London, N7 8DB. HMRS analyses (TOF MS ASAP+) were carried out by the EPSRC National Mass Spectrometry Service Centre at Swansea University, using the Atmospheric Solids Analysis Probe (XEVO G2-S ASAP). Infra red spectra (ν_{max}) were recorded on a Shimadzu Fourier transform IR Affinity-1 infrared spectrophotometer using the MIRacle^{TM} single reflection horizontal ATR accessory from Pike (ANSe single crystal). Only the characteristic peaks are quoted. Samples were directly placed on the crystal (ATR).

Representative characterisation data is provided for new products. In the case of already reported products, appropriate references from the literature are provided for the corresponding methodology and/or characterisation data.

7.2 Experimental data

7.2.1 Chapter 2

7.2.1.1 Optimisation of the C(sp^2)-S fluorination of 2,4,6-trimethylbenzene sulfonic acid dihydrate (1a).

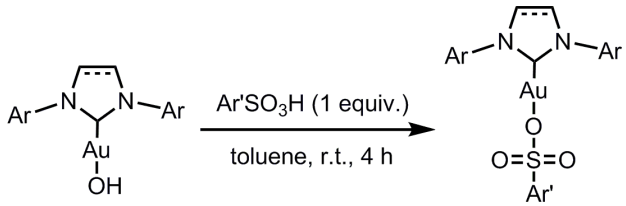


1a **2a** **Selectfluor**

A 3-mL screwcap vial equipped with a stirring bar was charged with **1a** (23.9 mg, 0.10 mmol), the catalyst, Selectfluor and solvent (0.3 mL). The mixture was stirred in air at the corresponding temperature and time. A freshly prepared solution of 1-bromo-3-fluorobenzene (0.5 mL, 0.2 M in $CDCl_3$) was then added to the reaction mixture. The sample was homogeinised, filtered through a small plug of cotton and analysed by ^{19}F-{^1H} NMR.

This compound has been reported before and the analytical data match the literature report.[8]

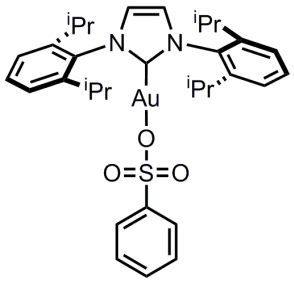
7.2.1.2 Synthesis of [Au(OSO_2Ar)(NHC)] complexes



AuOH **Au-X**

A 3-mL screwcap vial equipped with a stirring bar was charged with the Au complex (100 mg), the arylsulfonic acid (1 equiv.) and toluene (1.5 mL). The reaction mixture was stirred in air at room temperature for 4 h. The white slurry was concentrated under vacuum to about 1/4 of the total volume, and pentane (1 mL) was then added. The precipitate was filtered and washed with pentane (3x5 mL), and further dried under reduced pressure, obtaining the expected complexes.

[Au(OSO$_2$Ph)(IPr)] (Au-1)



White solid (123 mg, 93% yield)

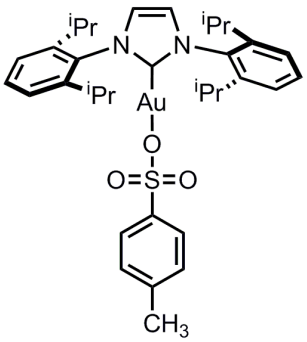
^{1}H NMR (400 MHz, CDCl$_3$, 298K): δ (ppm) = 7.60-7.52 (m, 4H, C*H*$_{Ar}$), 7.35-7.32 (m, 5H, C*H*$_{Ar}$), 7.24-7.19 (m, 4H, C*H*$_{Ar}$), 2.50 (sept, $^3J_{H\text{-}H}$ = 7.2 Hz, 4H, C*H*(CH$_3$)$_2$), 1.31 (d, $^3J_{H\text{-}H}$ = 6.4 Hz, 12H, CH(C*H*$_3$)$_2$), 1.23 (d, $^3J_{H\text{-}H}$ = 6.7 Hz, 12H, CH(C*H*$_3$)$_2$).

^{13}C-{^{1}H} NMR (101 MHz, CDCl$_3$, 298K): δ (ppm) = 164.4 (s, 1C, *C*$_{Ar}$), 145.7 (s, 4C, *C*$_{Ar}$), 133.8 (s, 2C, *C*$_{Ar}$), 131.1 (s, 1C, *C*H$_{Ar}$), 130.4 (s, 2C, *C*H$_{Ar}$), 128.2 (s, 2C, *C*H$_{Ar}$), 126.4 (s, 2C, *C*H$_{Ar}$), 124.5 (s, 4C, *C*H$_{Ar}$), 123.6 (s, 2C, *C*$_4$ and *C*$_5$), 29.0 (s, 4C, *C*H(CH$_3$)$_2$), 24.5 (s, 4C, CH(*C*H$_3$)$_2$), 24.3 (s, 4C, CH(*C*H$_3$)$_2$).
Elemental analysis: *Calculated* - C: 53.37, H: 5.56, N: 3.77 ; *found* - C: 53.27, H: 5.62, N: 3.74.

IR (solid): 754, 970, 1153, 1284, 1460, 2960 cm^{-1}

HRMS calcd. for C$_{33}$H$_{41}$AuN$_2$O$_3$S [M+H]$^+$ 743.2582, **found** 743.2589 ; **calcd. for C$_{33}$H$_{40}$AuN$_2$O$_3$SNa [M+Na]$^+$** 765.24, **found** 765.24.

[Au(OSO$_2$Tol)(IPr)] (Au-2)



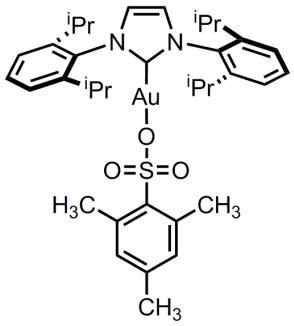
White solid (126 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.55 (t, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 2H, CH_{Ar}), 7.40 (d, br, $^{3}J_{H\text{-}H}$ = 6.8 Hz, 2H, CH_{Ar}), 7.31 (d, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 4H, CH_{Ar}), 7.21 (s, 2H, *H_4* and *H_5*), 2.48 (sept, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 4H, C*H*$(CH_3)_2$), 2.32 (s, 3H, C_{Ar}-CH_3), 1.29 (d, $^{3}J_{H\text{-}H}$ = 6.8 Hz, 12H, CH(CH_3)$_2$), 1.21 (d, $^{3}J_{H\text{-}H}$ = 7.3 Hz, 12H, CH(CH_3)$_2$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.5 (s, 1C, C_{Ar}), 145.7 (s, 4C, C_{Ar}), 140.4 (s, 1C, C_{Ar}), 133.8 (s, 2C, C_{Ar}), 131.0 (s, 2C, *C*H$_{Ar}$), 128.8 (s, 2C, *C*H$_{Ar}$), 126.4 (s, 2C, *C*H$_{Ar}$), 124.5 (s, 4C, *C*H$_{Ar}$), 123.6 (s, 2C, *C_4* and *C_5*), 29.0 (s, 4C, *C*H$(CH_3)_2$), 24.5 (s, 4C, CH(*C*H$_3$)$_2$), 24.3 (s, 4C, CH(*C*H$_3$)$_2$), 21.5 (s, 1C, C_{Ar}-*C*H$_3$).

This compound has been reported before and the analytical data match the literature report.[9]

[Au(OSO$_2$Mes)(IPr)] (Au-3)

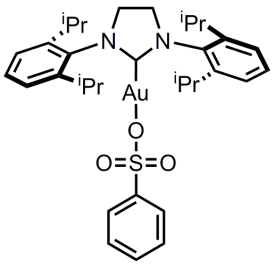


White solid (130 mg, 96% yield)

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.50 (t, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 2H, CH_{Ar}), 7.24 (m, 4H, CH_{Ar}), 7.17 (s, 2H, *H^4* and *H^5*), 6.65 (s, 2H, CH_{Ar}), 2.44 (sept, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 4H, C*H*$(CH_3)_2$), 2.30 (s, 6H, C_{Ar}CH_3), 2.19 (s, 3H, C_{Ar}CH_3) 1.24 (d, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$), 1.18 (d, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.8 (s, 1C, C_{Ar}), 145.6 (s, 4C, C_{Ar}), 137.7 (s, 1C, C_{Ar}), 133.7 (s, 2C, C_{Ar}), 131.0 (s, 2C, C_{Ar}), 130.9 (s, 2C, *C*H$_{Ar}$), 124.4 (s, 4C, *C*H$_{Ar}$), 123.5 (s, 2C, *C_4* and *C_5*), 28.9 (s, 4C, *C*H$(CH_3)_2$), 24.4 (s, 4C, CH(*C*H$_3$)$_2$), 24.2 (s, 4C, CH(*C*H$_3$)$_2$), 23.0 (s, 2C, C_{Ar}-*C*H$_3$), 20.9 (s, 1C, C_{Ar}-*C*H$_3$).

[Au(OSO$_2$Ph)(SIPr)] (Au-4)



White solid (103 mg, 84% yield)

^{1}H NMR (400 MHz, CDCl$_3$, 298K, TMS): δ (ppm) = 7.49-7.41 (m, 4H, CH_{Ar}), 7.31-7.24 (m, 5H, CH_{Ar}), 7.18-7.14 (m, 2H, CH_{Ar}), 4.10 (s, 4H, H_4 and H_5), 2.98 (sept, $^3J_{H\text{-}H}$ = 6.8 Hz, 4H, CH(CH$_3$)$_2$), 1.35 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$), 1.33 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$).

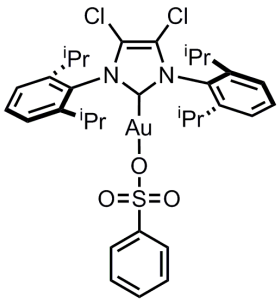
^{13}C-{^{1}H} NMR (101 MHz, CDCl$_3$, 298K): δ (ppm) = 186.8 (s, 1C, C_2), 146.7 (s, 4C, C_{Ar}), 143.1 (s, 1C, C_{Ar}), 133.8 (s, 2C, C_{Ar}), 130.4 (s, 2C, CH$_{Ar}$), 130.3 (s, 1C, CH$_{Ar}$), 128.2 (s, 2C, CH$_{Ar}$), 126.3 (s, 2C, CH$_{Ar}$), 124.9 (s, 4C, CH$_{Ar}$), 53.5 (s, 2C, C_4 and C_5), 29.2 (s, 4C, CH(CH$_3$)$_2$), 25.1 (s, 4C, CH(CH$_3$)$_2$), 24.4 (s, 4C, CH(CH$_3$)$_2$).

Elemental analysis: *Calculated* - C: 53.22, H: 5.82, N: 3.76 ; *found* - C: 53.05, H: 5.75, N: 3.84.

IR (solid): 758, 806, 1155, 1273, 1498, 2960 cm^{-1}

HRMS calcd. for C$_{33}$H$_{43}$AuN$_2$O$_3$S [M+H]$^+$ 745.2738, **found** 745.2737 ; **calcd. for C$_{33}$H$_{42}$AuN$_2$O$_3$S [M+Na]$^+$** 745.26, **found** 767.26.

[Au(OSO$_2$Ph)(IPr^{Cl})] (Au-5)



White solid (102 mg, 84% yield)

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.60 (t, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 2H, CH_{Ar}), 7.50-7.48 (m, 2H, CH_{Ar}), 7.35-7.30 (m, 5H, CH_{Ar}), 7.20 (m, 2H, CH_{Ar}), 2.39 (sept, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 4H, CH(CH_3)$_2$), 1.30 (d, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 12H, CH(CH_3)$_2$), 1.25 (d, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$).

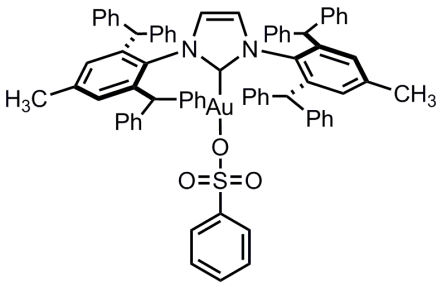
^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.1 (s, 1C, C_{Ar}), 146.2 (s, 4C, C_{Ar}), 131.9 (s, 2C, C_{Ar}), 131.0 (s, 1C, CH$_{Ar}$), 130.5 (s, 2C, CH$_{Ar}$),), 128.2 (s, 2C, CH$_{Ar}$), 126.4 (s, 2C, CH$_{Ar}$), 124.9 (s, 4C, CH$_{Ar}$), 119.4 (s, 2C, C_4 and C_5), 29.4 (s, 4C, CH(CH_3)$_2$), 24.6 (s, 4C, CH(CH$_3$)$_2$), 23.7 (s, 4C, CH(CH$_3$)$_2$).

Elemental analysis: *Calculated* - C: 48.84, H: 4.84, N: 3.45 ; *found* - C: 48.87, H: 4.87, N: 3.37.

IR (solid): 759, 804, 966, 1151, 1159, 1294, 2960 cm^{-1}

HRMS calcd. for $C_{33}H_{39}AuCl_2N_2O_3S$ [M+H]$^{+}$ 811.1802, **found** 811.1816 ; **calcd. for $C_{33}H_{38}AuCl_2N_2O_3SNa$ [M+Na]$^{+}$** 833.16, **found** 833.16.

[Au(OSO$_2$Ph)(IPr*)] (Au-6)



White solid (103 mg, 92% yield)

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.70-7.69 (m, 2H, CH_{Ar}), 7.24-7.22 (m, 1H, CH_{Ar}), 7.19-7.12 (m, 24H, CH_{Ar}), 7.10-7.03 (m, 10H, CH_{Ar}), 6.86 (m, 12H, CH_{Ar}), 5.78 (s, 2H, H_4 and H_5), 5.18 (s, 4H, CHPh$_2$), 2.27 (s, 6H, CH_3).

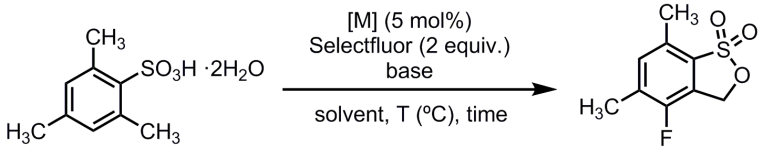
^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 177.1 (s, 1C, C_2), 164.1 (s, 1C, C_{Ar}), 143.1 (s, 4C, C_{Ar}), 142.1 (s, 4C, C_{Ar}), 141.0 (s, 4C, C_{Ar}), 140.5 (s, 2C, C_{Ar}), 133.5 (s, 2C, C_{Ar}), 130.4 (s, 4C, CH$_{Ar}$), 130.3 (s, 2C, CH$_{Ar}$), 129.8 (s, 8C, CH$_{Ar}$), 129.4 (s, 8C, CH$_{Ar}$), 128, 8 (s, 8C, CH$_{Ar}$), 128.5 (s, 8C, CH$_{Ar}$), 128.1 (s, 4C, C_{Ar}), 126.9 (s, 4C, C_{Ar}), 126.5 (s, 4C, C_{Ar}), 123.6 (s, 2C, C_4 and C_5), 51.4 (s, 4C, CHPh$_2$), 22.1 (s, 2C, CH$_3$).

Elemental analysis: *Calculated* - C: 71.08, H: 4.85, N: 2.21 ; *found* - C: 70.89, H: 4.66, N: 2.31

IR (solid): 759, 970, 1163, 1282, 1446, 1492, 3647 cm^{-1}

HRMS calcd. for $C_{75}H_{61}AuN_2O_3S$ $[M+H]^+$ 1267.4147, **found** 1267.4127 ; **calcd. for $C_{75}H_{60}AuN_2O_3SNa$ $[M+Na]^+$** 1289.40, **found** 1289.39 ; **calcd. for $C_{69}H_{57}N_2$ $[IPr^*+H]^+$** 913.45, **found** 913.45. Weak signals were obtained for these fragments (see Supporting Data CD - Chapter 2/Au-6/HRMS).

7.2.1.3 Optimisation of the sequential C(sp^2)-H fluorination/oxidative cyclisation of 2,4,6-trimethylbenzenesulfonic acid dihydrate (1a).



1a **3a**

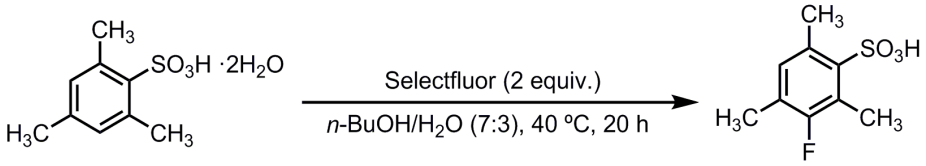
A 3-mL screwcap vial equipped with a stirring bar was charged with **1a** (24.4 mg, 0.10 mmol), Selectfluor (71.1 mg, 0.20 mmol, 2 equiv.), base and solvent (0.2 mL). The sample was stirred in air at the appropriate temperature and time. A freshly prepared solution of 1-bromo-3-fluorobenzene (0.5 mL, 0.2 M in $CDCl_3$) was then added to the reaction mixture. The sample was homogeinised, filtered through a small plug of cotton and analysed by ^{19}F-{^1H} NMR. CH_2Cl_2 (5 mL) and H_2O (5 mL) were added to the reaction mixture, and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (3x5 mL), and the organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, obtaining the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.03 (d, $^4J_{H\text{-}F}$ = 5.9 Hz, 1H, CH_{Ar}), 5.40 (s, 2H, CH_2), 2.52 (s, 3H, CH_3), 2.37 (s, 3H, CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 159.8 (d, $^1J_{C\text{-}F}$ = 248.8 Hz, 1C, *C*-F), 132.3 (d, $^2J_{C\text{-}F}$ = 20.0 Hz, 1C, C_{Ar}), 130.1 (d, $^3J_{C\text{-}F}$ = 3.2 Hz, 1C, C_{Ar}), 122.7 (d, $^3J_{C\text{-}F}$ = 5.2 Hz, 1C, *C*H$_{Ar}$), 121.2 (d, $^2J_{C\text{-}F}$ = 23.2 Hz, 1C, C_{Ar}), 70.2 (s, 1C, C_{Ar}), 29.8 (s, 1C, *C*H$_2$), 15.7 (d, $^3J_{C\text{-}F}$ = 4.4 Hz, 1C, *C*H$_3$), 10.0 (d, $^5J_{C\text{-}F}$ = 3.6 Hz, 1C, *C*H$_3$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -118.9 (s, 1F, C-*F*).

7.2.1.4 Optimised C(sp^2)-H fluorination of 2,4,6-trimethylbenzene sulfonic acid (1a).



1a **3'a**

A 3-mL screwcap vial equipped with a stirring bar was charged with **1a** (120 mg, 0.50 mmol), Selectfluor (373 mg, 1.00 mmol, 2 equiv.), *n*-butanol (1.1 mL) and water (0.4 mL). The mixture was stirred in air at 40 ºC for 20 h. The mixture was concentrated under reduced pressure, and CH_2Cl_2 (2 mL) were added to the residue, and the sample was filtered through a plug of cotton. The operation was repeated twice with the crude residue. The gathered organic phases were concentrated under reduced pressure. H_2O (0.3 mL) was added and the sample was again concentrated under reduced pressure. This operation was repeated twice, obtaining **3'a** as a brownish oil.

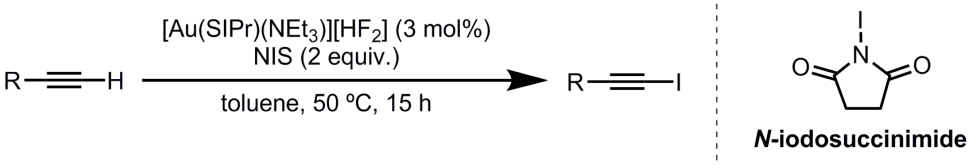
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 10.3 (s, bs, SO_3H), 6.73 (d, $^4J_{H\text{-}F}$ = 4.0 Hz, 1H, CH_{Ar}), 2.35 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.17 (s, 3H, CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 157.9 (d, $^1J_{H\text{-}F}$ = 242.2 Hz, 1C, *C*-F), 136.7 (s, bs, 1C, C_{Ar}), 132.5 (d, $^4J_{C\text{-}F}$ = 4.0 Hz, 1C, C_{Ar}-CH_3), 132.4 (d, $^3J_{C\text{-}F}$ = 4.9 Hz, 1C, *C*H_{Ar}), 127.9 (d, $^2J_{C\text{-}F}$ = 19.8 Hz, 1C, C_{Ar}-CH_3), 124.8 (d, $^2J_{C\text{-}F}$ = 18.4 Hz, 1C, C_{Ar}-CH_3), 22.2 (s, 1C, *C*H_3), 14.8 (d, $^3J_{C\text{-}F}$ = 3.6 Hz, 1C, *C*H_3), 12.4 (d, $^3J_{C\text{-}F}$ = 7.7 Hz, 1C, *C*H_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -120.1 (s, 1F, C-*F*).

7.2.2 Chapter 3

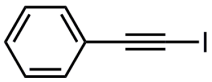
7.2.2.1 Au-catalysed iodination of terminal alkynes



***N*-iodosuccinimide**

A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 15.0 μmol, 3 mol%), *N*-iodosuccinimide (237 mg, 1.00 mmol, 2 equiv.), toluene (0.5 mL) and the terminal alkyne (0.50 mmol). The vial was briefly flushed with N_2, and the reaction mixture was stirred at 50 ºC for 15 h. The reaction crude was purified by column chromatography (SiO_2), obtaining the expected compounds.

(Iodoethynyl)benzene (5a)



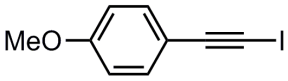
The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a pale yellow oil (203 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.46-7.40 (m, 2H, CH_{Ar}), 7.34-7.29 (m, 3H, CH_{Ar}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 132.5 (s, 2C, *C*H_{Ar}), 128.9 (s, 1C, *C*H_{Ar}), 128.4 (s, 2C, *C*H_{Ar}), 123.5 (s, 1C, *C*$_{Ar}$), 94.3 (s, 1C, *C*≡CI), 6.3 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[10]

1-(Iodoethynyl)-4-methoxybenzene (5b)



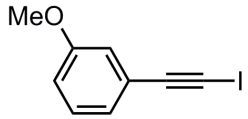
The general procedure afforded the title compound after column chromatography (SiO_2, hexane:AcOEt, 8:2), as a yellow solid (108 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.37 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 2H, CH_{Ar}), 6.82 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 2H, CH_{Ar}), 3.80 (s, 3H, OCH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 160.1 (s, *C*$_{Ar}$), 133.9 (s, 2C, *C*H_{Ar}), 115.7 (s, *C*$_{Ar}$), 114.0 (s, 2C, *C*H_{Ar}), 94.1 (s, 1C, *C*≡CI), 55.4 (s, 1C, O*C*H_3), 3.9 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[11]

1-(Iodoethynyl)-3-methoxybenzene (5c)



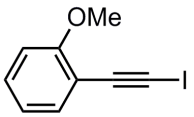
The general procedure afforded the title compound after column chromatography (SiO_2, hexane:AcOEt, 9:1), as a pale yellow solid (126 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.21 (t, $^3J_{H-H}$ = 8.0 Hz, 1H, C*H*$_{Ar}$), 7.03 (d, ^{3}J = 8.0 Hz, 1H, C*H*$_{Ar}$), 7.03 (d, ^{3}J = 8.0 Hz, 1H, C*H*$_{Ar}$), 6.95 (br, s, 1H, C*H*$_{Ar}$), 6.88 (dd, $^3J_{H-H}$ = 8.0 Hz, $^4J_{H-H}$ = 2.5 Hz, 1H, C*H*$_{Ar}$), 3.79 (s, 3H, O*C*H$_3$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 159.3 (s, 1C, *C*-OCH$_3$), 129.4 (s, 1C, *C*H$_{Ar}$), 125.0 (s, 1C, *C*H$_{Ar}$), 124.4 (s, 1C, *C*$_{Ar}$), 117.2 (s, 1C, *C*H$_{Ar}$), 115.7 (s, 1C, *C*H$_{Ar}$), 94.2 (s, 1C, *C*≡CI), 55.4 (s, 1C, O*C*H$_3$), 6.2 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[10]

1-(Iodoethynyl)-2-methoxybenzene (5d)



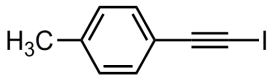
The general procedure afforded the title compound after column chromatography (SiO_2, hexane:AcOEt, 9:1), as a yellow oil (52 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.40 (dd, $^4J_{H-H}$ = 1.6 Hz, $^3J_{H-H}$ = 7.6 Hz, 1H, C*H*$_{Ar}$), 7.29 (td, $^4J_{H-H}$ = 1.6 Hz, $^3J_{H-H}$ = 8.0 Hz, 1H, C*H*$_{Ar}$), 6.86-6.91 (m, 2H, C*H*$_{Ar}$), 3.88 (s, 3H, O*C*H$_3$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 161.1 (s, 1C, *C*-OCH$_3$), 134.5 (s, 1C, *C*H$_{Ar}$), 130.4 (s, 1C, *C*H$_{Ar}$), 120.4 (s, 1C, *C*H$_{Ar}$), 112.7 (s, 1C, *C*$_{Ar}$), 110.7 (s, 1C, *C*H$_{Ar}$), 90.5 (s, 1C, *C*≡CI), 55.9 (s, 1C, O*C*H$_3$), 9.4 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[12]

1-(Iodoethynyl)-4-methylbenzene (5ea)



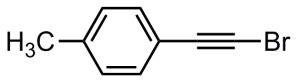
The general procedure afforded the title compound after column chromatography (SiO_2, hexane), as a yellow oil (113 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.32 (d, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, CH_{Ar}), 7.10 (d, $^3J_{H\text{-}H}$ = 6.0 Hz, 2H, CH_{Ar}), 2.34 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 139.1 (s, 1C, C_{Ar}), 132.3 (s, 2C, CH$_{Ar}$), 129.1 (s, 2C, CH$_{Ar}$), 120.5 (s, 1C, C_{Ar}), 94.4 (s, 1C, C≡CI), 21.7 (s, 1C, Ar-CH$_3$), 5.1 (s, 1C, C-I).

This compound has been reported before and the analytical data match the literature report.[10]

1-(Bromoethynyl)-4-methylbenzene (5eb)



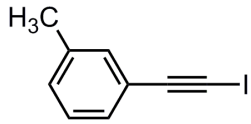
The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a yellow liquid (88 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.33 (d, 2H, $^3J_{H\text{-}H}$ = 7.8 Hz, CH_{Ar}), 7.11 (d, 2H, $^3J_{H\text{-}H}$ = 7.8 Hz, CH_{Ar}), 2.34 (s, 3H, C-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 139.0 (s, 1C, C_{Ar}), 132.0 (s, 2C, CH$_{Ar}$), 129.2 (s, 2C, CH$_{Ar}$), 119.8 (s, 1C, C_{Ar}), 80.3 (s, 1C, C≡CBr), 48.9 (s, 1C, CBr), 21.7 (s, 1C, Ar-CH$_3$).

This compound has been reported before and the analytical data match the literature report.[13]

1-(Iodoethynyl)-3-methylbenzene (5fa)



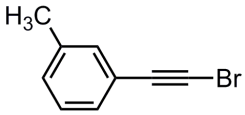
The general procedure afforded the title compound after column chromatography (SiO_2, hexane), as a yellow oil (110 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.22-7.25 (m, 2H, CH_{Ar}), 7.19 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 1H, CH_{Ar}), 7.11-7.13 (m, 1H, CH_{Ar}), 2.31 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 138.1 (1C, C_{Ar}), 133.0 (1C, CH$_{Ar}$), 129.8 (1C, CH$_{Ar}$), 129.5 (1C, CH$_{Ar}$), 128.2 (1C, CH$_{Ar}$), 123.3 (1C, C_{Ar}), 94.4 (1C, C≡CI), 21.3 (1C, Ar-CH$_3$), 5.7 (1C, C-I).

This compound has been reported before and the analytical data match the literature report.[13]

1-(Bromoethynyl)-3-methylbenzene (5fb)



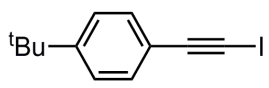
The general procedure optimized for 1-bromoalkynes was employed, and afforded the title compound after column chromatography (SiO_2, pentane), as a pale yellow oil (88 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.27-7.24 (m, 2H, CH_{Ar}), 7.21-7.13 (m, 2H, CH_{Ar}), 2.32 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 138.2 (1C, C_{Ar}), 132.7 (1C, CH$_{Ar}$), 129.7 (1C, CH$_{Ar}$), 129.2 (1C, CH$_{Ar}$), 128.4 (1C, CH$_{Ar}$), 122.6 (1C, C_{Ar}), 80.3 (1C, C≡CBr), 49.4 (1C, C-Br), 21.3 (1C, Ar-CH$_3$).

This compound has been reported before and the analytical data match the literature report.[13]

4-(*tert*-Butyl)-1-(iodoethynyl)benzene (5g)



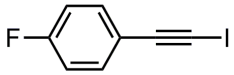
The general procedure afforded the title compound after column chromatography (SiO_2, hexane), as a white solid (116 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.31-7.38 (m, 4H, CH_{Ar}), 1.30 (s, 9H, C(CH_3)$_3$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 152.3 (s, 1C, C_{Ar}), 132.2 (s, 2C, C_{Ar}), 125.4 (s, 2C, C_{Ar}), 120.5 (s, 1C, C_{Ar}), 94.4 (s, 1C, *C*≡CI), 35.0 (s, 1C, *C*(CH$_3$)$_3$), 31.3 (s, 3C, C(*C*H$_3$)$_3$), 5.0 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[10]

4-Fluoro-1-(iodoethynyl)benzene (5h)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a yellow oil (103 mg, 84%).

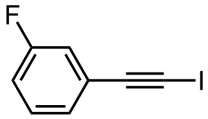
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.41 (m, 2H, CH_{Ar}), 7.00 (t, $^{3}J_{H-H}$ = 8.6 Hz, 2H, CH_{Ar}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 162.4 (d, $^{1}J_{C-F}$ = 250.4 Hz, 1C, *C*-F), 134.4 (d, $^{3}J_{C-F}$ = 8.5 Hz, 2C, *C*H$_{Ar}$), 119.6 (d, $^{4}J_{C-F}$ = 3.4 Hz, 1C, C_{Ar}), 115.7 (d, $^{2}J_{C-F}$ = 22.2 Hz, 2C, *C*H$_{Ar}$), 93.1 (s, 1C, *C*≡CI), 6.1 (s, 1C, *C*-I).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -109.7 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[14]

3-Fluoro-1-(iodoethynyl) benzene (5i)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as an orange oil (98 mg, 80%).

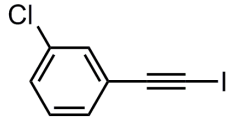
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.19-7.31 (m, 2H, CH_{Ar}), 7.10-7.14 (m, 1H, CH_{Ar}), 7.00-7.07 (m, 1H, CH_{Ar}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 162.3 (d, $^{1}J_{C\text{-}F}$ = 246.9 Hz, 1C, *C*-F), 129.9 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz, 1C, *C*H$_{Ar}$), 128.4 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz, 1C, *C*H$_{Ar}$), 125.2 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz, 1C, *C*$_{Ar}$), 119.3 (d, $^{2}J_{C\text{-}F}$ = 22.9 Hz, 1C, *C*H$_{Ar}$), 116.4 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz, 1C, *C*H$_{Ar}$), 92.9 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz, 1C, *C*≡CI), 8.3 (s, 1C, *C*-I).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -112.5 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[15]

3-Chloro-1-(iodoethynyl)benzene (5j)



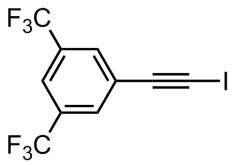
The general procedure afforded the title compound after column chromatography (SiO_2, hexane), as a yellow oil (125 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.41 (t, $^{4}J_{H\text{-}H}$ = 1.7 Hz, 1H, C*H*$_{Ar}$), 7.29-7.32 (m, 2H, C*H*$_{Ar}$), 7.21-7.25 (m, 1H, C*H*$_{Ar}$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 134.2 (s, 1C, C$_{Ar}$), 132.4 (s, 1C, C*H*$_{Ar}$), 130.6 (s, 1C, C*H*$_{Ar}$), 129.6 (s, 1C, C*H*$_{Ar}$), 129.3 (s, 1C, C*H*$_{Ar}$), 125.1 (s, 1C, C$_{Ar}$), 92.8 (s, 1C, *C*≡CI), 8.5 (s, 1C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[16]

1-iodoethynyl-3,5-bis(trifluoromethyl)benzene (5k)



The general procedure afforded the title compound in 24 h after column chromatography (SiO_2, pentane), as a yellow oil (147 mg, 81%).

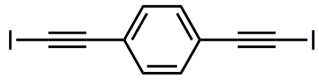
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.87 (s, bs, 2H, C*H*$_{Ar}$), 7.81 (s, bs, 1H, C*H*$_{Ar}$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 132.4 (q, $^{3}J_{C\text{-}F}$ = 2.9 Hz, 2C, CH_{Ar}), 132.1 (q, $^{2}J_{C\text{-}F}$ = 33.8 Hz, 2C, C_{Ar}), 125.7 (s, 1C, C_{Ar}), 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.9 Hz, 2C, CF_3), 122.3 (sept, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 1C, CH_{Ar}), 91.3 (s, 1C, C≡CI), 12.7 (1C, *C*-I).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -63.2 (s, 6F, CF_3)

HRMS calcd. for C_9H_7I [M]$^+$ 363.9184, **found** 363.9183.

1,4-Bis(iodoethynyl)benzene (5l)



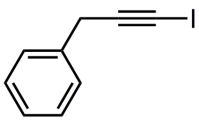
The general procedure using 6 mol% of catalyst afforded the title compound after column chromatography (SiO_2, hexane), as a white solid (159 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.36 (s, 4H, CH_{Ar})

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 132.3 (s, 4C, CH_{Ar}), 123.9 (s, 2C, C_{Ar}), 93.7 (s, 2C, C≡CI), 9.2 (s, 2C, *C*-I).

This compound has been reported before and the analytical data match the literature report.[13]

3-Phenyl-1-iodo-1-propyne (5m)



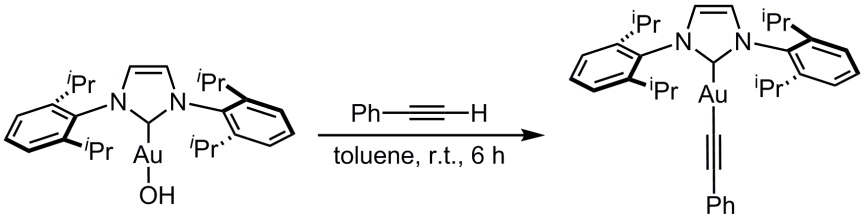
The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a yellow oil (73 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.35-7.30 (m, 4H, CH_{Ar}), 7.26-7.23 (m, 1H, CH_{Ar}), 3.77 (s, 2H, CH_2).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 136.0 (s, 1C, CH_{Ar}), 128.6 (s, 2C, CH_{Ar}), 127.9 (s, 2C, CH_{Ar}), 126.8 (s, 1C, C_{Ar}), 92.0 (s, 1C, C≡CI), 27.1 (s, 1C, CH_2), -4.1 (s, 1C, *C*-I).

HRMS calcd. for C_9H_7I $[M]^+$ 241.9593, **found** 241.9599.

7.2.2.2 Synthesis of Au(I)-NHC catalytic intermediates: [Au(C≡CPh)(IPr)] (D) and [Au(succinimide)(IPr)] (E).



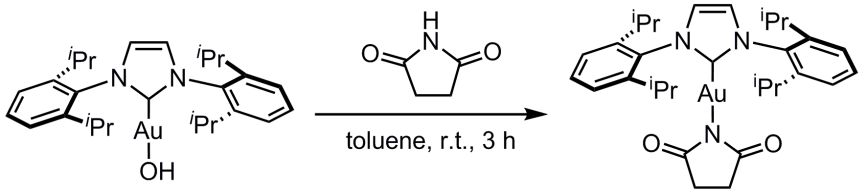
[Au(OH)(IPr)] **[Au(C≡CPh)(IPr)]**

A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(OH)(IPr)] (100 mg, 0.17 mmol), **4a** (19 μL, 0.18 mmol, 1.03 equiv.) and toluene (0.5 mL). The mixture was stirred in air at room temperature for 6 h. The solvent was removed under reduced pressure, and pentane (2 mL) was then added. The precipitate was recovered by filtration and washed with pentane (3x10 mL), obtaining **D** as a white solid (103 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.49 (t, $^3J_{H\text{-}H}$ = 7.9 Hz, 2H, CH_{Ar}), 7.30-7.28 (m, 6H, CH_{Ar}), 7.12-7.02 (m, 5H, CH_{Ar} + H_4 and H_5), 2.61 (sept, $^3J_{H\text{-}H}$ = 6.8 Hz, 4H, CH(CH_3)$_2$), 1.38 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$), 1.22 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 191.1 (s, 1C, C_2), 145.7 (s, 4C, C_{Ar}), 134.5 (s, 2C, C_{Ar}), 132.4 (s, 2C, CH$_{Ar,Ph}$), 130.6 (s, 2C, C_4 and C_5), 129.4 (s, 1C, $C_{Ar,Ph}$), 127.6 (s, 2C, CH$_{Ar,Ph}$), 126.1 (s, 1C, C≡C-Au), 125.8 (s, 1C, CH$_{Ar,Ph}$), 124.3 (s, 4C, CH$_{Ar}$), 123.3 (s, 2C, CH$_{Ar}$), 103.8 (s, 1C, C≡C-Au), 28.9 (s, 4C, CH(CH_3)$_2$), 24.8 (s, 4C, CH(CH$_3$)$_2$), 24.2 (s, 4C, CH(CH$_3$)$_2$).

This compound has been reported before and the analytical data match the literature report.[17]



[Au(OH)(IPr)] **[Au(succinimide)(IPr)]**

A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(OH)(IPr)] (100 mg, 0.17 mmol), succinimide (17.2 mg, 0.17 mmol, 1.02 equiv.) and toluene (0.5 mL). The mixture was stirred in air at room temperature for 3 h. The solvent was removed under reduced pressure, and pentane (2 mL) was then added. The precipitate was recovered by filtration and washed with cold H_2O (2x1 mL) and pentane (3x10 mL), obtaining **E** as a white solid (108 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.49 (t, $^3J_{H\text{-}H}$ = 7.8 Hz, 2H, CH_{Ar}), 7.29 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 4H, CH_{Ar}), 7.19 (s, 2H, H_4 and H_5), 2.57 (sept, $^3J_{H\text{-}H}$ = 7.0 Hz, 4H, CH(CH_3)$_2$), 2.33 (s, 4H, CH_2), 1.39 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 12H, CH(CH_3)$_2$), 1.23 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 12H, CH(CH_3)$_2$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 188.1 (s, 1C, C_2), 177.2 (s, 2C, C=O), 145.9 (s, 4C, C_{Ar}), 134.1 (s, 2C, C_{Ar}), 130.7 (s, 2C, CH$_{Ar}$), 124.3 (s, 4C, CH$_{Ar}$), 123.2 (s, 2C, C_4 and C_5), 31.6 (s, 2C, CH$_2$), 29.0 (s, 4C, CH(CH_3)$_2$), 24.5 (s, 4C, CH(CH$_3$)$_2$), 24.2 (s, 4C, CH(CH$_3$)$_2$).

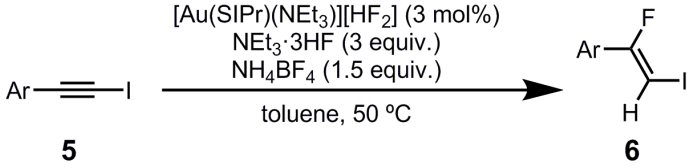
Elemental analysis: *Calculated* - C: 54.46, H: 5.90, N: 6.15 ; *found* - C: 54.40, H: 5.92, N: 6.21.

IR (solid): 1228, 1346, 1456, 1471, 1651, 2960 cm^{-1}

HRMS calcd. for $C_{31}H_{40}AuN_3O_2$ [M+H]$^+$ 684.2864, **found** 684.2867 ; **calcd. for $C_{31}H_{39}AuN_3O_2Na$ [M+Na]$^+$** 706.27, **found** 706.27.

7.2.3 Chapter 4

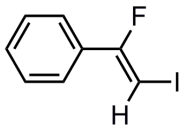
7.2.3.1 Au-catalysed hydrofluorination of 1-iodoalkynes



5 **6**

A 2-mL plastic screwcap vial equipped with a stirring bar was charged with the substrate (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (10.9 mg, 15.0 µmol, 3 mol%), NH_4BF_4 (81.0 mg, 750 µmol, 1.5 equiv.) and toluene (1.00 mL). NEt_3·3HF (0.25 mL, 1.50 mmol, 3 equiv.) was added dropwise while stirring. The vial was briefly flushed with N_2, and the reaction mixture was stirred at 50 ^oC for the specified time. The conversion was monitored by ^1H NMR ($CDCl_3$). After full conversion of the starting material, the crude mixture was purified by column chromatography (SiO_2).

(*Z*)-2-Fluoro-1-iodo-2-phenylethene (6a)



The general procedure afforded the title compound in 2 h after column chromatography (SiO_2, pentane), as a yellow oil (109 mg, 88 %).

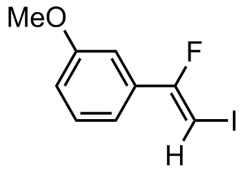
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.53-7.50 (m, 2H, CH_{Ar}), 7.40-7.37 (m, 3H, CH_{Ar}), 6.09 (d, $^3J_{H\text{-}F}$ = 36.0 Hz, 1H, CH_{vinyl}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 163.2 (d, $^1J_{C\text{-}F}$ = 252.2 Hz, 1C, *C*-F), 130.9 (d, $^2J_{C\text{-}F}$ = 29.0 Hz, 1C, C_{Ar}), 130.0 (s, 2C, CH_{Ar}), 128.8 (s, 1C, CH_{Ar}), 124.8 (d, $^3J_{C\text{-}F}$ = 6.1 Hz, 2C, CH_{Ar}), 53.6 (d, $^2J_{C\text{-}F}$ = 29.0 Hz, 1C, CH_{vinyl}).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -90.0 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[18]

(*Z*)-2-Fluoro-1-iodo-2-(3-methoxyphenyl)ethene (6c)



The general procedure afforded the title compound in 3 h after column chromatography (SiO_2, pentane:AcOEt, 9:1), as a yellow oil (126 mg, 91%).

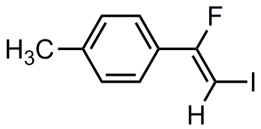
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.31-7.26 (m, 1H, C*H*$_{Ar}$), 7.11-7.09 (m, 1H, C*H*$_{Ar}$), 7.03-7.02 (m, 1H, C*H*$_{Ar}$), 6.93 (m, 2H, C*H*$_{Ar}$), 6.08 (d, $^3J_{H\text{-}F}$ = 34.3 Hz, 1H, CH_{vinyl}), 3.82 (s, 3H, OCH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 163.0 (d, $^1J_{C\text{-}F}$ = 252.3 Hz, 1C, *C*-F), 159.8 (d, $^4J_{C\text{-}F}$ = 1.8 Hz, 1C, *C*$_{Ar}$), 132.2 (d, $^3J_{C\text{-}F}$ = 28.9 Hz, 1C *C*$_{Ar}$), 129.9 (d, $^4J_{C\text{-}F}$ = 1.2 Hz, 1C, *C*H$_{Ar}$), 117.3 (d, $^3J_{C\text{-}F}$ = 6.2 Hz, 1C, *C*H$_{Ar}$), 115.7 (s, 1C, *C*H$_{Ar}$), 110.2 (d, $^3J_{C\text{-}F}$ = 6.4 Hz, 1C, *C*H$_{Ar}$), 55.5 (s, 1C, O-*C*H$_3$), 53.9 (d, $^2J_{C\text{-}F}$ = 29.1 Hz, 1C, CH_{vinyl}).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -89.5 (s, 1F, C-*F*)

HRMS calcd. for C_9H_8FIO [M]$^+$ 277.9598, **found** 277.9603

(*Z*)-2-Fluoro-1-iodo-2-(4-methylphenyl)ethene (6ea)



The general procedure afforded the title compound in 2 h after column chromatography (SiO_2, pentane), as a white solid (107 mg, 82%).

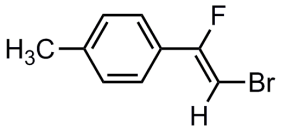
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.40 (dt, $^3J_{H\text{-}H}$ = 8.4 Hz, $^4J_{H\text{-}F}$ = 2.0 Hz, 2H, C*H*$_{Ar}$), 7.17 (m, 2H, C*H*$_{Ar}$), 5.99 (d, $^3J_{H\text{-}F}$ = 34.6 Hz, 1H, CH_{vinyl}), 2.35 (s, 3H, C-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 163.3 (d, $^1J_{C\text{-}F}$ = 251.8 Hz, 1C, *C*-F), 140.2 (s, 1C, *C*$_{Ar}$), 129.5 (d, $^4J_{C\text{-}F}$ = 1.0 Hz, 2C, *C*H$_{Ar}$), 128.3 (d, $^2J_{C\text{-}F}$ = 29.2 Hz, 1C, *C*$_{Ar}$), 124.7 (d, $^3J_{C\text{-}F}$ = 6.1 Hz, 2C, *C*H$_{Ar}$), 52.4 (d, $^2J_{C\text{-}F}$ = 29.2 Hz, 1C, CH_{vinyl}), 21.5 (s, 1C, *C*H$_3$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -89.8 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[19]

(*Z*)-1-Bromo-2-fluoro-2-(4-methylphenyl)ethene (6eb)



The general procedure afforded the title compound in 2 h after column chromatography (SiO_2, pentane), as a white solid (90 mg, 84%).

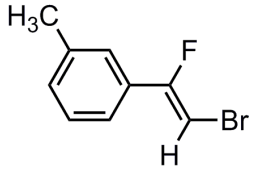
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.38 (m, 2H, C*H*$_{Ar}$), 7.19 (d, $^{3}J_{H-H}$ = 8.1 Hz, 2H, C*H*$_{Ar}$), 6.05 (d, $^{3}J_{H-F}$ = 27.8 Hz, 1H, C*H*$_{vinyl}$), 2.36 (s, 3H, C-C*H*$_3$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 159.8 (d, $^{1}J_{C-F}$ = 253.8 Hz, 1C, *C*-F), 140.2 (s, 1C, *C*$_{Ar}$), 129.6 (s, 2C, *C*H$_{Ar}$), 128.0 (d, $^{2}J_{C-F}$ = 27.5 Hz, 1C, *C*$_{Ar}$), 124.4 (d, $^{3}J_{C-F}$ = 6.0 Hz, 2C, *C*H$_{Ar}$), 83.9 (d, $^{2}J_{C-F}$ = 24.3 Hz, 1C, *C*H$_{vinyl}$), 21.5 (s, 1C, *C*H$_3$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -104.4 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[19]

(*Z*)-1-Bromo-2-fluoro-2-(3-methylphenyl)ethene (6fb)



The general procedure afforded the title compound in 2 h after column chromatography (SiO_2, pentane), as a yellow oil (97 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.30-7.25 (m, 3H, C*H*$_{Ar}$), 7.22-7.20 (m, 1H, C*H*$_{Ar}$), 6.10 (d, $^{3}J_{H-F}$ = 27.9 Hz, 1H, C*H*$_{vinyl}$), 2.38 (s, 3H, C*H*$_3$).

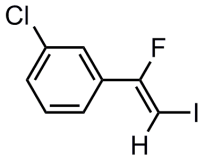
^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 159.8 (d, $^{1}J_{C-F}$ = 253.1 Hz, 1C, *C*-F), 138.7 (d, $^{4}J_{C-F}$ = 1.5 Hz, 1C, *C*$_{Ar}$), 130.8 (s, 1C, CHAr), 130.7 (d, $^{2}J_{C-F}$ = 27.1 Hz,

1C, C_{Ar}), 128.8 (d, $^{4}J_{C\text{-}F}$ = 1.5 Hz, 1C, CH$_{Ar}$), 125.1 (d, $^{3}J_{C\text{-}F}$ = 5.9 Hz, 1C, CH$_{Ar}$), 121.7 (d, $^{3}J_{C\text{-}F}$ = 5.9 Hz, 1C, CH$_{Ar}$), 84.7 (d, $^{2}J_{C\text{-}F}$ = 24.2 Hz, 1C, CH$_{vinyl}$), 21.6 (s, 1C, CH$_3$)

^{19}F-{^{1}H} NMR (377 MHz, CDCl$_3$, 298K): δ (ppm) = -104.4 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[19]

(*Z*)-2-Fluoro-1-iodo-2-(3-chlorophenyl)ethene (6j)



The general procedure afforded the title compound in 3 h after column chromatography (SiO_2, pentane), as an orange oil (123 mg, 87%).

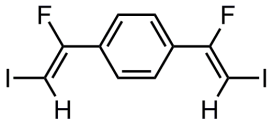
^{1}H NMR (400 MHz, CDCl$_3$, 298K, TMS): δ (ppm) = 7.49 (t, $^{4}J_{H\text{-}H}$ = 1.8 Hz, 1H, CH_{Ar}), 7.40-7.31 (m, 3H, CH_{Ar}), 6.16 (d, $^{3}J_{H\text{-}F}$ = 34.2 Hz, 1H, CH_{vinyl}).

^{13}C-{^{1}H} NMR (101 MHz, CDCl$_3$, 298K): δ (ppm) = 161.9 (d, $^{1}J_{C\text{-}F}$ = 252.3 Hz, 1C, *C*-F), 134.9 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz, 1C, C_{Ar}), 132.6 (d, $^{2}J_{C\text{-}F}$ = 29.8 Hz, 1C, C_{Ar}), 130.1 (d, $^{5}J_{C\text{-}F}$ = 1.2 Hz, 1C, CH$_{Ar}$), 130.0 (s, 1C, C_{Ar}), 124.9 (d, $^{3}J_{C\text{-}F}$ = 6.4 Hz, 1C, CH$_{Ar}$), 122.9 (d, $^{3}J_{C\text{-}F}$ = 6.0 Hz, 1C, CH$_{Ar}$), 55.2 (d, $^{2}J_{C\text{-}F}$ = 28.7 Hz, 1C, CH_{vinyl}).

^{19}F-{^{1}H} NMR (377 MHz, CDCl$_3$, 298K): δ (ppm) = -90.4 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[19]

1,4-Bis-[(*Z*)-2-fluoro-1-iodoethen-2-yl]benzene (6l)



The general procedure afforded the title compound in 4 h after column chromatography (SiO_2, pentane), as an orange solid (180 mg, 86%).

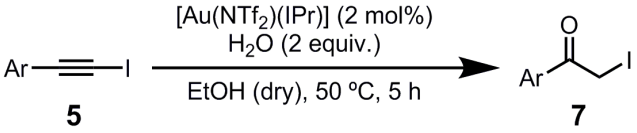
^{1}H NMR (400 MHz, CDCl$_3$, 298K, TMS): δ (ppm) = 7.51 (s, 4H, CH_{Ar}), 6.21 (d, $^{3}J_{H\text{-}F}$ = 34.3 Hz, 2H, CH_{vinyl}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 162.3 (d, $^{1}J_{C\text{-}F}$ = 251.7 Hz, 2C, *C*-F), 131.9 (d, $^{2}J_{C\text{-}F}$ = 29.4 Hz, 2C, C_{Ar}), 125.0 (d, $^{3}J_{C\text{-}F}$ = 4.7 Hz, 4C, *C*H$_{Ar}$), 55.4 (d, $^{2}J_{C\text{-}F}$ = 28.8 Hz, 2C, C*H*$_{vinyl}$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -90.9 (s, 1F, C-*F*)

HRMS calcd. for $C_{10}H_6F_2I_2$ [M]$^+$ 417.8527, **found** 417.8537.

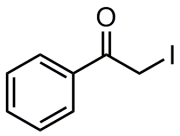
7.2.3.2 Au-catalysed hydration of 1-iodoalkynes



5 **7**

A 3-mL screwcap vial equipped with a stirring bar was charged with the iodoalkyne (0.50 mmol), [Au(NTf$_2$)(IPr)] (8.6 mg, 0.01 mmol, 2 mol%), dry EtOH (1.5 mL) and water (18 μL, 1.00 mmol, 2 equiv.). The reaction mixture was stirred at 50 ºC for 5 h. The solvent was removed under reduced pressure and the product was purified by column chromatography (SiO_2), obtaining the desired compound.

2-Iodo-1-phenylethanone (7a)



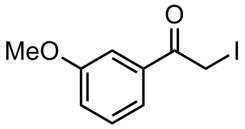
The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt 90:10), as a dark red oil (117 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 8.00-7.98 (m, 2H, C*H*$_{Ar}$), 7.62-7.58 (m, 1H, C*H*$_{Ar}$), 7.51-7.47 (m, 2H, C*H*$_{Ar}$), 4.37 (s, 2H, C*H*$_2$I).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 192.9 (1C, *C*=O), 133.9 (1C, C_{Ar}), 133.6 (1C, *C*H$_{Ar}$), 129.1 (2C, *C*H$_{Ar}$), 129.0 (2C, *C*H$_{Ar}$), 1.8 (1C, *C*H$_2$I).

This compound has been reported before and the analytical data match the literature report.[20]

2-Iodo-1-(3-methoxyphenyl)ethanone (7c)



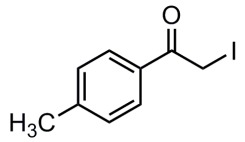
The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 8:2), as a yellow solid (112 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.58-7.51 (m, 1H, CH_{Ar}), 7.52-7.51 (m, 1H, CH_{Ar}), 7.39 (t, $^4J_{H\text{-}H}$ = 7.9 Hz, 1H, CH_{Ar}), 7.15 (ddd, $^3J_{H\text{-}H}$ = 8.3 Hz, $^4J_{H\text{-}H}$ = 2.7 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 1H, CH_{Ar}), 4.36 (s, 2H, CH_2I), 3.87 (s, 3H, OCH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 192.8 (1C, *C*=O), 160.1 (1C, C_{Ar}), 134.9 (1C, C_{Ar}), 129.9 (1C, *C*H$_{Ar}$), 121.8 (1C, *C*H$_{Ar}$), 120.6 (1C, *C*H$_{Ar}$), 113.3 (1C, *C*H$_{Ar}$), 55.6 (1C, O*C*H$_3$) 1.8 (1C, *C*H$_2$I).

HRMS calcd. for C_9H_7I [M+H]$^+$ 276.9725, **found** 276.9727.

2-Iodo-1-(4-methylphenyl)ethanone (7d)



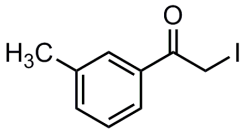
The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 9:1), as a yellow oil (116 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.90-7.88 (m, 2H, CH_{Ar}), 7.29-7.27 (m, 2H, CH_{Ar}), 4.34 (s, 2H, CH_2I), 2.43 (s, 3H, CH_3)

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 192.6 (1C, C=O), 144.9 (1C, C_{Ar}), 131.1 (1C, C_{Ar}), 129.7 (2C, *C*H$_{Ar}$), 129.3 (2C, *C*H$_{Ar}$), 21.9 (1C, Ar-*C*H$_3$), 1.9 (1C, *C*H$_2$I).

This compound has been reported before and the analytical data match the literature report.[21]

2-Iodo-1-(3-methylphenyl)ethanone (7e)



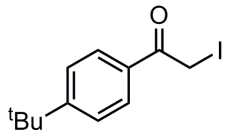
The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 9:1), as a yellow oil (124 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.80-7.77 (m, 2H, C*H*$_{Ar}$), 7.42-7.35 (m, 2H, C*H*$_{Ar}$), 4.36 (s, 2H, C*H*$_2$I), 2.43 (s, 3H, C*H*$_3$)

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 193.2 (1C, *C*=O), 138.9 (1C, *C*$_{Ar}$), 134.8 (1C, *C*$_{Ar}$), 133.6 (1C, *C*H$_{Ar}$), 129.6 (1C, *C*H$_{Ar}$), 128.8 (1C, *C*H$_{Ar}$), 126.4 (1C, *C*H$_{Ar}$), 21.5 (1C, Ar-*C*H$_3$), 1.98 (1C, *C*H$_2$I).

This compound has been reported before and the analytical data match the literature report.[21]

2-Iodo-1-(4-*t*-butylphenyl)ethanone (7f)



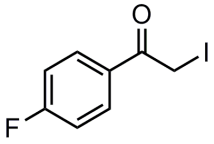
The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 9:1) as a yellow oil (136 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.95-7.93 (m, 2H, C*H*$_{Ar}$), 7.51-7.49 (m, 2 H, C*H*$_{Ar}$), 4.34 (s, 2 H, C*H*$_2$I), 1.35 (s, 9H, C-C*H*$_3$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 192.6 (1C, *C*=O), 157.9 (1C, *C*$_{Ar}$), 131.0 (1C, *C*$_{Ar}$), 129.2 (2C, *C*H$_{Ar}$), 125.9 (2C, *C*H$_{Ar}$), 35.4 (1C, *C*(CH$_3$)$_3$), 31.2 (3C, *C*H$_3$), 1.8 (1C, *C*H$_2$I).

This compound has been reported before and the analytical data match the literature report.[22]

1-(4-Fluorophenyl)-2-iodoethanone (7g)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 9:1), as a pale yellow oil (113 mg, 86%).

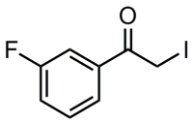
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 8.05-8.00 (m, 2H, CH_{Ar}), 7.19-7.13 (m, 2H, CH_{Ar}), 4.33 (s, 2H, CH_2I)

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 191.5 (s, 1C, C=O), 166.2 (d, $^1J_{C-F}$ = 257.6 Hz, 1C, *C*-F), 131.9 (d, $^3J_{C-F}$ = 9.1 Hz, 1C, *C*H$_{Ar}$), 130.0 (d, $^4J_{C-F}$ = 3.0 Hz, 1C, C_{Ar}), 116.2 (d, $^2J_{C-F}$ = 22.2 Hz, 1C, *C*H$_{Ar}$), 1.4 (s, 1C, *C*H$_2$I).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -103.5 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[20]

1-(3-Fluorophenyl)-2-iodoethanone (7h)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 9:1), as a yellow oil (103 mg, 83%).

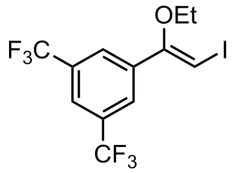
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.78 (m, 1H, CH$_{Ar}$), 7.68 (m, 1H, CH_{Ar}), 7.48 (m, 1H, CH_{Ar}), 7.31 (tdd, $^3J_{H-H}$ = 8.2 Hz, $^4J_{H-H}$ = 2.6 Hz, $^4J_{H-H}$ = 1.0 Hz, 1H, CH_{Ar}), 4.34 (s, 2H, CH_2I)

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 191.7 (1C, *C*=O), 161.0 (d, $^1J_{C-F}$ = 249.5 Hz, 1C, *C*-F), 135.6 (d, $^3J_{C-F}$ = 6.1 Hz, 1C, C_{Ar}), 130.6 (d, $^2J_{C-F}$ = 8.1 Hz, 1C, *C*H$_{Ar}$), 124.9 (d, $^4J_{C-F}$ = 3.0 Hz, 1C, *C*H$_{Ar}$), 121.1 (d, $^3J_{C-F}$ = 21.2 Hz, 1C, *C*H$_{Ar}$), 115.9 (d, $^2J_{C-F}$ = 23.2 Hz, 1C, *C*H$_{Ar}$), 1.3 (s, 1C, *C*H$_2$I)

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -111.1 (s, 1F, C-*F*)

HRMS calcd. for C_9H_7I $[M+H]^+$ 264.9526, **found** 264.9523.

(*Z*)-1-(1-ethoxy-2-iodovinyl)-3,5-bis(trifluoromethyl)benzene (7''k)



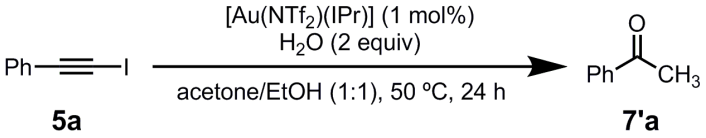
The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a yellow oil (162 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.88 (s, 2H, CH_{Ar}), 7.86 (s, 1H, CH_{Ar}), 6.18 (s, 1H, CH_{vinyl}), 3.84 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2), 1.39 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3)

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 158.8 (s, 1C, *C*O$_{vinyl}$), 136.9 (s, 1C, C_{Ar}), 132.4 (q, $^3J_{C\text{-}F}$ = 33.6 Hz, 2C, C_{Ar}), 126.4 (q, br, 2C, *C*H$_{Ar}$), 123.2 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2C, *C*F$_3$), 122.7 (sept, $^3J_{C\text{-}F}$ = 3.7 Hz, 1C, *C*H$_{Ar}$), 67.3 (s, 1C, *C*H$_2$), 66.2 (s, 1C, *C*-I), 15.5 (s, 1C, *C*H$_3$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = - 62.9 (s, 1F, C-*F*).

7.2.3.3 Au-catalysed hydration/deiodination of 5a



5a **7'a**

A 3-mL screwcap vial equipped with a stirring bar was charged with the iodoalkyne (0.50 mmol), [Au(NTf$_2$)(IPr)] (4.30 mg, 5.00 μmol, 1 mol%), acetone (0.75 mL), dry EtOH (0.75 mL) and water (18 μL, 1.00 mmol, 2 equiv.). The reaction mixture was stirred at 50 ºC for 24 h. The solvents were removed under reduced pressure and the product was purified by column chromatography (SiO_2, pentane:AcOEt, 8:2), obtaining **7'a** as a colourless liquid (56 mg, 93%).

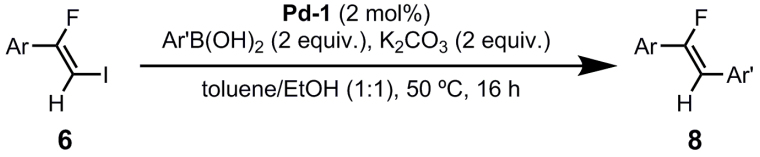
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.98-7.96 (m, 2H, CH_{Ar}), 7.59-7.55 (m, 1H, CH_{Ar}), 7.49-7.45 (m, 2H, s, 1H, CH_{Ar}), 2.62 (s, 3H, CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 198.3 (s, 1C, *C*=O), 137.3 (s, 1C, C_{Ar}), 133.3 (s, 1C, CH_{Ar}), 128.7 (s, 2C, CH_{Ar}), 128.5 (s, 2C, CH_{Ar}), 26.8 (s, 1C, CH_3).

This compound has been reported before and the analytical data match the literature report.[23]

7.2.4 Chapter 5

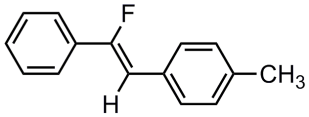
7.2.4.1 Cross-coupling of 2-fluoro-1-iodoalkenes and aryl boronic acids with Pd-1.



6 **8**

A 3-mL screwcap vial equipped with a stirring bar was charged with fluoroalkene (0.50 mmol), boronic acid (1.00 mmol, 2 equiv.), K_2CO_3 (138 mg, 1.00 mmol, 2 equiv.), [Pd(η^3-cinnamyl)(Cl)(IPr)] (6.50 mg, 10.0 μmol, 2 mol%), toluene (0.25 mL) and EtOH (0.25 mL) in air. The reaction mixture was stirred at 50 ^{o}C for 16 h. The solvents were removed under reduced pressure and the residue was purified by column chromatography (SiO_2), obtaining the desired product.

(*Z*)-1-(2-fluoro-2-phenylvinyl)-4-methylbenzene (8aa)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane), as a white solid (91 mg, 86%).

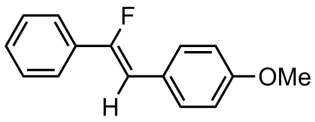
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.63 (d, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 2H, CH_{Ar}), 7.54 (d, $^{3}J_{H\text{-}H}$ = 7.6 Hz, 2H, CH_{Ar}), 7.43-7.32 (m, 3H, CH_{Ar}), 7.18 (d, $^{3}J_{H\text{-}H}$ = 7.8 Hz, 2H, CH_{Ar}), 6.29 (d, $^{3}J_{H\text{-}F}$ = 39.9 Hz, 1H, CH_{vinyl}), 2.36 (s, 3H, CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 156.8 (d, $^{1}J_{C\text{-}F}$ = 257.4 Hz, 1C, *C*-F), 137.4 (d, $^{6}J_{C\text{-}F}$ = 2.2 Hz, 1C, C_{Ar}), 133.0 (d, $^{2}J_{C\text{-}F}$ = 27.8 Hz, 1C, C_{Ar}), 130.9 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, 1C, C_{Ar}), 129.5 (s, 2C, CH_{Ar}), 129.0 (s, 2C, CH_{Ar}), 128.9 (d, $^{3}J_{C\text{-}F}$ = 16 Hz, 2C, CH_{Ar}), 128.7 (d, $^{4}J_{C\text{-}F}$ = 1.7 Hz, 2C, CH_{Ar}), 124.3 (d, $^{5}J_{C\text{-}F}$ = 7.4 Hz, 1C, CH_{Ar}), 105.9 (d, $^{2}J_{C\text{-}F}$ = 10.6 Hz, 1C, CH_{vinyl}), 21.4 (s, 1C, CH_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -115.2 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[24]

(*Z*)-4-[2-fluoro-2-phenylvinyl]-1-methoxybenzene (8ab)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 95:5) and recrystallisation from hot MeOH, as a white solid (96 mg, 84%).

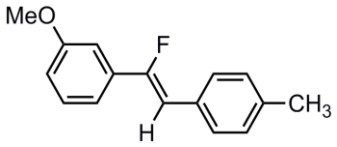
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.64-7.58 (m, 4H, CH_{Ar}), 7.42-7.38 (m, 2H, CH_{Ar}), 7.36-7.31 (m, 1H, CH_{Ar}), 6.92 (m, 2H, CH_{Ar}), 6.27 (d, $^3J_{H\text{-}F}$ = 39.9 Hz, 1H, CH_{vinyl}), 3.84 (s, 3H, OCH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 158.9 (d, $^6J_{C\text{-}F}$ = 11.8 Hz, 1C, C_{Ar}), 156.1 (d, $^1J_{C\text{-}F}$ = 255.7 Hz, 1C, *C*-F), 133.3 (d, $^2J_{C\text{-}F}$ = 28.0 Hz, 1C, C_{Ar}), 130.4 (d, $^4J_{C\text{-}F}$ = 8.1 Hz, 2C, CH_{Ar}), 128.7 (s, 2C, CH_{Ar}), 128.6 (s, 2C, CH_{Ar}), 126.6 (d, $^3J_{C\text{-}F}$ = 11.3 Hz, 1C, C_{Ar}), 124.1 (d, $^5J_{C\text{-}F}$ = 7.4 Hz, 1C, CH_{Ar}), 114.2 (s, 2C, CH_{Ar}), 105.5 (d, $^2J_{C\text{-}F}$ = 10.9 Hz, 1C, CH_{vinyl}), 55.4 (s, 1C, OCH_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -117.1 (s, 1F, C-*F*).

This compound has been reported before and the analytical data match the literature report.[25]

(*Z*)-1-[2-fluoro-2-(3-methoxyphenyl)vinyl]-4-methylbenzene (8c)



The general procedure afforded the title compound after column chromatography (SiO_2, pentane:AcOEt, 10:0 to 95:5), as a pale yellow oil (98 mg, 81%).

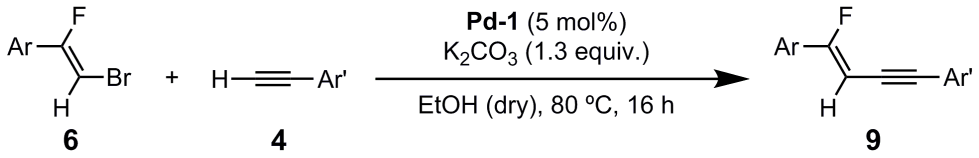
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.53 (m, 2H, CH_{Ar}), 7.30 (m, 1H, CH_{Ar}), 7.23-7.15 (m, 4H, CH_{Ar}), 6.89 (ddd, $^4J_{H\text{-}H}$ = 8.1 Hz, $^4J_{H\text{-}H}$ = 2.6 Hz, $^3J_{H\text{-}H}$ = 0.9 Hz, 1H, CH_{Ar}), 6.27 (d, $^3J_{H\text{-}F}$ = 39.8 Hz, 1H, CH_{vinyl}), 3.84 (s, 4H, Ar-OCH_3), 2.36 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 159.9 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, 1C, *C*-OCH_3), 156.6 (d, $^{1}J_{C\text{-}F}$ = 257.4 Hz, 1C, *C*-F), 137.4 (d, $^{3}J_{C\text{-}F}$ = 2.4 Hz, 1C, C_{Ar}), 134.5 (d, $^{2}J_{C\text{-}F}$ = 27.9 Hz, 1C, C_{Ar}), 130.9 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, 1C, C_{Ar}), 129.7 (d, $^{5}J_{C\text{-}F}$ = 1.6 Hz, 1C, CH_{Ar}), 129.4 (s, 2C, CH_{Ar}), 129.0 (d, $^{4}J_{C\text{-}F}$ = 8.0 Hz, 2C, CH_{Ar}), 116.8 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz, 1C, CH_{Ar}), 114.6 (s, 1C, CH_{Ar}), 109.8 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, 1C, CH_{Ar}), 106.2 (d, $^{2}J_{C\text{-}F}$ =10.6 Hz, 1C, CH_{vinyl}), 55.4 (s, 1C, OCH_3), 21.4 (s, 1C, CH_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K): δ (ppm) = -114.6 (s, 1F, C-*F*)

HRMS calcd. for $C_{16}H_{16}FO$ $[M+H]^+$ 243.1180, **found** 243.1179.

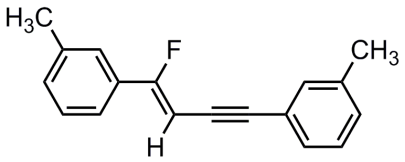
7.2.4.2 Cross-coupling of bromofluoroalkenes and terminal alkynes with Pd-1.



6 **4** **9**

A 3-mL screwcap vial equipped with a septa cap and a stirring bar was charged with **Pd-1** (16.3 mg, 2.50 μmol, 5 mol%), K_2CO_3 (89.7 mg, 0.65 mmol, 1.3 equiv.), the terminal alkyne (1.00 mmol, 2 equiv.) and dry EtOH (0.5 mL). A solution of the bromoalkene (0.50 mmol) in EtOH (0.5 mL) was then added. Two needles attached to balloons were inserted through the septa cap, and the resulting system was stirred in air at 80 ^{o}C for 16 h. The sample was diluted in CH_2Cl_2 (3 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by column chromatography (SiO_2), obtaining the desired compound.

(*Z*)-3,3'-(1-Fluorobut-1-en-3-yne-1,4-diyl)bis(methylbenzene) (9fa)



The optimised procedure afforded the title compound as a mixture of isomers (98:2, *Z:E*) after column chromatography (SiO_2, pentane:AcOEt, gradient from 99:1 to 95:5), as a pale yellow oil (113 mg, 90%).

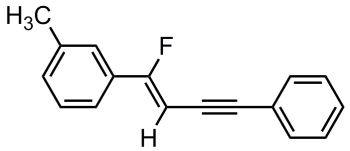
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.38-7.37 (m, 2H, CH_{Ar}), 7.33-7.26 (m, 3H, CH_{Ar}), 7.24-7.19 (m, 2H, CH_{Ar}), 7.14-7.12 (m, 1H, CH_{Ar}), 5.77 (d, $^{3}J_{H-F}$ = 32 Hz, 1H, CH_{vinyl}), 2.38 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.9 (d, $^{1}J_{C-F}$ = 264.8 Hz, 1C, *C*-F), 138.6 (d, $^{4}J_{C-F}$ = 2.0 Hz, 1C, C_{Ar}), 138.1 (s, 1C, C_{Ar}), 132.2 (s, 1C, *C*H_{Ar}), 131.2 (d, $^{2}J_{C-F}$ = 26.3 Hz, 1C, C_{Ar}), 130.9 (s, 1C, *C*H_{Ar}), 129.4 (s, 1C, *C*H_{Ar}), 128.7 (s, 1C, *C*H_{Ar}), 128.4 (s, 1C, *C*H_{Ar}), 124.8 (d, $^{3}J_{C-F}$ = 7.1 Hz, 1C, *C*H_{Ar}), 123.3 (s, 1C, C_{Ar}), 121.5 (d, $^{3}J_{C-F}$ = 7.1 Hz, 1C, *C*H_{Ar}), 96.5 (d, $^{3}J_{C-F}$ = 6.1 Hz, 1C, C_{alkyne}), 87.2 (d, $^{2}J_{C-F}$ = 17.2 Hz, 1C, *C*H_{vinyl}), 82.3 (d, $^{4}J_{C-F}$ = 2.0 Hz, 1C, C_{alkyne}), 21.6 (s, 1C, Ar-*C*H_3), 21.4 (s, 1C, Ar-*C*H_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -102.9 (s, 1F, C-*F*, *Z* isomer), -101.7 (s, 1F, C-*F*, *E* isomer)

HRMS calcd. for $C_{18}H_{15}F$ $[M+H]^+$ 251.1236, **found** 251.1228.

(*Z*)-1-(1-Fluoro-4-phenylbut-1-en-3-yn-1-yl)-3-methylbenzene (9fb)



The optimised procedure afforded the title compound as an inseparable mixture of isomers (95:5, *Z:E*) after column chromatography (SiO_2, pentane:AcOEt, 99:1), as a pale yellow oil (100 mg, 85%).

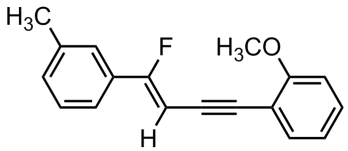
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.51-7.49 (m, 2H, CH_{Ar}), 7.39-7.37 (m, 2H, CH_{Ar}), 7.34-7.26 (m, 4H, CH_{Ar}), 7.21-7.19 (m, 1H, CH_{Ar}), 5.77 (d, $^{3}J_{H-F}$ = 32 Hz, 1H, CH_{vinyl}), 2.38 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 165.0 (d, $^{1}J_{C-F}$ = 262.3 Hz, 1C, *C*-F), 138.6 (d, $^{4}J_{C-F}$ = 1.8 Hz, 1C, C_{Ar}), 131.7 (s, 2C, *C*H_{Ar}), 131.2 (d, $^{2}J_{C-F}$ = 25.2 Hz, 1C, C_{Ar}), 131.0 (s, 1C, *C*H_{Ar}), 128.8 (d, $^{4}J_{C-F}$ = 1.7 Hz, 1C, *C*H_{Ar}), 128.5 (s, 2C, *C*H_{Ar}), 128.4 (s, 1C, *C*H_{Ar}), 124.9 (d, $^{3}J_{C-F}$ = 7.0 Hz, 1C, *C*H_{Ar}), 123.5 (s, 1C, C_{Ar}), 121.6 (d, $^{3}J_{C-F}$ = 7.0 Hz, 1C, *C*H_{Ar}), 96.3 (d, $^{3}J_{C-F}$ = 6.1 Hz, 1C, C_{alkyne}), 87.2 (d, $^{2}J_{C-F}$ = 16.2 Hz, 1C, *C*H_{vinyl}), 82.7 (d, $^{3}J_{C-F}$ = 3.0 Hz, 1C, C_{alkyne}), 21.6 (s, 1C, Ar-*C*H_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -102.7 (s, 1F, C-*F*, *Z* isomer), -101.3 (s, 1F, C-*F*, *E* isomer)

HRMS calcd. for $C_{17}H_{13}F$ [M+H]$^+$ 237.1080, **found** 237.1070.

(*Z*)-1-(4-Fluoro-4-(*m*-tolyl)but-3-en-1-yn-1-yl)-2-methoxybenzene (9fc)



The optimised procedure afforded the title compound as a mixture of isomers (94:6, *Z:E*) after column chromatography (SiO_2, pentane:AcOEt, 9:1), as an orange oil (133 mg, 69%).

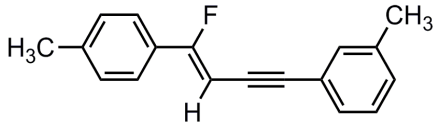
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.49-7.46 (dd, $^{3}J_{H-H}$ = 7.5 Hz, $^{4}J_{H-F}$ = 4.0 Hz, 1H, CH_{Ar}), 7.39-7.37 (m, 2H, CH_{Ar}), 7.32-7.26 (m, 2H, CH_{Ar}), 7.21-7.19 (m, 1H, CH_{Ar}), 5.86 (d, $^{3}J_{H-F}$ = 36.0 Hz, 1H, CH_{vinyl}), 3.92 (s, 3H, Ar-OCH_3), 2.38 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.7 (d, $^{1}J_{C-F}$ = 262.6 Hz, 1C, *C*-F), 159.9 (s, 1C, *C*-OCH_3), 138.5 (d, $^{4}J_{C-F}$ = 2.1 Hz, 1C, C_{Ar}), 133.6 (s, 1C, *C*H_{Ar}), 131.3 (d, $^{2}J_{C-F}$ = 26.3 Hz, 1C, C_{Ar}), 130.9 (s, 1C, *C*H_{Ar}), 129.9 (s, 1C, *C*H_{Ar}), 128.7 (d, $^{4}J_{C-F}$ = 2.0 Hz, 1C, *C*H_{Ar}), 124.8 (d, $^{3}J_{C-F}$ = 7.1 Hz, 1C, *C*H_{Ar}), 121.5 (d, $^{3}J_{C-F}$ = 7.1 Hz, 1C, *C*H_{Ar}), 120.6 (s, 1C, *C*H_{Ar}), 112.7 (s, 1C, C_{Ar}), 110.7 (s, 1C, *C*H_{Ar}), 92.6 (d, $^{3}J_{C-F}$ = 6.1 Hz, 1C, C_{alkyne}), 87.5 (d, $^{2}J_{C-F}$ = 16.2 Hz, 1C, *C*H_{vinyl}), 86.7 (d, $^{4}J_{C-F}$ = 2.0 Hz, 1C, C_{alkyne}), 56.0 (s, 1C, Ar-O*C*H_3), 21.6 (s, 1C, Ar-*C*H_3).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -102.9 (s, 1F, C-*F*, *Z* isomer), -102.6 (s, 1F, C-*F*, *E* isomer).

HRMS calcd. for $C_{18}H_{15}FO$ [M+H]$^+$ 267.1185, **found** 267.1217

(*Z*)-1-(4-Fluoro-4-(*p*-tolyl)but-3-en-1-yn-1-yl)-3-methylbenzene (9ea)



The optimised procedure afforded the title compound as a mixture of isomers (96:4, *Z:E*) after column chromatography (SiO_2, pentane:AcOEt, 99:1), as a white solid (114 mg, 91%).

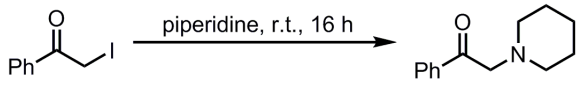
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 7.48-7.45 (m, 2H, CH_{Ar}), 7.32-7.29 (m, 2H, CH_{Ar}), 7.23-7.19 (m, 3H, CH_{Ar}), 7.13-7.11 (m, 1H, CH_{Ar}), 5.73 (d, $^3J_{H\text{-}F}$ = 36.0 Hz, 1H, CH_{vinyl}), 2.38 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 164.9 (d, $^1J_{C\text{-}F}$ = 261.6 Hz, 1C, *C*-F), 140.5 (s, 1C, C_{Ar}), 138.1 (s, 1C, C_{Ar}), 132.2 (s, 1C, *C*H$_{Ar}$), 129.5 (d, $^4J_{C\text{-}F}$ = 1.7 Hz, 1C, CH_{Ar}), 129.3 (s, 1C, *C*H$_{Ar}$), 128.7 (s, 1C, *C*H$_{Ar}$), 128.3 (s, 1C, *C*H$_{Ar}$), 124.3 (d, $^3J_{C\text{-}F}$ = 7.0 Hz, 1C, CH_{Ar}), 123.3 (s, 1C, C_{Ar}), 96.3 (d, $^3J_{C\text{-}F}$ = 5.9 Hz, 1C, C_{alkyne}), 86.4 (d, $^2J_{C\text{-}F}$ = 16.9 Hz, 1C, *C*H$_{vinyl}$), 82.4 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, 1C, C_{alkyne}), 21.5 (s, 1C, Ar-*C*H$_3$), 21.4 (s, 1C, Ar-*C*H$_3$).

^{19}F-{^{1}H} NMR (377 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = -103.0 (s, 1F, C-*F*, *Z* isomer), -101.8 (s, 1F, C-*F*, *E* isomer)

HRMS calcd. for $C_{18}H_{15}F$ $[M+H]^+$ 251.1236, **found** 251.1235

7.2.4.3 Nucleophilic substitution chemistry of 5a: reaction with piperidine[26]



7a **10a:** 93%

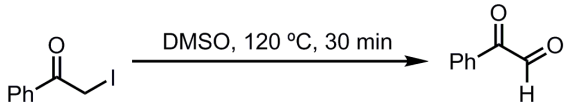
A 3-mL screwcap vial equipped with a stirring bar was charged with **7a** (61.5 mg, 0.25 mmol) and piperidine (0.5 mL), and the resulting sample mas stirred in air at room temperature for 16 h. The sample was diluted with AcOEt (5 mL), washed with water (3x5 mL), and the organic phases gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, pentane:AcOEt, 6:4) obtaining the title compound as a pale yellow oil (47 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 8.02-7.99 (m, 2H, CH_{Ar}), 7.57-7.53 (m, 1H, CH_{Ar}), 7.47-7.41 (m, 2H, CH_{Ar}), 3.75 (s, 2H, CH_2-N), 2.53 (t, $^{3}J_{H\text{-}H}$ = 4.5 Hz, 4H, C$H_{2,pip}$), 1.68-1.60 (m, 4H, C$H_{2,pip}$), 1.46 (t, $^{3}J_{H\text{-}H}$ = 5.9 Hz, 2H, C$H_{2,pip}$).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 196.9 (s, 1C, C=O), 136.0 (s, 1C, C_{Ar}), 133.0 (s, 1C, CH$_{Ar}$), 128.5 (s, 2C, CH$_{Ar}$), 128.3 (s, 2C, CH$_{Ar}$), 65.4 (s, 1C, CH$_2$-N), 54.9 (s, 2C, C$H_{2,pip}$), 25.8 (s, 2C, C$H_{2,pip}$), 23.8 (s, 1C, C$H_{2,pip}$).

This compound has been reported before and the analytical data match the literature report.[27]

7.2.4.4 Kornblum oxidation of 5a.[28]



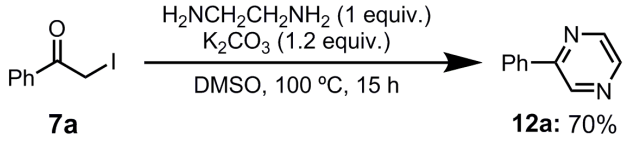
7a **11a:** 99%

A screwcap vial equipped with a stirring bar was charged with **7a** (61.5 mg, 0.25 mmol) and DMSO (1 mL), and the resulting sample mas stirred in air at 120 ^{o}C for 30 minutes. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, petroleum ether:AcOEt, 6:4), obtaining the title compound as a yellow oil (33.2 mg, 99% yield). No clean NMR spectra could be obtained due to fast polymerisation/hydration under ambient conditions, and the sample was used as obtained in subsequent reaction steps.

This compound has been reported before and the analytical data match the literature report.[28]

7.2.4.5 One-pot Kornblum oxidation/functionalisation of 11a

Example 1:[29]



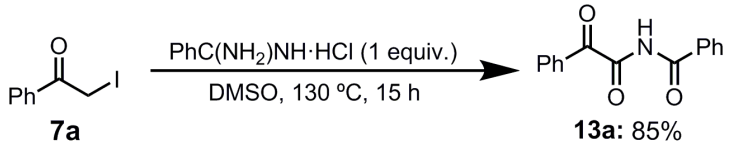
A screwcap vial equipped with a stirring bar was charged with **7a** (33.5 mg, 0.25 mmol), ethylenediamine (34.1 µL, 0.50 mmol, 1.00 equiv.), K_2CO_3 (82.9 mg, 0.60 mmol, 1.20 equiv.) and DMSO (1 mL), and the resulting sample mas stirred in air at 100 ^oC for 15 h. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, pentane:AcOEt, 6:4) to obtain the title compound as a light yellow solid (55 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 9.02 (d, $^3J_{H\text{-}H}$ = 1.4 Hz, 1H, CH_{HetAr}), 8.65-8.63 (m, 1H, CH_{HetAr}), 8.50 (d, $^3J_{H\text{-}H}$ = 2.4 Hz, 1H, CH_{HetAr}), 8.03-7.98 (m, 2H, CH_{Ar}), 7.57-7.45 (m, 3H, CH_{Ar}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 152.9 (s, 1C, C_{HetAr}=N), 144.2 (s 1C, CH$_{HetAr}$), 142.9 (s 1C, CH$_{HetAr}$), 142.0 (s 1C, CH$_{HetAr}$), 136.5 (s, 1C, C_{Ar}), 129.8 (s, 1C, CH$_{Ar}$), 129.1 (s, 2C, CH$_{Ar}$), 127.1 (s, 2C, CH$_{Ar}$).

This compound has been reported before and the analytical data match the literature report.[29]

Example 2:[30]



A screwcap vial equipped with a stirring bar was charged with **7a** (33.5 mg, 0.25 mmol), benzamidine hydrochloride (82.4 mg, 0.50 mmol, 1.00 equiv.) and DMSO (1 mL), and the resulting sample mas stirred in air at 130 ^oC for 15 h. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The organic phases

were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, SiO_2, pentane:AcOEt, 1:1) to obtain the title compound as a yellow solid (53.8 mg, 85% yield).

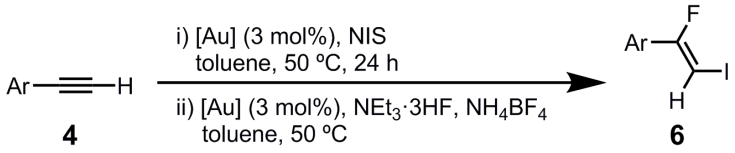
^{1}H NMR (400 MHz, $CDCl_3$, 298K, TMS): δ (ppm) = 10.1 (s, bs, 1H, N-*H*), 8.11 (d, $^3J_{H\text{-}H}$ = 7.3 Hz, 2H, CH_{Ar}), 8.02–7.93 (m, 2H, CH_{Ar}), 7.67–7.57 (m, 2H, CH_{Ar}), 7.55–7.50 (m, 4H, CH_{Ar}).

^{13}C-{^{1}H} NMR (101 MHz, $CDCl_3$, 298K): δ (ppm) = 186.8 (s, 1C, C=O), 165.7 (s, 1C, C=O), 146.6 (s, 1C, C=O), 134.7 (s, 1C, C_{Ar}), 134.2 (s, 1C, C_{Ar}), 132.3 (s, 1C, CH$_{Ar}$), 130.5 (s, 1C, CH$_{Ar}$), 129.8 (s, 2C, CH$_{Ar}$), 129.0 (s, 2C, CH$_{Ar}$), 128.9 (s, 2C, CH$_{Ar}$), 128.2 (s, 2C, CH$_{Ar}$).

This compound has been reported before and the analytical data match the literature report.[30]

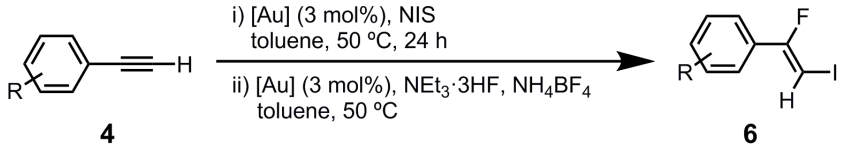
7.2.4.6 Sequential synthesis: terminal alkynes

7.2.4.6.1 Iodination/hydrofluorination of terminal alkynes



A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 15.0 μmol, 3 mol%), *N*-iodosuccinimide (146 mg, 0.65 mmol, 1.3 equiv.), toluene (1 mL) and the alkyne (0.50 mmol). The mixture was stirred at 50 ^{o}C for 24 h. The crude mixture was filtered through a plug of cotton, into a plastic screwcap vial containing [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 15.0 μmol, 3 mol%) and NH_4BF_4 (81.0 mg, 0.750 mmol, 1.5 equiv.). The cotton plug was further washed with toluene (0.4 mL) for complete recovery of the halogenated intermediate. NEt_3·3HF (0.25 mL, 1.50 mmol, 3 equiv.) was then added dropwise. The reaction mixture was stirred at 50 ^{o}C for the required time. The crude mixture was purified by column chromatography (SiO_2), obtaining the desired compound.

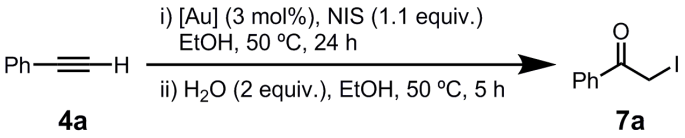
Table 1. Examples of sequential iodination/hydrofluorination of terminal alkynes (**4**) for the synthesis of fluoroiodoalkenes (**6**).



Entry	R	Product	Time ii)	Conversion of 6a (%)[b]
1	H	**6a**	3 h (4 h)[c]	82 (88%)[c]
2	*m*-OMe	**6c**	4 h	88
3	*m*-Cl	**6j**	4 h	78

[a] Reaction conditions: i) alkyne (0.50 mmol), [Au(SIPr)(NEt_3)][HF_2] (3 mol%), NIS (0.65 mmol), toluene (1 mL); ii) [Au(SIPr)(NEt_3)][HF_2] (3 mol%), NH_4BF_4 (0.75 mmol), NEt_3·3HF (1.50 mmol), toluene (1 mL), 50 ºC. [b] Isolated yields. [c] 5 mmol scale in parenthesis.

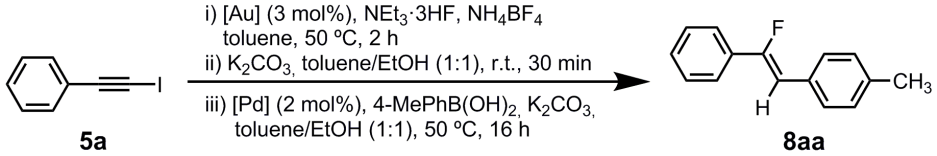
7.2.4.7 Sequential iodination/hydration of 4a



A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(NTf_2)(IPr)] (8.70 mg, 15.0 μmol, 3 mol%), *N*-iodosuccinimide (131 mg, 0.55 mmol, 1.1 equiv.), EtOH (0.9 mL) and phenylacetylene (56.0 μL, 0.50 mmol). The reaction mixture was stirred in air at 50 ^{o}C for 15 h. Water (18.0 μL in 0.1 mL dry EtOH) was then added, and the reaction mixture was further stirred at 50 ^{o}C for 5 h. The solvent was removed under vacuum, and the residue was purified by column chromatography (SiO_2, pentane:AcOEt, 9:1), obtaining **7a** as a dark red oil (97 mg, 79% yield).

7.2.4.8 Sequential synthesis: 1-iodoalkynes

7.2.4.8.1 Hydrofluorination/cross-coupling of 5a



5a **8aa**

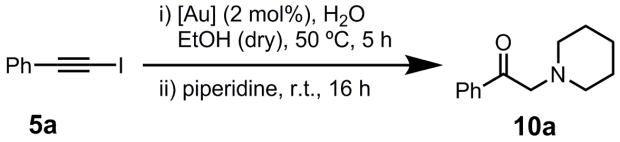
A 2-mL plastic screwcap vial equipped with a stirring bar was charged with **5a** (114 mg, 0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (10.9 mg, 15.0 µmol, 3 mol%), NH_4BF_4 (81.0 mg, 0.75 µmol, 1.5 equiv.) and toluene (0.8 mL). NEt$_3$·3HF (0.25 mL, 1.50 mmol, 3 equiv.) was added dropwise while stirring. The vial was briefly flushed with N_2, and the reaction mixture was stirred at 50 ^oC for 3 h. The crude mixture was allowed to cool to room temperature, and the top layer of the biphasic system was separated and recovered in a screwcap vial. While stirring, EtOH (same amount as recovered organic phase) and K_2CO_3 (345 mg, 2.50 mmol, 5 equiv., in small portions) were added, and the mixture was stirred at 20 ^oC for 30 minutes. Under stirring, *p*-tolylboronic acid (140 mg, 1.00 mmol, 2 equiv.), K_2CO_3 (138 mg, 1.00 mmol, 2 equiv.) and **Pd-1** (6.50 mg, 0.01 mmol, 2 mol%) were added in air. The reaction mixture was stirred at 50 ^oC for 16 h. The solvents were evaporated under reduced pressure, and the crude mixture was purified by column chromatography (SiO_2, pentane), obtaining **8aa** as a white solid (89.2 mg, 84% yield).

7.2.4.8.2 Hydration/functionalisation of 5a

General hydration step:

A screwcap vial equipped with a stirring bar was charged with the **1a** (114 mg, 0.50 mmol), [Au(NTf$_2$)(IPr)] (8.90 mg, 0.01 mmol, 2 mol%) and dry EtOH (1.50 mL). Water (18 µL, 1.00 mmol) was then added, and the resulting mixture was stirred in air at 50 ^oC for 5 h. The solvents were removed under reduced pressure, and the residue was further treated according to the required reaction (see examples below).

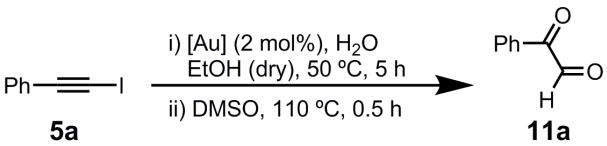
Example 1:



5a **10a**

To the residue obtained using the general hydration step, piperidine (0.3 mL) was added, and the resulting sample mas stirred in air at room temperature for 16 h. The sample was diluted with AcOEt (5 mL), washed with water (3x5 mL), and the organic phases gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, pentane:AcOEt, 6:4) to obtain the title compound as a pale yellow oil (89 mg, 88% yield).

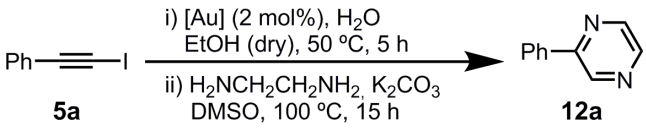
Example 2:



5a **11a**

To the residue obtained using the general hydration step, DMSO (1 mL) was added, and the resulting sample mas stirred in air at 110 ^oC for 30 minutes. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, AcOEt) to obtain the title compound as a yellow oil (60 mg, 90% yield).

Example 3:

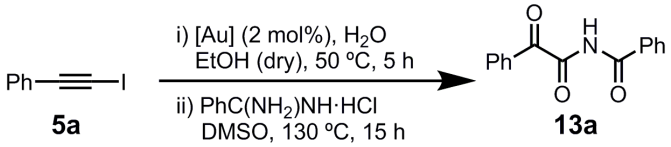


5a **12a**

To the residue obtained using the general hydration step, ethylenediamine (34.1 µL, 0.50 mmol, 1.00 equiv.), K_2CO_3 (82.9 mg, 0.60 mmol, 1.20 equiv.) and DMSO (1 mL) were added, and the resulting sample mas stirred in air at 100 ^oC for 15 h. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The

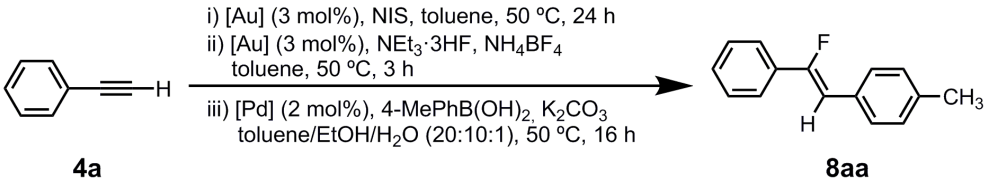
organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, pentane:AcOEt, 6:4) to obtain the title compound as a light yellow solid (55 mg, 70% yield).

Example 4:



To the residue obtained using the general hydration step, benzamidine hydrochloride (82.4 mg, 0.50 mmol, 1.00 equiv.) and DMSO (1 mL) were added, and the resulting sample mas stirred in air at 130 ^{o}C for 15 h. The sample was poured onto water (5 mL), and extracted with AcOEt (3x5 mL). The organic phases were gathered, dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, pentane:AcOEt, 1:1) to obtain the title compound as a yellow solid (98 mg, 77% yield).

7.2.4.9 Sequential synthesis: iodination/hydrofluorination/cross-coupling of 4a



A 3-mL screwcap vial equipped with a stirring bar was charged with [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 15.0 µmol, 3 mol%), *N*-iodosuccinimide (146 mg, 0.65 mmol, 1.3 equiv.), toluene (1 mL) and **5a** (56.0 µL, 0.50 mmol). The mixture was stirred at 50 ^{o}C for 24 h. The crude mixture was filtered through a plug of cotton, into a plastic screwcap vial containing [Au(SIPr)(NEt_3][HF_2] (10.9 mg, 15.0 µmol, 3 mol%) and NH_4BF_4 (81.0 mg, 0.75 mmol, 1.5 equiv.). The cotton plug was further washed with toluene (0.4 mL) for complete recovery of the halogenated intermediate. NEt_3·3HF (0.25 mL, 1.50 mmol, 3 equiv.) was then added dropwise and the reaction mixture was further stirred at 50 ^{o}C for 3 h. The crude mixture was allowed to cool down to room

temperature, and the top layer of the biphasic system was separated and recovered in a screwcap vial with a stirring bar. While stirring, EtOH (1.5 mL), water (0.15 mL) and K_2CO_3 (345 mg, 2.50 mmol, 5 equiv., added in small portions) were added, and the mixture was stirred at 20 ^oC for 30 minutes. Under stirring, *p*-tolylboronic acid (140 mg, 1.00 mmol, 2 equiv.), K_2CO_3 (138 mg, 1.00 mmol, 2 equiv.) and **Pd-1** (6.50 mg, 0.01 mmol, 2 mol%) were added in air. The reaction mixture was stirred at 50 ^oC for 16 h. The sample was passed through a small plug of $MgSO_4$, washed with AcOEt (2x3 mL) and the gathered fractions were concentrated under reduced pressure. The crude mixture was purified by column chromatography (SiO_2, pentane), obtaining **8aa** as a white solid (64.7 mg, 61% yield).

7.3 References

(1) F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan and S. P. Nolan, *Chem. Cat. Chem.* 2015**, 7**, 240.

(2) L. Ricard and F. Gagosz, *Organometallics*, 2007, **26**, 4704.

(3) A. Gómez-Suárez, R. S. Ramón, A. M. Z. Slawin and S. P. Nolan, *Dalton Trans.* 2012, **41**, 5461.

(4) A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin, and S. P. Nolan, *Chem. Commun.* 2013, **49**, 5541.

(5) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.* 2010, **46**, 2742.

(6) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, S. P. *J. Am. Chem. Soc.* 2006, **128**, 4101.

(7) M. S. Viciu, R. M. Kissling, E. D. Stevens and S. P. Nolan, *Org. Lett.* 2002, **4**, 2229.

(8) R. V. Andreev, G. I. Borodkin and V. G. Shubin, *Russ. J. Org. Chem.* 2009, **45**, 1483.

(9) L. Biasiolo, M. Trinchillo, P. Belanzoni, L. Belpassi, V. Busico, G. Ciancaleoni, A. D'Amora, A. Macchioni, F. Tarantelli and D. Zuccaccia, *Chem. Eur. J.* 2016, **20**, 14594

(10) G. Pelletier, S. Lie, J. J. Mousseau and A. B. Charette, *Org. Lett.* 2012, **14**, 5464.

(11) J. Yan, J. Li and D. Cheng, *Synlett*, 2007, **15**, 2442.

(12) S. Mehta and R. C. Larock, *J. Org. Chem.* 2010, **75**, 1652.

(13) M. Li, Y. Li, B. Zhao, F. Liang and L.-Y. Jin, *RCS Adv.* 2014, **4**, 30046.

(14) S. Lal, H. S. Rzepa and S. Díez-González, *ACS Catal.* 2014, **4**, 2274.

(15) P. Starkov, F. Rota, J. M. D'Oyley, T. D. Sheppard, *Adv. Synth. Catal.* 2012, **354**, 3217.

(16) T. H. Vaughn, J. A. Nieuwland, *J. Am. Chem. Soc.* 1934, **56**, 1207.

(17) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.* 2010, **46**, 2742.

(18) M. Yoshida, A. Komata and S. Hara, *Tetrahedron,* 2006, **62**, 8636.

(19) Y. Li, X. Liu, D. Ma, B. Liu and H. Jiang, *Adv. Synth. Catal.* 2012, **354**, 2683.

(20) M. M. Reddy, P. Swamya, M. Naresha, K. Srujana, C. Durgaiah, T. V. Rao and N. Narender, *RSC Adv.* 2015, **5**, 12186.

(21) M. M. Reddy, M. A. Kumar, P. Swamy and N. Narender, *Tetrahedron Lett.* 2011, **52**, 6554.

(22) T. Nobuta, S.-I. Hirashima, N. Tada, T. Miura and A. Itoh, *Synlett,* 2010, **15**, 2335.

(23) H. Liu, Y. Wei and C. Cai, *Synlett,* 2016, **27**, 2378.

(24) W. Zhang, W. Huang and J. Hu, *Angew. Chem. Int. Ed.* 2009**, 48**, 9858.

(25) J. Xu and D. J. Burton, *J. Org. Chem.* 2006, **71**, 3743.

(26) For the experimental procedure, see: X. Zhang and L. Wang, L. *Green. Chem.* 2012**, 14**, 2141.

(27) For the complete characterisation data, see: G. Tang, T. Ji, A.-F. Hu and Y.-F. Zhao, *Synlett,* 2008, **12**, 1907.

(28) H. P. Kalmode, K. S. Vadagaonkar and A. C. Chaskar, *RSC Adv.* 2014, **4**, 60316.

(29) K. K. D. R. Viswanadham, M. P. Reddy, P. Sathyanarayana, O. Ravi, R. Kant and S. R. Bathula, *Chem. Commun.* 2014, **50**, 13517.

(30) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.* 2014**, 16**, 2888.