Decarboxylative and direct functionalisations of aromatic compounds

A thesis submitted to The University of Manchester for the degree of
Doctor of Philosophy
in the Faculty of Engineering and Physical Sciences

2014

Sangwon Seo

School of Chemistry

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Abstract

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Aromatic rings are privileged structures found in a diverse range of natural and synthetic compounds, thus synthetic methods for their functionalisations are important in organic synthesis. Despite significant advancements made, especially in the field of transition metal catalysis, work still continues for the development of milder, more efficient, and more atom economical reactions. We describe here our efforts towards the development of decarboxylative/direct C(aryl)–N and C(aryl)–C bond forming reactions using aromatic carboxylic acids and unfunctionalised arenes as cheap and widely available aromatic sources.

The investigations into copper-catalysed and copper/palladium-catalysed intermolecular and copper/silver/palladium-catalysed intramolecular decarboxylative amination of aromatic carboxylic acids are reported. A new approach to decarboxylation of benzoic acids is also described. The reaction uses silver (I) catalyst and peroxydisulfate salt to generate aryl radicals *via* oxidative decarboxylation. The applications of this approach in intra- and intermolecular decarboxylative C–H arylation, and protodecarboxylation are described. Also described is the development of silver-catalysed trifluoromethylation of simple arenes and heteroarenes. The reaction proceeds *via* radical trifluoromethylation using trimethyl(trifluoromethyl)silane as the trifluoromethyl radical source. This method has been applied to the trifluoromethylation of complex agrochemical molecules, proving its synthetic utility in late-stage functionalisation. Furthermore, we describe the exploitation of trifluoroacetate derivatives as cheap trifluoromethylating reagents in copper-mediated decarboxylative C–H trifluoromethylation of 2-phenylpyridine.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification at this or any other university or other institute of learning.

Part of this work has been published in peer-reviewed journals:

a) Seo, S.; Slater, M.; Greaney, M. F., *Org. Lett.* **2012,** *14*, 2650-2653.

b) Seo, S.; Taylor, J. B.; Greaney, M. F., *Chem. Commun.* **2012,** *48*, 8270-8272.

c) Seo, S.; Taylor, J. B.; Greaney, M. F., *Chem. Commun.* **2013,** *49*, 6385-6387.

Copyright statements

Acknowledgements

I would like to start by thanking my supervisor Professor Michael Greaney for giving me the opportunity to work in his group. His help, support and guidance have been indispensable for the progress I have made throughout the course of my PhD. I would also like to thank my industrial supervisors Dr. Mark Slater and John Taylor from Syngenta for their help and ideas into my chemistry, and John in particular for organising my three month placement at Syngenta and for making it an enjoyable experience.

Thanks to all the past and present members of the Greaney group: Boris, Catherine, Chris Smith, Chris Teskey, Didier, Donnie, Fengzhi, Gabri, Humera, Jen, Jose, Kallol, Laura, Meliha, Naim, Pete, Sachin, Sarah, Sinead, Tom Storr, Tom Williams, Tracey, Vaibhav, Venu. Of these, I would especially like to thank Fengzhi for his help with the decarboxylative amination projects, Pete for letting me experience a bit of his cyano michael-aldol cascade chemistry, and Vaibhav for the helpful discussion and suggestion on the decarboxylative trifluoromethylation work. A big thank you also goes to Chris Smith and Tom Storr for proofreading part of this thesis.

The first year of my PhD was spent at the University of Edinburgh, and I would like to thank everybody there who helped me in any way, especially Dr. Peter Kirsop for his supervision during my teaching activities. The University of Manchester and Syngenta are thanked for the financial support.

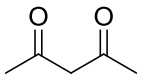
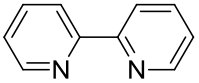
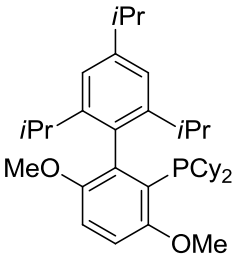
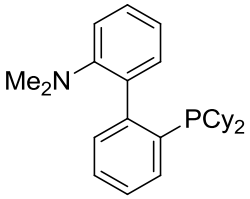
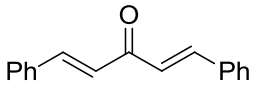
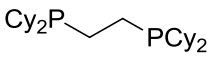
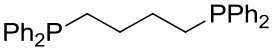
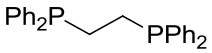
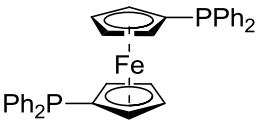
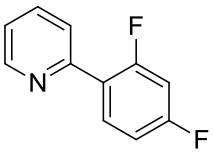
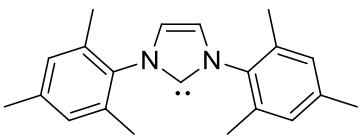
Finally and foremost, I would like to thank my family for their support and encouragement, especially my wife Danbee for her love and patience throughout my studies. I would not have survived my time here without her and her amazing food.

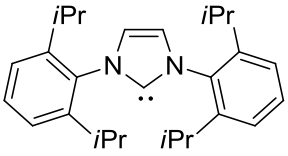
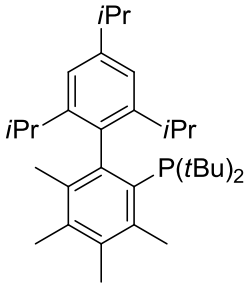
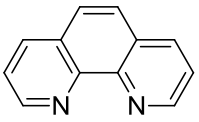
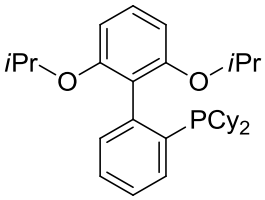
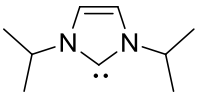
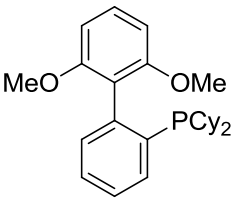
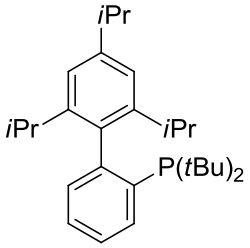
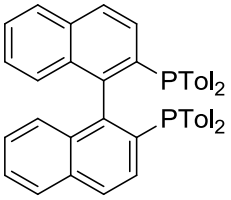
Abbreviations

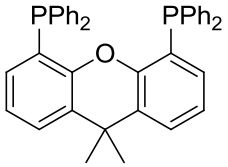
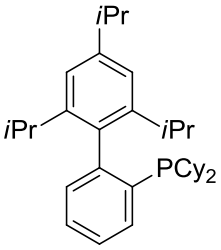
Ac	acetyl
Ad	adamantyl
Alq_3	Tris(8-hydroxyquinolinato)aluminium
Ar	aryl
atm	atmosphere
Boc	*tert*-butoxycarbonyl
BQ	1,4-benzoquinone
bs	broad singlet
cat	catalytic
CMD	concerted metallation-deprotonation
cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DG	directing group
DMA	*N*,*N*-dimethylacetamide
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
CSA	camphorsulfonic acid
EPR	electron paramagnetic resonance
ESR	electron spin resonance
Et	ethyl
equiv.	equivalent
Gly	glycine
Het	heteroaryl
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
*i*Pr	*iso*-propyl
LC/MS	liquid chromatography/mass spectrometry
m	multiplet

Me	methyl
Mes	mesitylene
MFSDA	methyl fluorosulfonyldifluoroacetate
Mp	melting point
M.S.	molecular sieves
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NPB	*N*,*N*'-di(1-naphthyl)-*N*,*N*'-diphenyl-(1,1'-biphenyl)-4,4'-diamine
OLED	Organic Light-Emitting Diode
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate (*p*-toluenesulfonate)
Ph	phenyl
Piv	pivalate
PivOH	pivalic acid
q	quartet
RT	room temperature
s	singlet
SM	starting material
*t*Bu	*tert*-butyl
t	triplet
T	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
$TESCF_3$	triethyl(trifluoromethyl)silane
TFA	trifluoroacetic acid
TM	transition metal
TMS	trimethylsilyl
$TMSCF_3$	trimethyl(trifluoromethyl)silane
Tol	tolyl
W	watt

Ligand list

acac	acetylacetonate	
bpy	Bipyridine	
BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl	
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl	
dba	Dibenzylideneacetone	
dcpe	1,2-bis(dicyclohexylphosphino)ethane	
dppb	1,4-bis(diphenylphosphino)butane	
dppe	1,2-bis(diphenylphosphino)ethane	
dppf	1,1'-Bis(diphenylphosphino)ferrocene	
Fppy	2-(2,4-difluorophenyl)pyridine	
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene	

IPr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene	
Me_4-*t*Bu-XPhos	di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphine	
phen	1,10-phenanthroline	
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl	
Sl*i*Pr	1,3-di-*iso*-propylimidazolin-2-ylidene	
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl	
t-BuXPhos	2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl	
Tol-BINAP	2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl	

XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene	
XPhos	dicyclohexyl(2',4',6'-triisopropyl[1,1'-biphenyl]-2-yl)phosphine	

1 Introduction

1.1 Aromatic functionalisation *via* transition metal catalysis

Aromatic systems are found in a diverse range of natural and synthetic products. Biaryls are known to show some biological activities, increasingly being incorporated into pharmaceutical and agrochemical compounds. Polyaromatics have interesting electronic and optical properties that suit for use in organic conductors or semiconductors, hence, are often found in advanced materials such as polymers, liquid crystalline displays and organic light emitting diodes (Figure 1). The presence of these privileged structures in many valuable compounds has in turn attracted synthetic chemists for the development of their functionalisation reactions.[1]

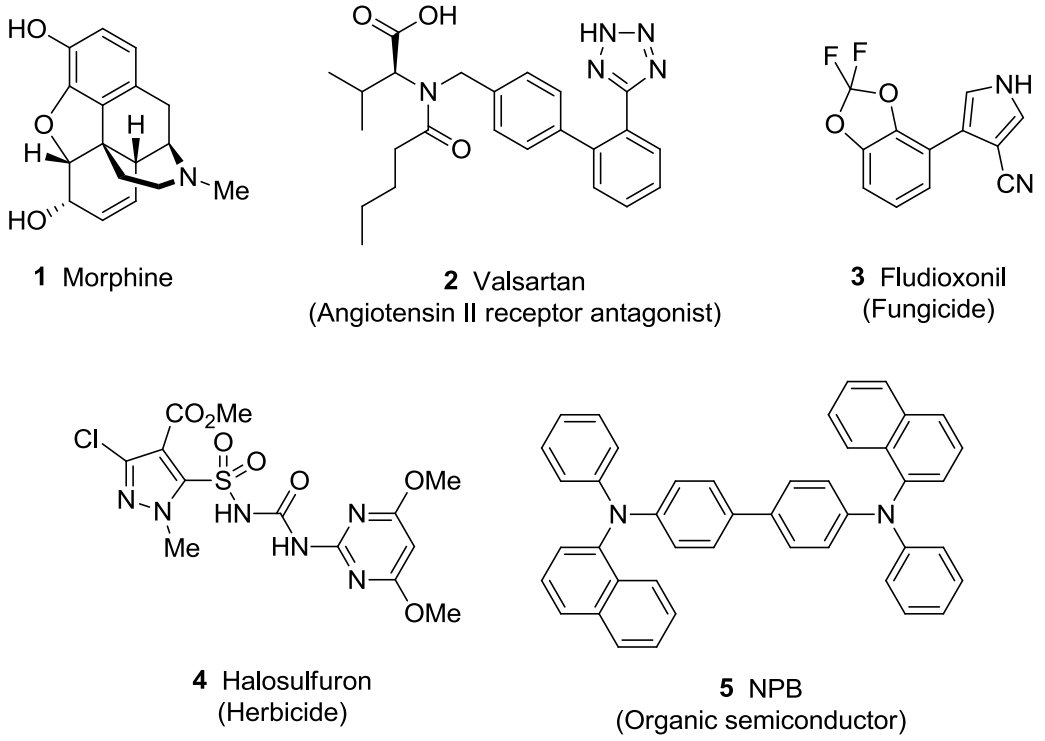
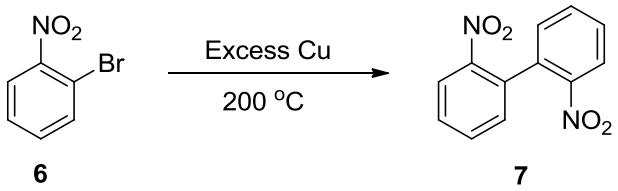


Figure 1 Natural and synthetic compounds containing aromatic systems.

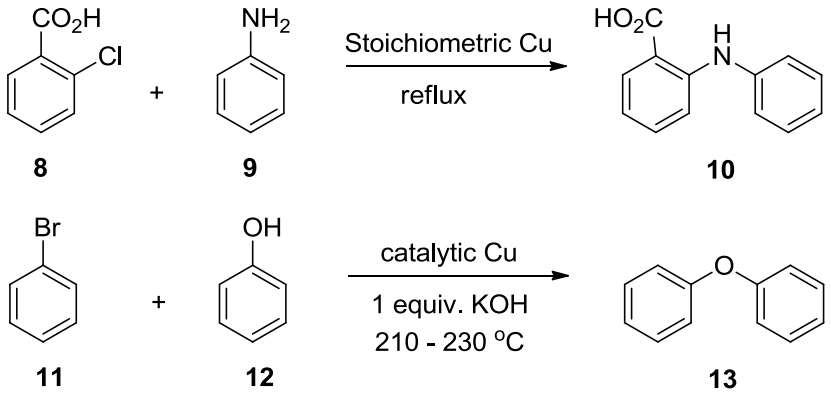
Amongst many available methods, the functionalisations of aromatic compounds have been dominated by transition metal-catalysed reactions over the past decades.[2,3] The first examples of these types could be found from the pioneering work of Ullmann in the 1900s. The original Ullmann reaction was first reported in 1901, describing the

homocoupling of 2-bromonitrobenzene **6** to the biaryl **7** in the presence of excess metallic copper (Scheme 1).[4]



Scheme 1 Ullmann reaction.

This was then followed by discoveries of copper-mediated C–N[5] and C–O[6] bond forming reactions in 1903 and 1905 respectively, with the later example employing a catalytic amount of copper (Scheme 2).

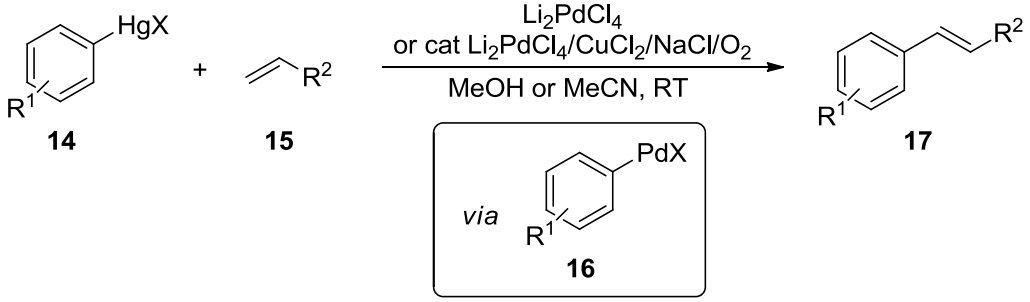


Scheme 2 Ullmann condensation reactions: C–N and C–O bond formations.

These initial findings were remarkable since they showed, for the first time, that copper is effective for functionalising aryl halide species for subsequent C–C and C–heteroatom bond formations. However, these reactions suffered from harsh reaction conditions with the heating temperature exceeding above 200 °C, and had selectivity issues and disadvantages of using stoichiometric metal reagents. Some improved copper-mediated methodologies were later reported but most of these still had similar limitations.[7,8]

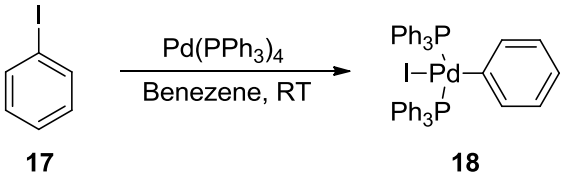
Copper had remained as almost the only transition metal studied for aromatic functionalisations for the next 70 years since the first discovery, but this all changed when palladium-catalysed reactions were introduced in the late 1960s.[3,9,10] The seven back-to-back papers by Heck in 1968 described several palladium-promoted reactions

of organomercurial compounds **14** with alkenes **15**.[11,12,13,14,15,16,17] The author investigated various transition metals, and found palladium salts to be the most useful in activating the organomercurial compounds **14**. *In situ* generation of the organopalladium intermediate **16** was suggested, which would then react with alkenes **15** to give a number of different products depending on the alkene functionalities. The first paper described the formation of substituted alkenes **17** (Scheme 3), which set the basis for the development of the Mizoroki-Heck reaction.



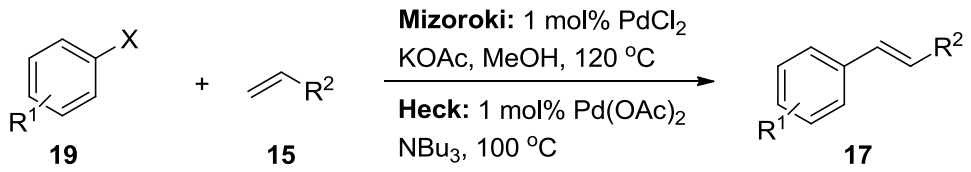
Scheme 3 Pd-promoted coupling reaction of organomercuries with alkenes.

This reaction was limited by the need of the highly toxic organomercurial starting materials **14**. Also, the reaction was proposed to proceed *via* reduction of a Pd^{II} intermediate to an inactive Pd^{0} species, thus requiring either a stoichiometric amount of an expensive palladium source or a palladium catalyst in combination with an external oxidant. These limitations could be solved by introducing the concept of oxidative addition. In 1968, Fitton reported the first oxidative addition product **18** from the reaction of tetrakis(triphenylphosphine)palladium with iodobenzene **17** (Scheme 4).[18]



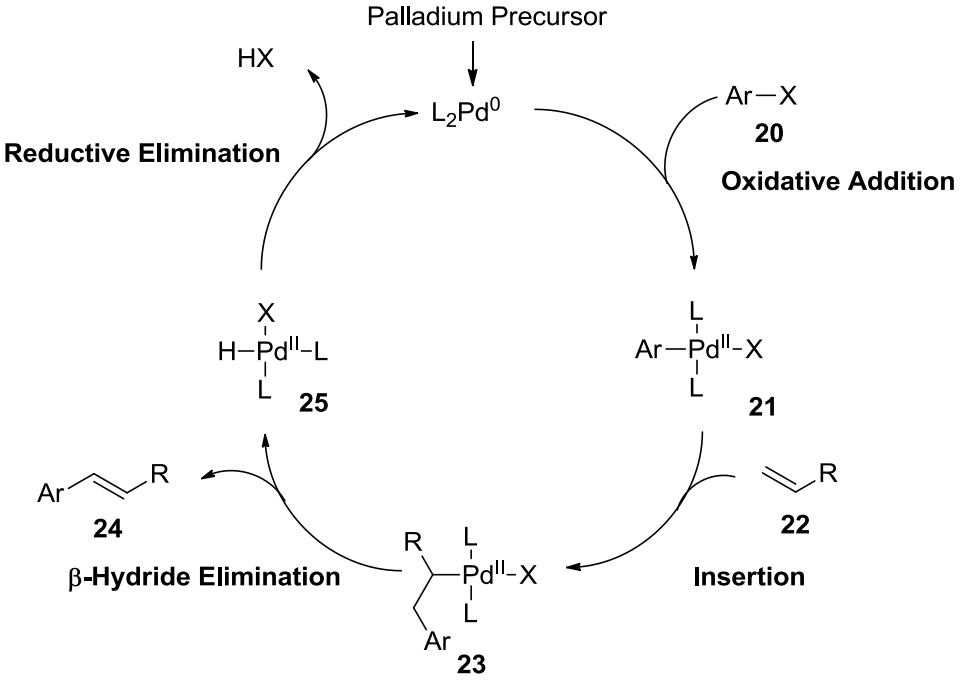
Scheme 4 Oxidative addition of iodobenzene to palladium.

Using this chemistry, Mizoroki[19] and Heck[20] independently reported the palladium-catalysed reactions of aryl halides **19** with alkenes **15** in 1971 and 1972 respectively (Scheme 5). One of the C–H bonds of alkenes **15** is substituted with the carbon group of aryl halides **19** to result in the substituted alkene products **17**.



Scheme 5 Pd-catalysed reactions of aryl halides **19** with alkenes **15**

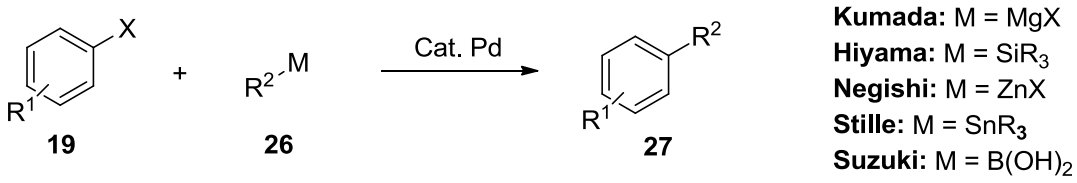
This reaction, now known as the Mizoroki-Heck reaction, is the first example of C–C bond forming reactions that follow a Pd^0/Pd^{II} catalytic cycle (Scheme 6). It is the first oxidative addition step that makes differences to the Heck's earlier work using organomercurial compounds (Scheme 3) and that enables the reaction to be catalytic. The *in situ* generated Pd^0 catalyst oxidatively adds to the Ar–X bond, giving the Pd^{II} intermediate **21**. Insertion of **21** to the alkene **22** is followed by β-hydride elimination of the resulting Pd^{II} species **23** to give the substituted alkene product **24**, and reductive elimination to regenerate the Pd^0 catalyst and complete the catalytic cycle.



Scheme 6 Pd^0/Pd^{II} catalytic cycle of the Mizoroki-Heck reaction.

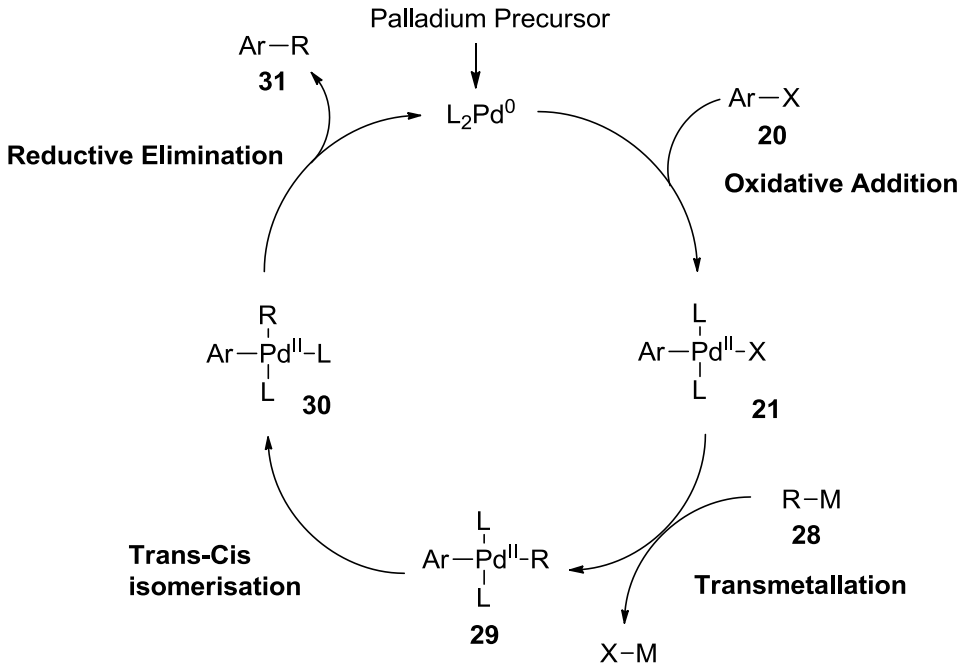
This original work laid the foundation not only for this particular reaction, but also for many other well-known palladium-catalysed reactions reported since. Around the same period, further examples of C–C bond cross-coupling reactions continued to appear, demonstrating unique strengths of palladium catalysis. Prominent among these were the

coupling reactions between organic halides **19** and organometallic compounds **26** to give the C–C bond forming products **27** (Scheme 7).



Scheme 7 Pd-catalysed cross-coupling between aryl halides and organometallic compounds.

These reactions proceed *via* a similar Pd^0/Pd^{II} catalytic cycle to that of the Mizoroki-Heck reaction (Scheme 8). The two coupling partners are bound to the metal centre *via* oxidative addition and transmetallation, and the subsequent reductive elimination leads to the formation of the new C–C bond whilst regenerating the Pd^0 catalyst.



Scheme 8 Pd^0/Pd^{II} catalytic cycle of the reaction between aryl halides and organometallic compounds.

Organolithium and Grignard reagents were one of the first organometallic coupling partners to be employed in these types of reactions, with a number of groups successfully reporting the palladium-catalysed Kumada reactions in the late

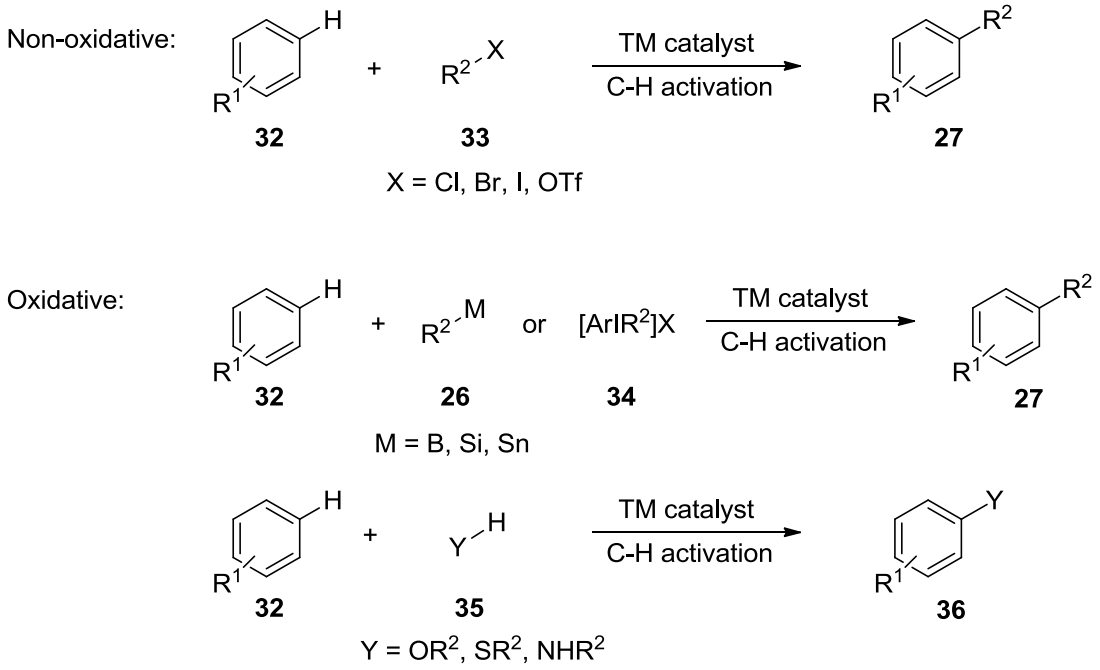
1970s.[21,22,23] Compared to the original reactions that used a nickel catalyst,[24,25] the palladium catalysis in the Kumada reaction offered several advantages; high selectivity, high yields, broader substrate scope of the organometallic coupling partner, and mild reaction conditions. Subsequently, many additional palladium-catalysed reactions were followed, with organozinc (Negishi),[26] organotin (Stille),[27] organoboron (Suzuki)[28] and organosilicon (Hiyama)[29] reagents all showing similar high efficiency as well as improved compatibility with many functional groups.

The palladium-catalysed cross-coupling reactions have since been greatly extended with much research carried out into the modification of reaction parameters. The choice of ligand, in particular, has been regarded significant since this greatly influences the reactivity and effectiveness of the palladium catalyst. It is now well appreciated that the use of bidentate ligands, normally phosphine-based, increases the overall rate of the reaction, which in turn reduces the formation of by-products. The efforts made in this area have allowed various C–C and C–heteroatom cross-coupling reactions to be performed under increasingly mild conditions with high catalyst activity, high turnover numbers and high degrees of selectivity.[3] With the subsequent improvements, palladium-catalysed cross-coupling reactions have been routinely used both in academia and industry and applied as key steps in syntheses of several natural products[30] and drug molecules.[31,32,33] The importance of this chemistry was highlighted in 2010 with the awarding of the Nobel Prize in chemistry to Richard Heck, Ei-ichi Nigeshi and Akira Suzuki, for their individual contributions in this area.

Despite significant advancements made in this field, work still continues towards the development of milder, more efficient, and more step and atom economical reactions. The major drawback of the conventional named reactions between organic halides and organometallic compounds would be the need of coupling partners that are both preactivated. The installation of activating groups generally involves a number of synthetic steps, and generates undesirable wastes during the preparation and subsequent cross-coupling reactions. As a consequence, recent research has sought to replace one or both of the two preactivated coupling partners with a low-energy reagent.

1.2 Direct functionalisation of aromatic C–H bonds

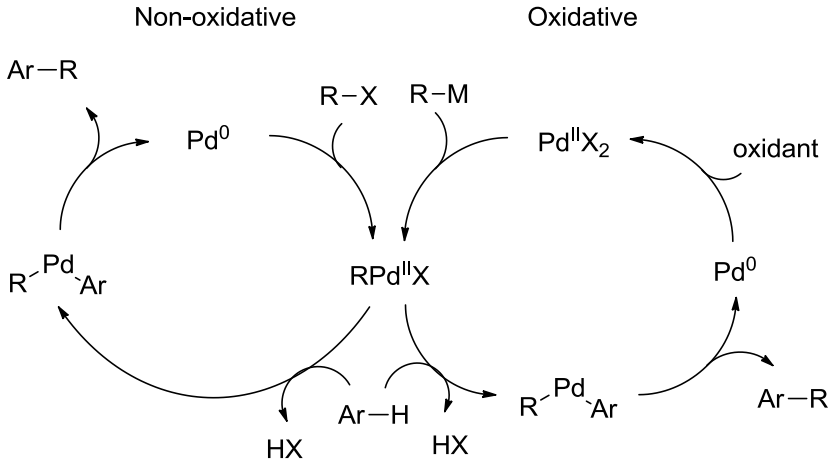
The most desirable approach towards aromatic functionalisations would be through directly activating C–H bonds of simple aromatic compounds, most of which are of low costs and widely available. This approach, so called C–H activation, in transition metal-catalysed cross-coupling reactions has advanced rapidly over the past few years, and has emerged as a reliable alternative to the conventional methods.[34,35,36,37,38] There are two classes of aromatic C–H activation reactions; non-oxidative and oxidative reactions (Scheme 9).



Scheme 9 Non-oxidative and oxidative C–H activation reactions.

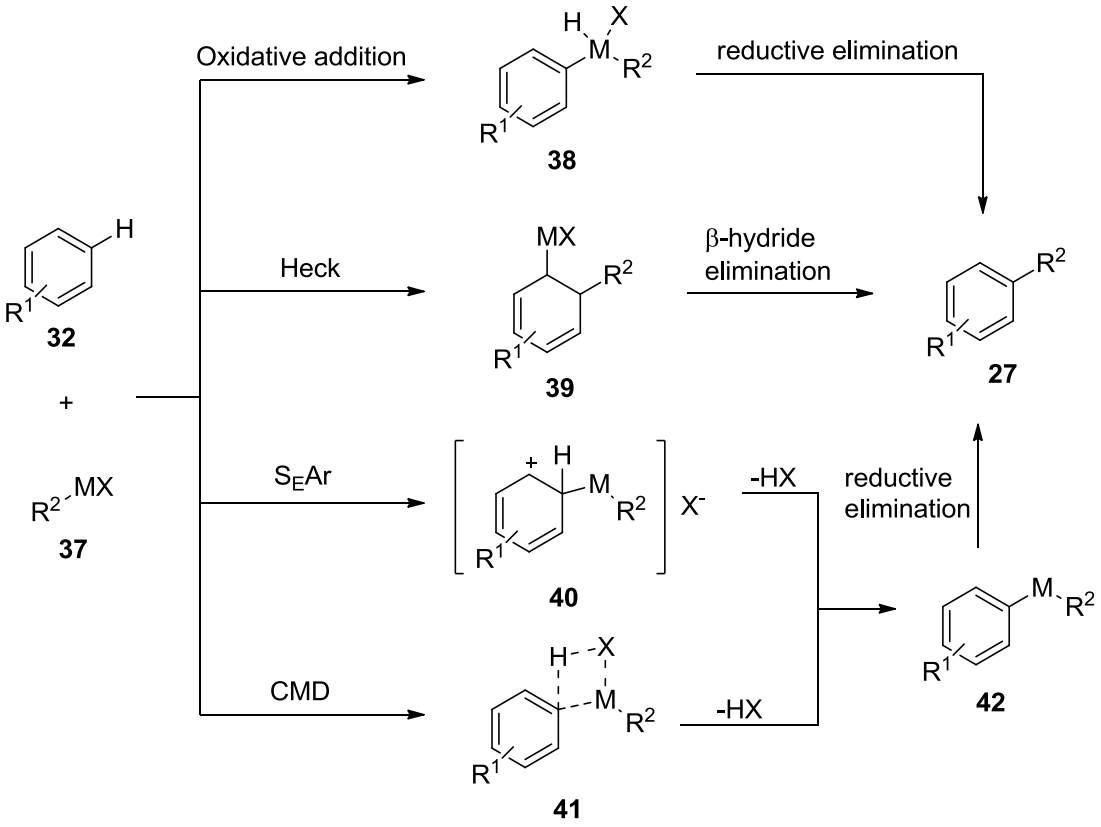
In the non-oxidative pathway, simple C–H coupling components are employed in place of organometallic reagents, and react with organic halides or pseudohalides *via* oxidative addition/C–H activation/reductive elimination mechanisms. The transition metal redox process enables the reactions to be catalytic, making this approach the most intensively studied aromatic C–H activation reactions. On the other hand, the oxidative pathway requires the presence of external oxidants, and is less exploited for this reason. The absence of oxidation process within the catalytic cycle means that a sacrificial oxidant is required to regenerate the active transition metal catalyst (Scheme 10). The coupling reactants employed in the oxidative reactions include organometallic reagents,

iodonium salts and simple C–H aromatic compounds for C–C bond formations, and unfunctionalised heteroatoms for C–heteroatom bond formations.



Scheme 10 Pd^0/Pd^{II} catalytic cycle of C–H activation reactions.

There are a number of different mechanistic pathways proposed for the insertion of transition metal into the aromatic C–H bonds: oxidative C–H insertion,[39] Heck type,[40] electrophilic aromatic substitution (S_EAr),[41] and concerted metallation-deprotonation (CMD)[42] mechanisms (Scheme 11). The two that have received the most support are S_EAr mechanism for electron-rich heteroarenes and CMD mechanism for simple arenes, but the exact mechanism for any given reactions would depend on the reaction parameters.[35]



Scheme 11 Proposed mechanisms for C–H activation.

One important task in the C–H activation chemistry is how to achieve the metal insertion in a regioselective manner. Aromatic molecules usually contains a number of C(sp^2)–H bonds with similar dissociation energies, hence, controlling the regioselectivity of aromatic C–H functionalisations is quite challenging. Two factors that influence the regioselectivity are the electronics of the aromatic systems and the presence of substituents that can direct the metal insertion into selective positions. The inherent electronic bias of electron-rich heteroarenes is often sufficient for the regioselective C–H functionalisations; as a consequence, relatively secure predictions can be made on the expected sites of these systems, although other factors such as the steric nature of the substrate, solvent, additives, and the electronic and steric nature of the catalyst can sometimes alter the regiochemical outcome (Figure 2).[35]

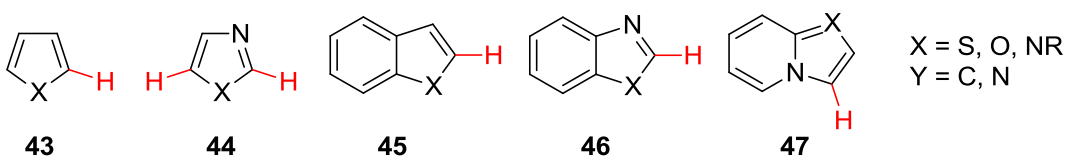
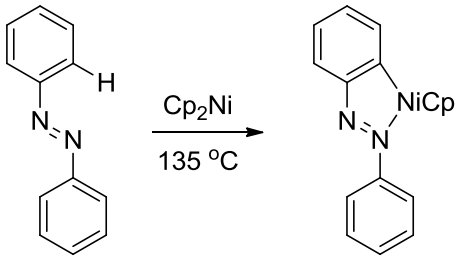


Figure 2 Heterocycles with activated C-H bonds.

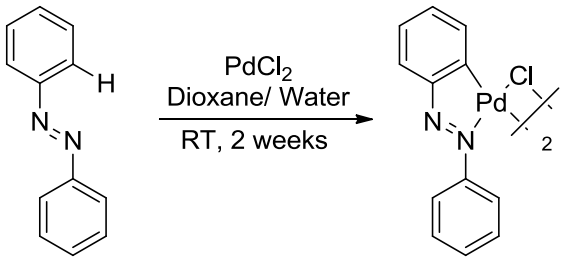
In contrast, the regioselectivity of simple aromatic and electron-poor heteroaromatic systems is generally controlled through the use of a directing group. The directing group assisted C-H activation was first observed in 1963, when Kleinman and Dubeck reported the preparation of the nickel complex **49** through the *ortho*-selective functionalisation of 1,2-diphenyldiazene **48** with dicyclopentadienylnickel (Scheme 12).[43]



48 **49**

Scheme 12 The first example of C–H activation using a directing group.

This was shortly followed by the work of Cope and Siekman in 1965, which described an analogous chemistry with palladium for the synthesis of a palladacyclic compound **50** (Scheme 13).[44]



48 **50**

Scheme 13 The first examples of palladium-catalysed *ortho*-directed C–H activation.

In these examples, the transition metal C–H insertion is directed by the nitrogen coordinating group, resulting in the formation of the kinetically and thermodynamically favoured 5-membered metallacycles. It is mainly this approach that has been employed in the C–H activation chemistry to control the regioselectivity of various C(aryl)–C and C(aryl)–heteroatom bond forming reactions. Common directing groups bear a lone pair of electrons that can coordinate to the transition metal and direct it into the selective C–H position. These include nitrogen and oxygen containing functional groups such as

amides **51**, imines **52**, N-containing heterocycles **53**, anilides **54** and carbonyl functionalities **55** (Figure 3).

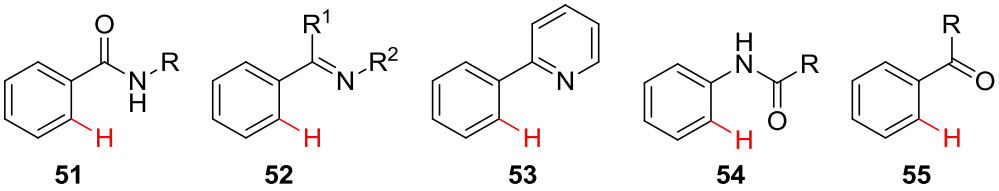


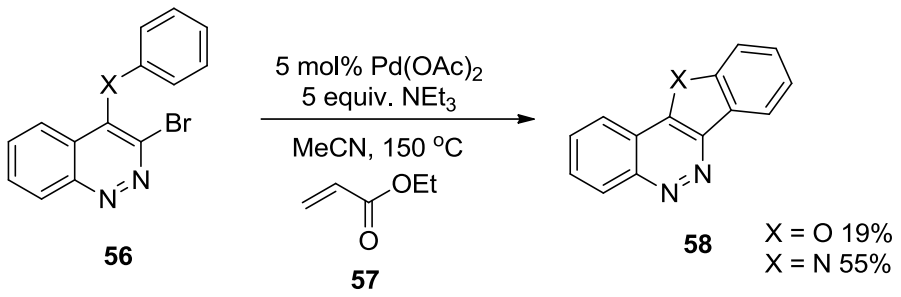
Figure 3 Directing group assisted C–H activation.

Like the conventional transition metal catalysed methods, the second-row transition metals in low oxidation states have emerged as the preferred catalysts for aromatic C–H functionalisations, with palladium being of dominance, and rhodium and ruthenium being increasingly employed in recent years. A vast number of C–H activation reactions have been reported over the past years, and some of the selected examples of C–C bond forming reactions are highlighted herein.

1.2.1 Non-oxidative C–H activation reactions

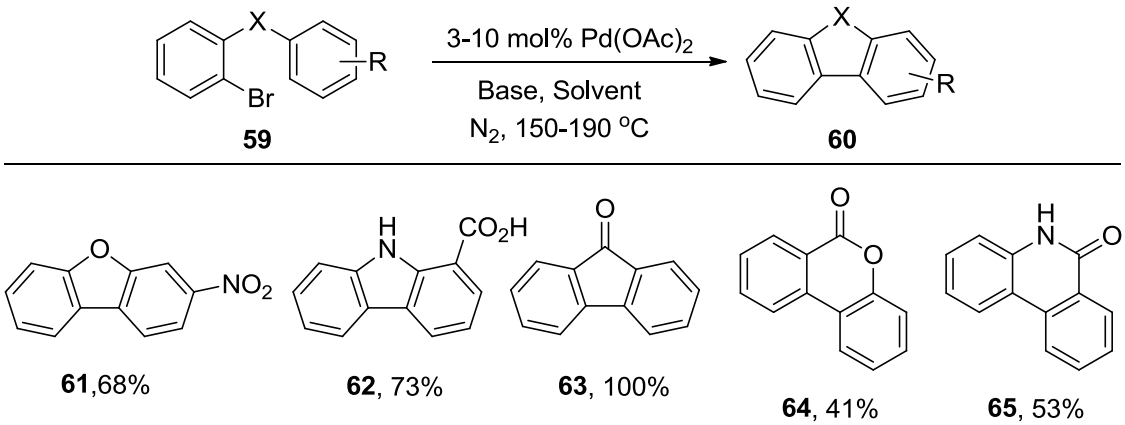
1.2.1.1 Intramolecular direct arylation

The coupling reaction of a simple aromatic compound with an organic halide has been largely studied, especially for the aryl–aryl bond formation. Initial successes in this field are found in the intramolecular reactions, where a tether limits the degree of freedom in a system, thereby controlling the regioselectivity of the reaction. The first examples were reported by Ames in the early 1980s (Scheme 14).[45] During their investigations into palladium-catalysed intermolecular Mizoroki-Heck reactions of 3-bromocinnolines **56**, the unexpected cyclisation product **58** was obtained.



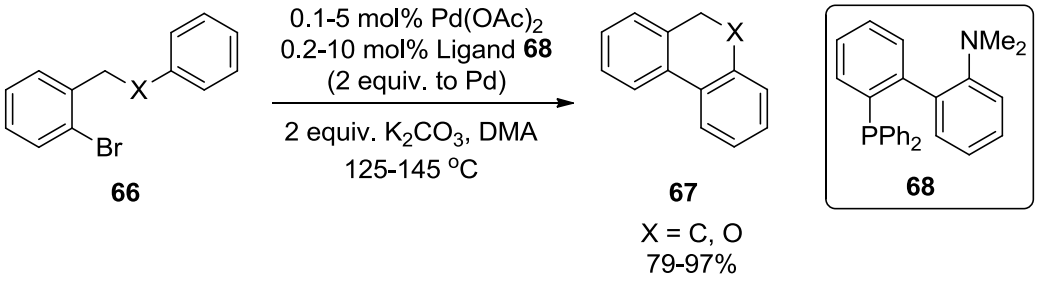
Scheme 14 The first example of Pd-catalysed intramolecular direct arylation reactions.

The same author further investigated this reaction to successfully prepare various 5-membered (dibenzofurans **61**, carbazoles **62** and fluorenones **63**) and 6-membered benzo-fused rings (lactones **64** and lactams **65**) under similar conditions (Scheme 15).[46,47] It was suggested that *in situ* generated Pd^0 catalyst oxidatively inserts into the Ar–Br bond, and the resulting Pd^{II} is put in place for the *ortho*-selective C–H activation of the adjacent aromatic ring. The selectivity between unsymmetrical *ortho* positions is influenced by steric effects, hence, the reaction of 3-substituted substrates (**61**) is more favoured at the less hindered 6-position than the 2-position.



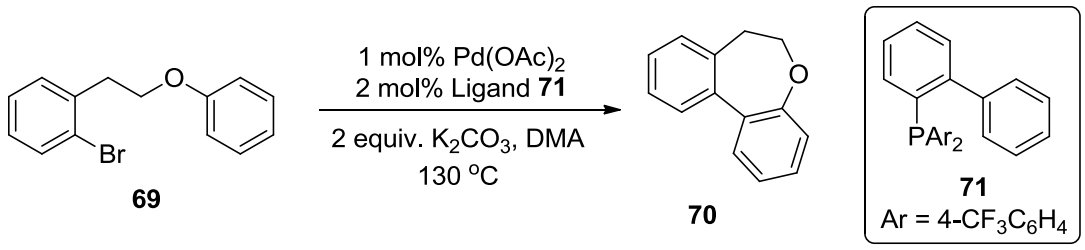
Scheme 15 5-Membered and 6-membered ring formations *via* Pd-catalysed intramolecular direct arylation reactions.

These early examples were limited to high catalyst loadings and narrow substrate scope, with the low yields being reported for the synthesis of 6-membered rings. In 2004, Fagnou reported an improved protocol using palladium(II) acetate in combination with a phosphine ligand **68** to obtain a number of six-membered rings **67** in excellent yields (Scheme 16).[48]



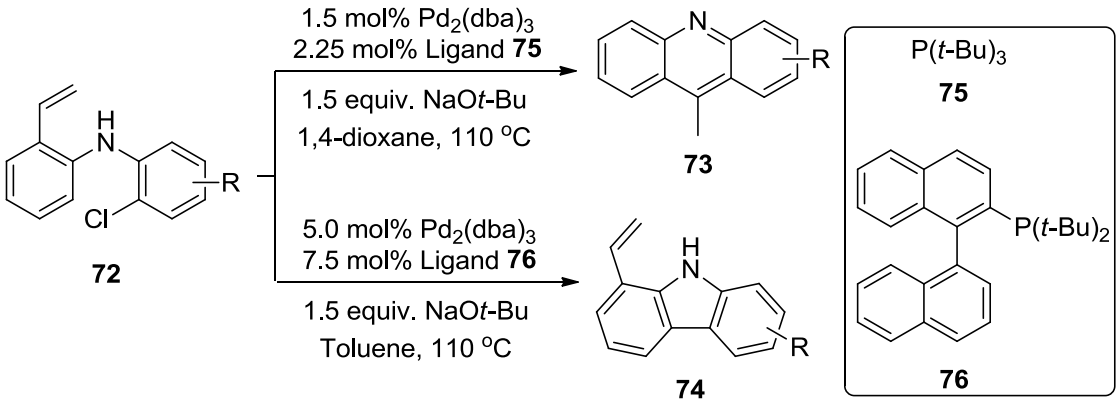
Scheme 16 An improved protocol for Pd-catalysed intramolecular direct arylation reactions.

The enhanced catalytic activity allowed less reactive substrates to react with catalyst loadings as low as 0.1 mol%. This method was also efficiently applied in the formation of a more challenging 7-membered ring **70** from the tethered aryl bromide **69** (Scheme 17). The use of an electron-deficient phosphine ligand **71** was crucial in increasing the reactivity of the catalyst and achieving the high yield.



Scheme 17 7-Membered ring formations *via* Pd-catalysed intramolecular direct arylation reactions.

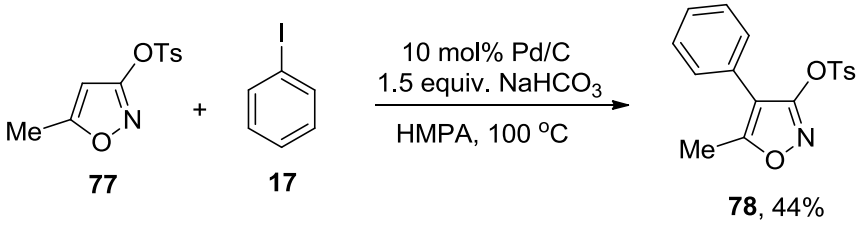
A number of different catalytic systems have since been developed, allowing even less reactive aryl chlorides to react. More recently, Buchwald further demonstrated the importance of the ligand choice by showing that the intramolecular transformations of the chlorodiarylamines **72** could be ligand controlled to give either acrinidines **73** or carbazoles **74** (Scheme 18).[49] The use of the bulky ligand **76** altered the reactivity and resulted in the exclusive formation of aromatic C–H activation products.



Scheme 18 Ligand controlled Pd-catalysed intramolecular reactions of 2-chloro-*N*-(2-vinylphenyl)aniline.

1.2.1.2 Intermolecular direct arylation of electron-rich heteroarenes

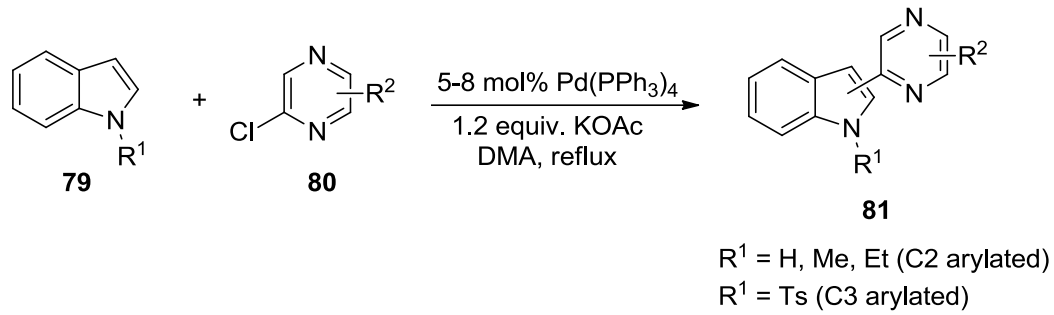
The intermolecular reaction between a simple aromatic C–H bond and an aryl halide has become a useful tool for the construction of biaryl motifs. In this reaction, unfunctionalised arenes are used as alternative nucleophiles in place of undesired organometallic compounds that are employed in the conventional cross-coupling reactions, offering many advantages thereby. Electron-rich heteroarenes are prominently featured in the early examples of this reaction, where the benefit of enhanced nucleophilicity is clearly demonstrated. In 1982, Tajima reported the palladium-catalysed direct arylation of isoxazole **77** with iodobenzene **17** (Scheme 19).[50] The reaction was heated in hexamethylphosphoramide at 100 ℃ in the presence of 10% palladium on charcoal to give 4-phenylisoxazole **78** in 44% yield.



Scheme 19 Pd-catalysed direct phenylation of isoxazole.

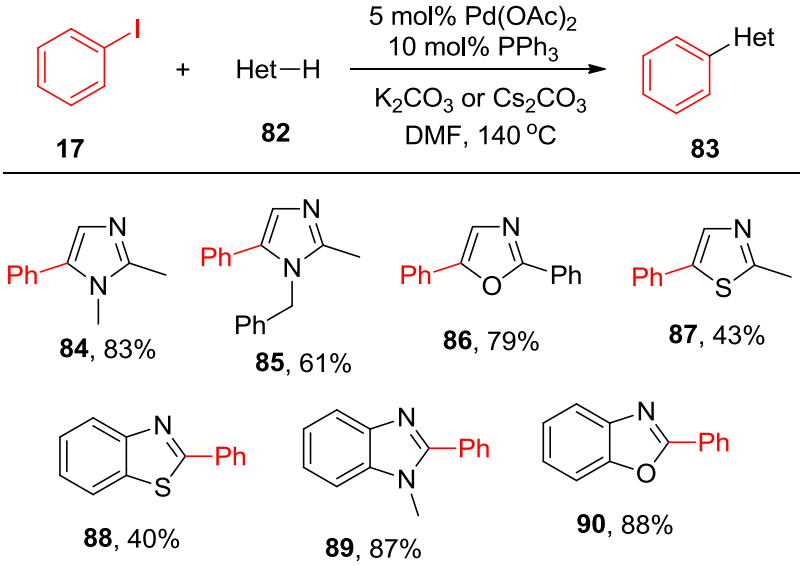
Ohta shortly reported interesting results on the palladium-catalysed arylation of indoles **79** with chloropyrazines **80** that afforded the C-2 or C-3 heteroarylated products **81**

(Scheme 20).[51,52] Unsubstituted and *N*-alkylindoles gave 2-pyrazinylindoles in modest yields while *N*-tosylindoles resulted in functionalisation at the 3-position, illustrating that the regioselectivity of such reaction could be altered with different nitrogen protecting groups.



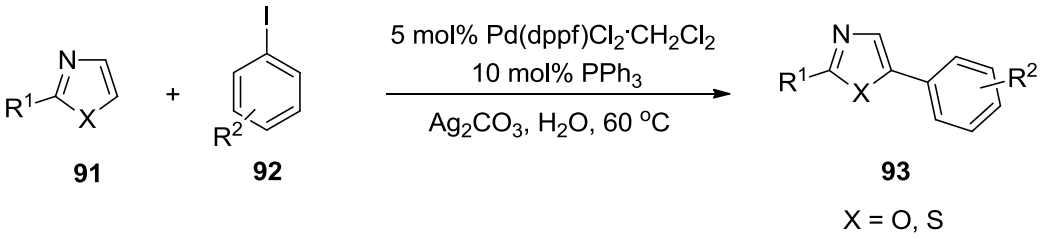
Scheme 20 Pd-catalysed direct arylation of indole with chloropyrazine.

Since these examples, palladium-catalysed direct arylations have been greatly extended to the reactions of numerous other 5- and 6-membered, as well as fused heteroaromatic systems. Earlier work by Miura gives a nice example, showing the reactivity of various azole compounds towards palladium-catalysed direct arylations (Scheme 21).[53] The reaction scope was fairly broad, with imidazole, oxazole, thiazole, benzothiazole, benzimidazole, and benzoxazole all affording arylated products in good to excellent yields.



Scheme 21 Pd-catalysed direct arylations of azole compounds by Miura.

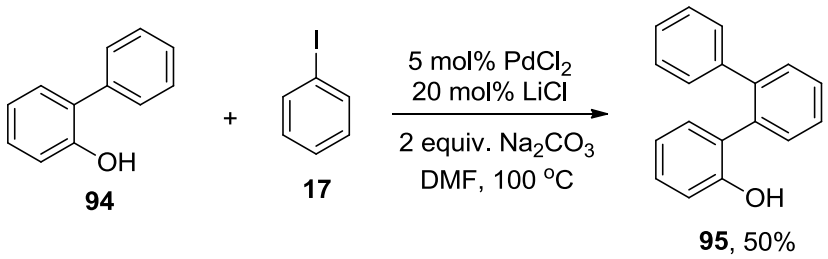
The Greaney group has also worked extensively in this area and developed an effective on water method for the C–H functionalisation of oxazole and thiazole compounds (Scheme 22).[54,55] A range of 2-substitued oxazoles and thiazoles were selectively arylated at the 5-position under far milder conditions than those previously reported.



Scheme 22 Pd-catalysed direct arylations of oxazoles and thiazoles.

1.2.1.3 Directing group assisted intermolecular direct arylation

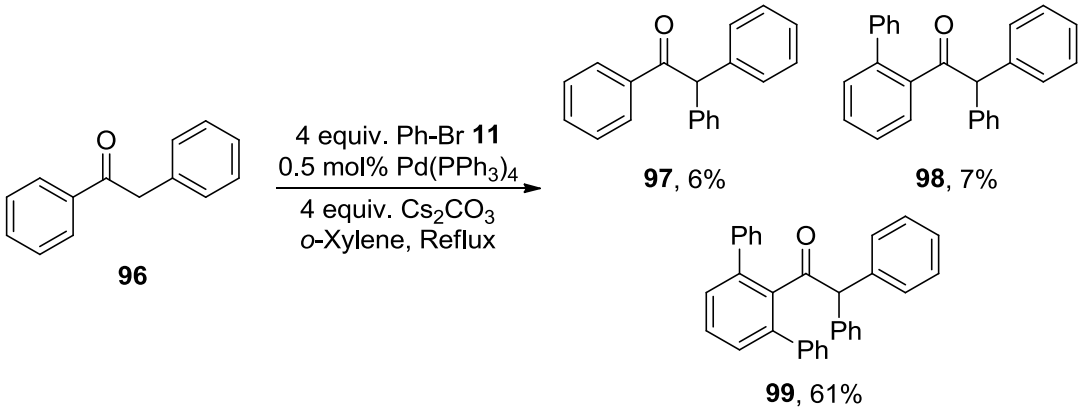
A number of procedures for simple aromatic compounds have been disclosed through directing group assisted reactions. The key discovery was made by Miura who described the first example of these types of direct arylation reactions in 1996.[56] Following their successful work on palladium-catalysed arylations of aldehyde C–H bonds, they found that the same methodology could be applied to the aromatic C–H bond activation of 2-phenylphenol **94** (Scheme 23). The hydroxyl functional group directs the palladium insertion selectively, leading to the *ortho*-phenylated product **95**.



Scheme 23 Pd-catalysed direct arylation of hydroxyarene.

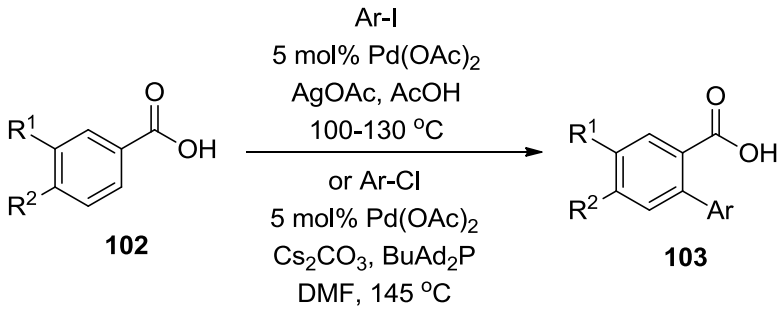
Improved conditions using a palladium(II) acetate/cesium carbonate catalytic system was described in the later publication, where both mono- and di-arylated products could be obtained more effectively.[39] The generation of di-arylated products were controlled by restricting the amounts of the base and aryl iodides. The same author shortly reported

other examples of *O*-directed arylations, showing that the directing group need not be phenolic in nature. One particularly interesting example is the keto-directed arylation of benzyl phenyl ketone **96** (Scheme 24).[57] The reaction with phenyl bromide **11** in the presence of tetrakis(triphenylphosphine)palladium and cesium carbonate in refluxing *o*-xylene afforded a mixture of mono-, di- and tri-arylated products. This example shows that not only is this protocol suitable for the arylation of C(sp^2)–H bonds, it can also be used to functionalise C(sp^3)–H bonds.



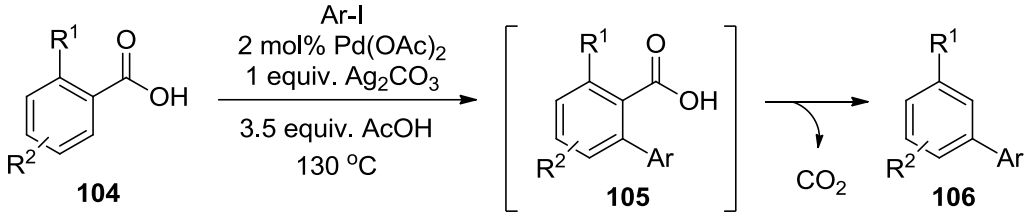
Scheme 24 Pd-catalysed direct arylations of benzyl phenyl ketones.

Many other examples of directing group assisted arylations have been reported since. More recently, Daugulis reported the palladium-catalysed direct arylation of benzoic acids **102** (Scheme 25).[58] Various benzoic acids were reacted with either aryl iodides or aryl chlorides under different palladium-catalytic conditions. Good yields were obtained in both reactions, with the arylation taking place at less hindered *ortho*-positions.



Scheme 25 Pd-catalysed direct arylations of benzoic acids.

The use of carboxylic acid directing group is particularly advantageous since this functional group can be removed by means of protodecarboxylation.[59] Directing groups are generally needed to achieve selective C–H activations, but mostly not wanted in the final products. Therefore, the use of a removable directing group is desirable for the application of this concept to the synthesis of important compounds.[60] Recently, Larrosa reported the palladium-catalysed tandem *ortho*-selective direct arylation/protodecarboxylation reaction of *ortho*-substituted benzoic acids **104** (Scheme 26).[61]



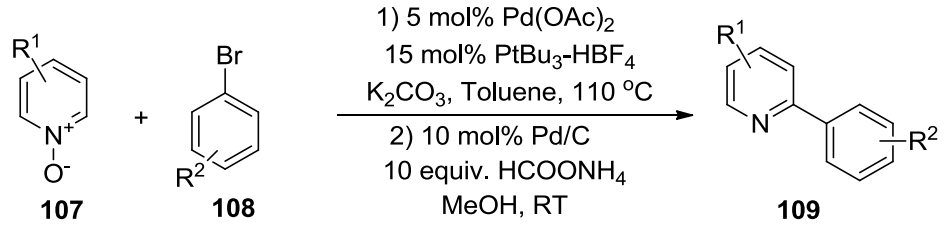
104 **105** **106**

Scheme 26 Pd-catalysed tandem *ortho*-selective direct arylation/protodecarboxylation.

The author initially tested the reaction of **104** using the conditions reported by Daugulis,[58] and found that lower catalyst loading and increasing the temperature allowed the tandem process to occur, exclusively producing the desired product **106**. Under the optimised conditions, the protodecarboxylation was chemoselective for the arylated benzoic acids **105** in the presence of the starting benzoic acids **104**. This indicates that the carboxylate group in the starting material can be used as a directing group for selective C–H arylation and then be removed once the C–C bond formation is complete. Benzoic acids are cheap and readily available starting materials, making this reaction an attractive method for the synthesis of *meta*-substituted biaryl compounds.

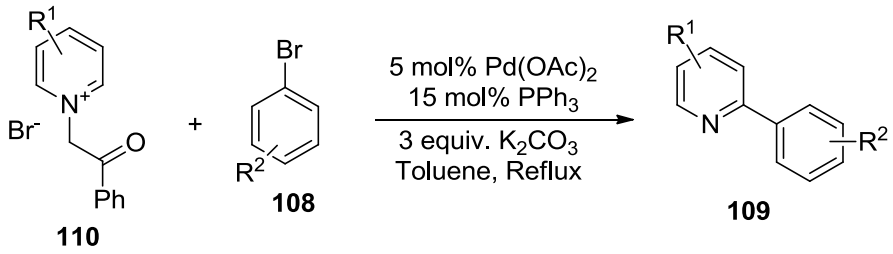
This strategy, using a removable directing group, has also been employed in the direct arylation of electron-deficient heteroarenes.[62] The C–H activation of such heteroarenes is particularly challenging due to their reluctance to undergo the CMD-type metallation, which has a strong nucleophilic component to the mechanism. In 2005, Fagnou reported the palladium-catalysed direct arylation of pyridines using *N*-oxide as a removable directing group (Scheme 27).[63] Under the optimised conditions, the arylation of pyridine *N*-oxides **107** with a wide range of aryl bromides **108** occurred in high yields and complete selectivity for the 2-position. The *N*-oxide moiety was then removed *via*

palladium catalysed reduction with ammonium formate to give the corresponding 2-arylpyridines **109**. In this example, the directing group not only controls the regioselectivity, but it also enhances the reactivity towards C–H activation by increasing the electron-density of the electron-deficient pyridine system.



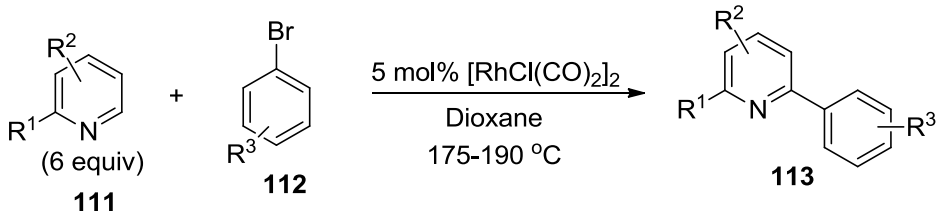
Scheme 27 Pd-catalysed direct arylation of pyridine *N*-oxides.

The scope of this chemistry has been extended to the arylation of other azine and azole *N*-oxides,[64,65] and also of pyridines with different *N*-functional groups.[66,67] Interestingly, Wang and Hu reported the reaction of *N*-phenacylpyridinium bromides **110**, where the *N*-phenacyl group regioselectively activates the *ortho* C–H bonds of azines and is then removed from the arylated products in one pot (Scheme 28). This reaction is highly efficient and tolerant of both electron-donating and electron-withdrawing substituents on the electrophilic coupling partners, and also shows good regioselectivities. However, the formation of di-arylated products could not be controlled under the optimised conditions, and moreover, the method is still limited by the need for installation of the phenacyl directing group.



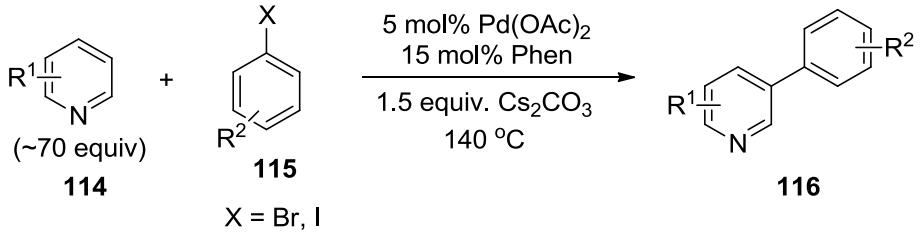
Scheme 28 Pd-catalysed direct arylation of *N*-phenacylpyridinium bromides.

Bergman and Ellman reported rhodium-catalysed *ortho*-selective arylations of unactivated azine compounds (Scheme 29).[68,69] Inexpensive and readily available pyridines **111** were used without the need for prefunctionalisation, which afforded 2-arylpyridines **113** in high efficiency and high selectivity.



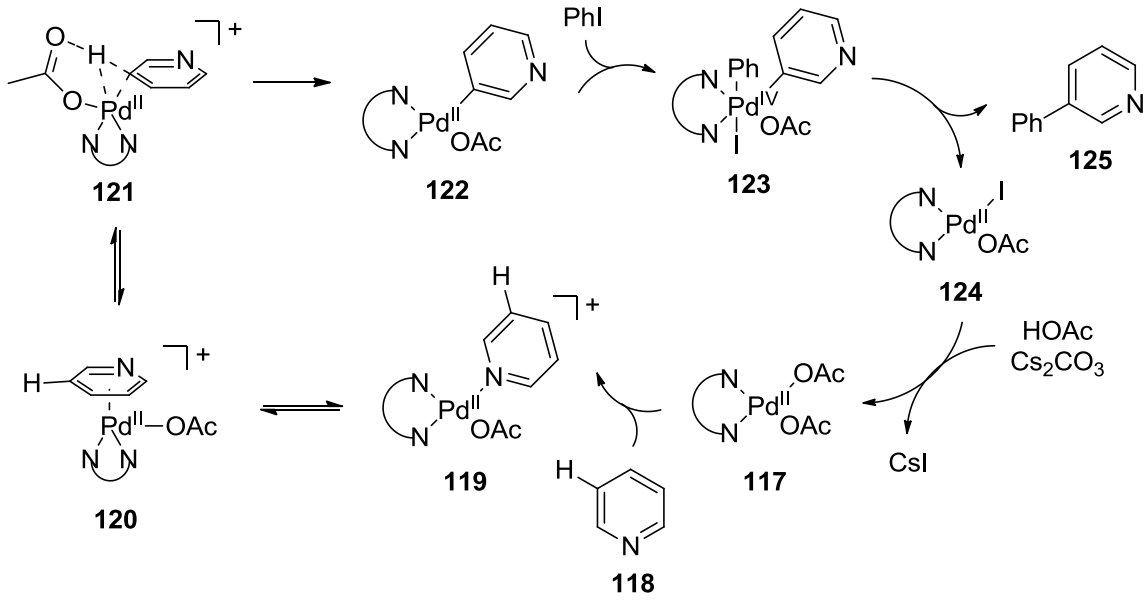
Scheme 29 Rh-catalysed *ortho*-arylations of unactivated pyridines.

Yu reported the palladium-catalysed *meta*-selective arylation of pyridines **114** using a catalyst generated *in situ* from palladium(II) acetate and 1,10-phenanthroline (Scheme 30).[70] An excess pyridine substrate was needed to obtain synthetically useful yields, with the reaction giving the best results when performed in neat pyridine. In addition, the author found that inorganic bases had a significant effect on the regioselectivity. Under the optimised conditions, a wide range of aryl bromides and iodides **115** were reacted with pyridines **114** to give *meta*-arylated products **116** in high selectivities.



Scheme 30 Pd-catalysed *meta*-arylations of unactivated pyridines.

This non-directed method is a great advancement over the previously reported work that utilised either an electronic[71] or a coordination[72] control to achieve the activation of otherwise unreactive *meta*-C–H bonds. How this works is not clear, but the author hypothesised that the *meta*-selectivity could be a result of the strong bidentate coordination of the phenanthroline ligand, which destabilises the *N*-metal coordination of the pyridine substrates. This would dissociate and put the pyridine substrates around the palladium centre in various orientations (**119** to **120**), and the *meta*-selective C–H activation could take place when the appropriate orientation between the π-system of the pyridine and palladium is assembled (**121** to **122**). It was proposed that the reaction would proceed *via* a Pd^{II}/Pd^{IV} catalytic cycle (Scheme 31). The same reaction using aryl tosylates as alternative electrophiles has also been reported recently by Tan,[73] but with no particular advantages over the original work.



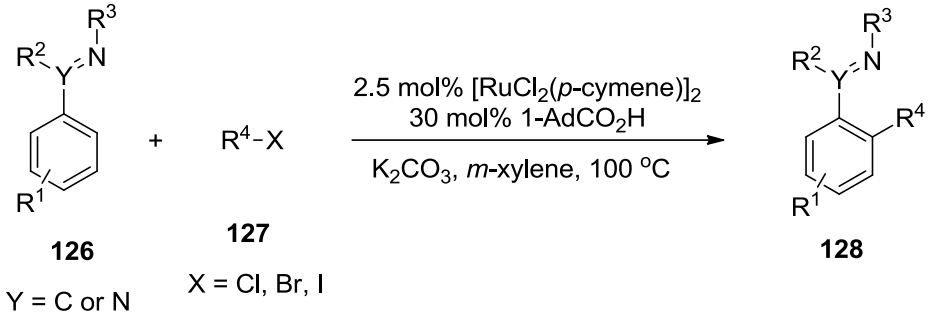
Scheme 31 Proposed mechanism for the Pd-catalysed *meta*-arylations of unactivated pyridines.

1.2.1.4 Direct alkylation with alkyl halides

In contrast to aryl halides, the C–H activation reactions with alkyl halides are less developed, mainly due to the common problems associated with the use of such substrates in transition metal catalysis: they are less reactive towards oxidative addition and the resulting alkyl metal species have a strong tendency to undergo β-hydride elimination reactions. Secondary alkyl halides are particularly challenging substrates since the added steric hindrance increases the energy barrier to oxidative addition, thus making transition metal-catalysed processes even more difficult.[74] There has been much research into the development of new catalytic systems for cross-coupling reactions of secondary alkyl halides, and a number of direct alkylation reactions have been reported very recently.

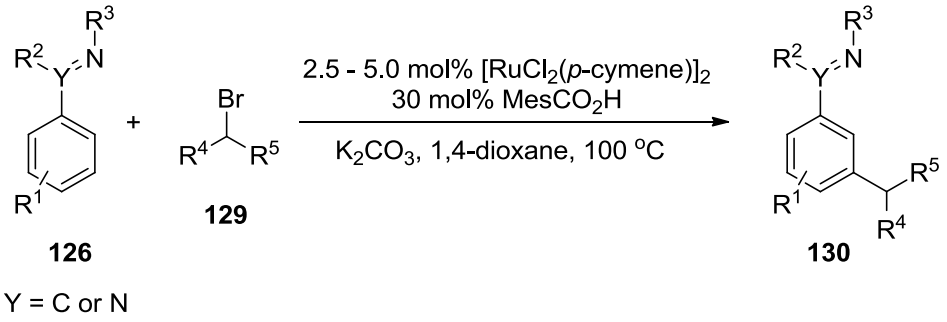
In 2009, Ackermann reported the ruthenium-catalysed *ortho*-selective alkylation of simple arenes **126** with unactivated alkyl halides bearing β-hydrogen atoms **127**, which also included a more challenging secondary alkyl halide substrate (Scheme 32).[75] Carboxylic acid additives were found to be crucial for improving the catalytic activity through *in situ* formation of ruthenium(II) carboxylate complex, with the sterically hindered 1-adamantylcarboxylic acid giving the best results. Pyridine, pyrazole and

ketimine functionalities were used as directing groups to control the regioselectivity in this reaction.



Scheme 32 Ru-catalysed direct alkylation of simple arenes.

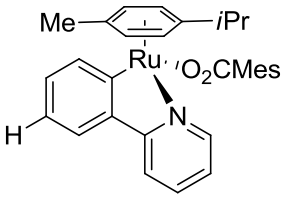
Following this work, the same group developed an alternative catalytic system that gave *meta*-selective alkylation of similar aromatic compounds with a wide range of secondary alkyl bromides **129** (Scheme 33).[76] High regioselectivity was obtained when using 1,4-dioxane as the solvent, and mesitylenecarboxylic acid was found to be an ideal co-catalytic additive for both selectivity and catalytic efficacy.



Scheme 33 Ru-catalysed *meta*-selective alkylation of simple arenes.

The author proposed that the reaction would proceed *via* the initial formation of the cyclometallated complex **131** (Figure 4), which would then be followed by a S_EAr-type alkylation at the *para*-position to the Ru-C(aryl) bond. The strong directing group effect of the Ru–C(aryl) σ-bond activates both the *ortho*- and *para*-positions, but the less hindered *para*-position would be selectively reacted. This proposed mechanism is comparable to the typical transition metal catalytic cycles that would give *ortho*-alkylated products instead through the insertion of alkyl halides into the ruthenium metal centre of **131** and subsequent reductive elimination. The former insertion process

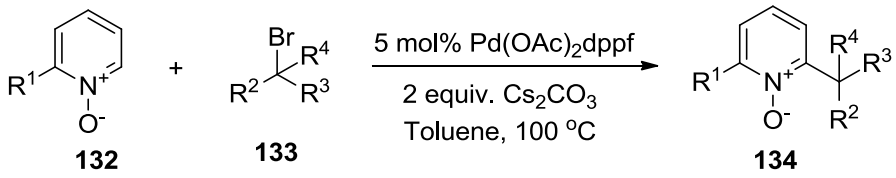
may not be favoured for the sterically demanding secondary alkyl halides, which may have resulted in this reaction to undergo a different pathway. Indeed, whereas *meta*-selectivity was obtained with secondary alkyl halides, an *ortho*-alkylated product was formed when a less sterically hindered primary alkyl halide was treated under the same reaction condition.



131

Figure 4 Cyclometalated ruthenium complex.

Fu developed a palladium-catalysed *ortho*-alkylation of pyridine *N*-oxides **132** not only with secondary alkyl halides, but also with a range of tertiary alkyl halides **133** (Scheme 34).[77] The reaction was compatible with many synthetically relevant functional groups, providing a novel protocol for the preparation of alkylpyridine derivatives **134**. Other metals such as copper,[78] cobalt[79] and nickel[80] have also been utilised in similar *ortho*-selective alkylation reactions.



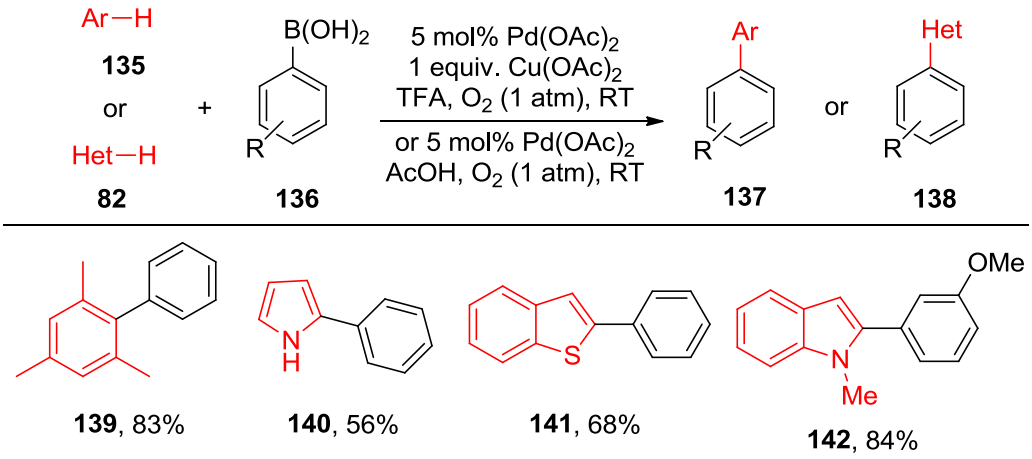
132 **133** **134**

Scheme 34 Pd-catalysed direct alkylation of pyridine *N*-oxides.

1.2.2 Oxidative C–H activation reactions

1.2.2.1 Direct arylation with organometallic reagents

Although the use of organometallic reagents as coupling partners is not favoured, the direct arylation using such reagents could be a nice alternative if the corresponding reaction with organic halides is not available. Several examples have been reported over the past few years, with some reactions proceeding under comparatively mild conditions. In 2008, Shi reported the palladium-catalysed direct arylation of electron-rich arenes **135** and heteroarenes **82** with arylboronic acids **136** that proceeds at room temperature (Scheme 35).[81] Undesired homocoupling of the boronic acid substrates **136** could be avoided by performing the reaction under acidic conditions. Dioxygen was used as a terminal oxidant for the reaction of heteroarenes, whereas copper(II) acetate was additionally required as a co-oxidant for arenes. Various methyl-substituted aromatic compounds, pyrroles, benzofurans, benzothiophenes and indoles were well-tolerated, with the selectivity being controlled by the electronic properties of the aromatic rings.

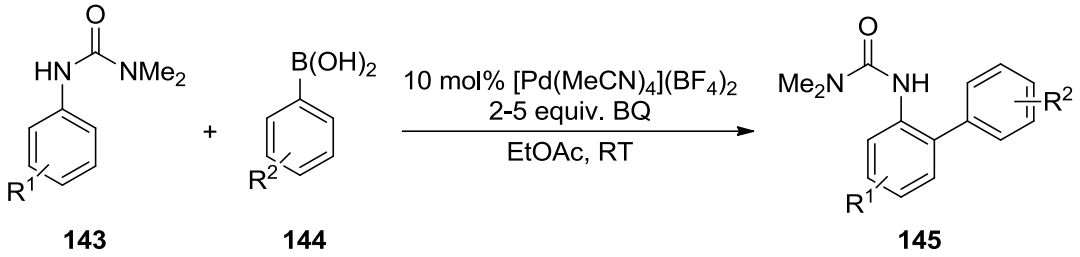


139, 83% **140**, 56% **141**, 68% **142**, 84%

Scheme 35 Pd-catalysed direct arylations of simple arenes and heteroarenes with arylboronic acids.

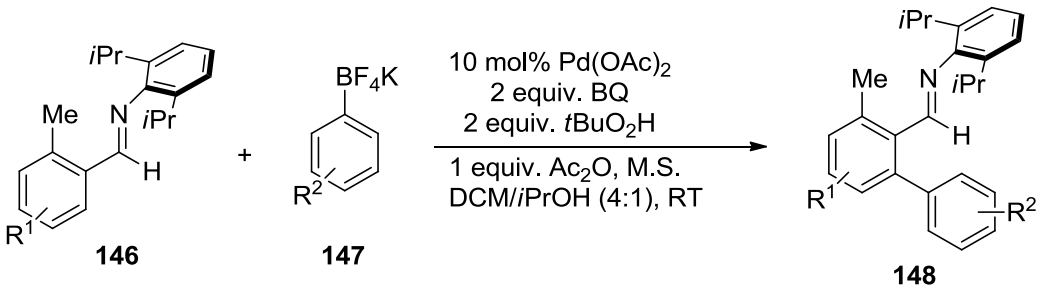
Similarly, Lipshutz reported the coupling reaction of aryl ureas **143** with arylboronic acids **144** using a cationic palladium(II) complex, which provided the *ortho*-arylated products **145** at room temperature (Scheme 36).[82] An additional experiment using palladium(II) acetate showed that such catalyst was also active in this reaction but only in the presence of a strong acid. This indicates that it is the cationic palladium(II)

species that allows the reaction to be carried out in non-acidic conditions. 1,4-Benzoquinone was used as an external oxidant, which is comparable to the above example by Shi that employed metal oxidants.



Scheme 36 Pd-catalysed direct arylations of aryl ureas with arylboronic acids.

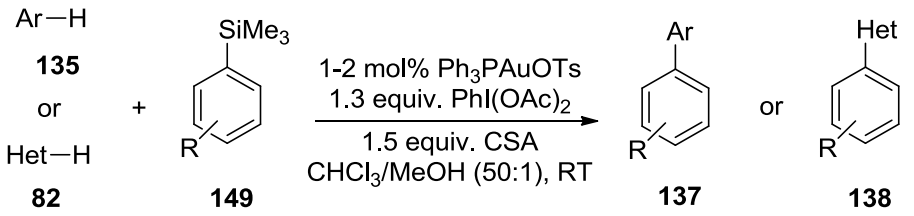
More recently, Gaunt reported the palladium-catalysed *ortho*-selective arylation of benzaldimines **146** with aryl tetrafluoroborate salts **147** that proceeds at room temperature (Scheme 37).[83] A wide range of both reactants were tolerated, and more importantly, this method could be applied to structurally complex molecules bearing labile stereogenic centres without loss of chiral integrity.



Scheme 37 Pd-catalysed direct arylations of benzaldimines with tetrafluoroborate salts.

Although boron-based reagents have been dominant, other organometallic reagents have also been utilised in the oxidative direct arylation reactions. One interesting example is the gold catalysed direct arylation reported by Lloyd-Jones and Russell in 2012, where a wide range of electron-rich arenes **135** and heteroarenes **82** were site-selectively arylated using arylsilane reagents **149** at room temperature (Scheme 38).[84] The reaction was conducted in the presence of a low concentration of methanol co-solvent, and using $Ph_3PAuOTs$ as a precatalyst and the active oxidant generated *in situ* from iodobenzene diacetate and camphorsulfonic acid. Diverse functional groups were introduced through both coupling partners, although longer reaction times or higher temperatures were

required for sterically hindered substrates, less electron-rich arenes and electron-deficient arylsilanes. With these reactivity trends, a S_EAr mechanism was proposed for the activation of both coupling partners.



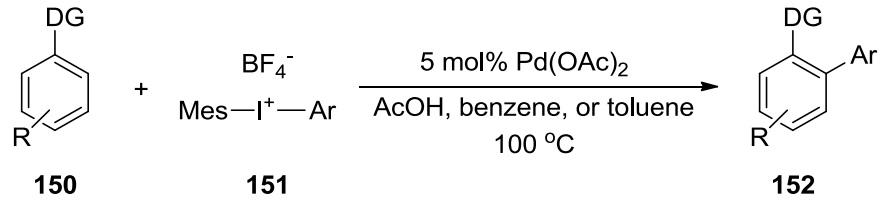
Scheme 38 Au-catalysed direct arylations of simple arenes and heteroarenes using arylsilane reagents.

1.2.2.2 Direct arylation with diaryliodonium salts

Diaryliodonium salts are mild, non-toxic and selective reagents that behave as aromatic electrophiles and as oxidants at the same time. The electrophilic nature of the iodine(III) centre results in the enhanced reactivity, and this, along with the ability to access higher oxidation states of transition metal catalysts, makes these reagents ideal for the use in cross-coupling reactions.[85] In recent years, a number of transition metal-catalysed C–H arylation reactions using diaryliodonium salts have been developed, offering new reaction pathways and conditions relative to their aryl halide and organometallic congeners.

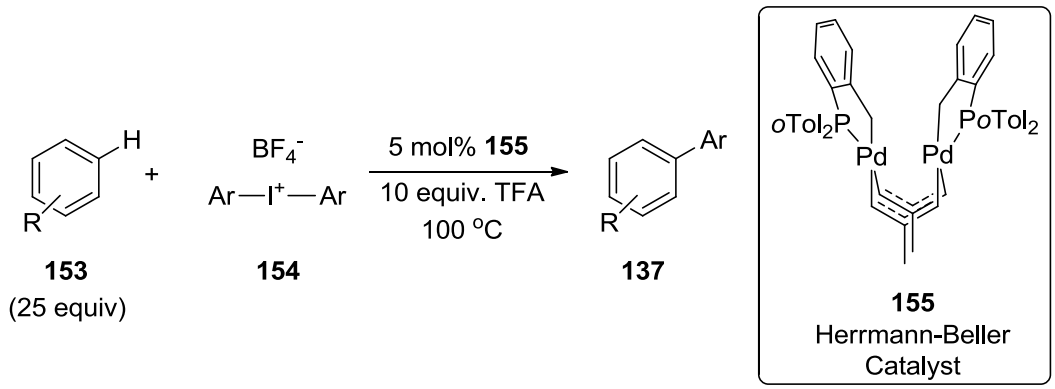
In 2005, Sanford reported the palladium-catalysed direct arylation of simple arenes **150** with unsymmetrical diaryliodonium tetrafluoroborates **151**, where the selective transfer of different aryl groups is achieved through steric controls, with smaller aryl groups reacting more rapidly than bulky mesityl groups (Scheme 39).[86] This reaction is compatible with ambient air and moisture, and proceeds under relatively mild and simple conditions to give *ortho*-arylated products **152**. A wide range of functional groups were well-tolerated, and diverse directing groups, including pyridines, quinolones, pyrrolidinones and oxazolidinones, were effective at promoting *ortho*-selective C–H activation. A Pd^{II}/Pd^{IV} catalytic cycle involving a monomeric Pd^{IV}

species was initially proposed in this work, but the further mechanistic studies suggested that a binuclear Pd^{III} species might be involved as a key intermediate.[87,88]



Scheme 39 Pd-catalysed directing group assisted C–H arylation of simple arenes with unsymmetrical diaryliodonium salts.

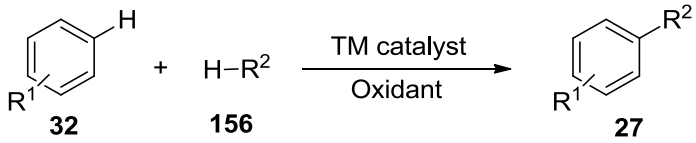
Following this work, the same group applied this chemistry to the reactions of other aromatic systems such as indoles[89] and naphthalenes.[90] A number of other palladium catalytic systems have been reported by others, including the recent work within the Greaney group on the non-directed C–H arylation of simple arenes **153** with symmetrical diaryliodonium trifluoroborates **154** (Scheme 40).[91] The key factors influencing the reaction success were the use of the Hermann-Beller palladacycle **155** as a precatalyst and stoichiometric trifluoroacetic acid to enhance the electrophilicity of the palladium catalyst. Under the optimised conditions, a wide range of electron-rich arenes were reacted to afford the arylated products **137** in good to excellent yields, with high functional group tolerance but little regioselectivity.



Scheme 40 Pd-catalysed non-directed C–H arylation of simple arenes with symmetrical diaryliodonium salts.

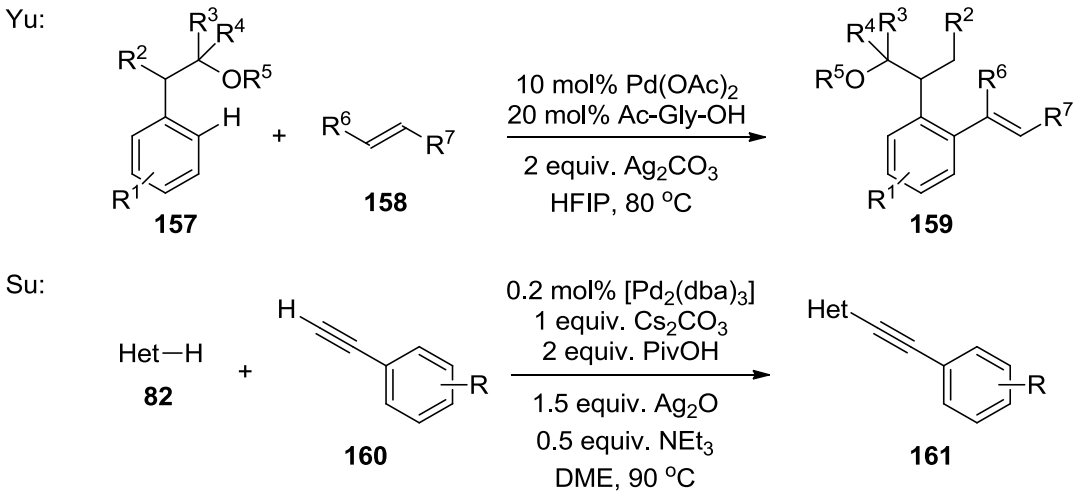
1.2.2.3 Oxidative cross-coupling reactions between two C–H bonds

The most desired approach of C–C bond forming reactions would be through activation of two C–H bonds, because this employs two readily available starting materials and does not generate any halogenated or organometallic waste (Scheme 41).[92] This process is thermodynamically unfavourable due to the low reactivity of C–H bonds, thus generally requiring an appropriate sacrificial oxidant as an external driving force. In addition to issues with reactivity, achieving regioselective activation of one C–H bond in the presence of others, and reacting that selectively with another C–H bond is very challenging.



Scheme 41 Oxidative cross-coupling between two C–H bonds.

The coupling reactions of arene C–H bonds with either alkene C–H bonds or alkyne C–H bonds can take place through combination of C–H activation with either Heck-type alkenylation or Sonogashira-type alkynylation reactions respectively. In these reactions, the regioselectivity of arene C–H bonds is controlled through directing groups or by their electronic properties, that of alkene C–H bonds can be predicted based on the well-established mechanism of the Heck reaction, and terminal alkynes have only one C–H bonds to be reacted with. The recent and independent work by Yu[93] and Su[94] on respective palladium-catalysed C–H alkenylation and C–H alkynylation are nice examples of these types of reactions (Scheme 42).

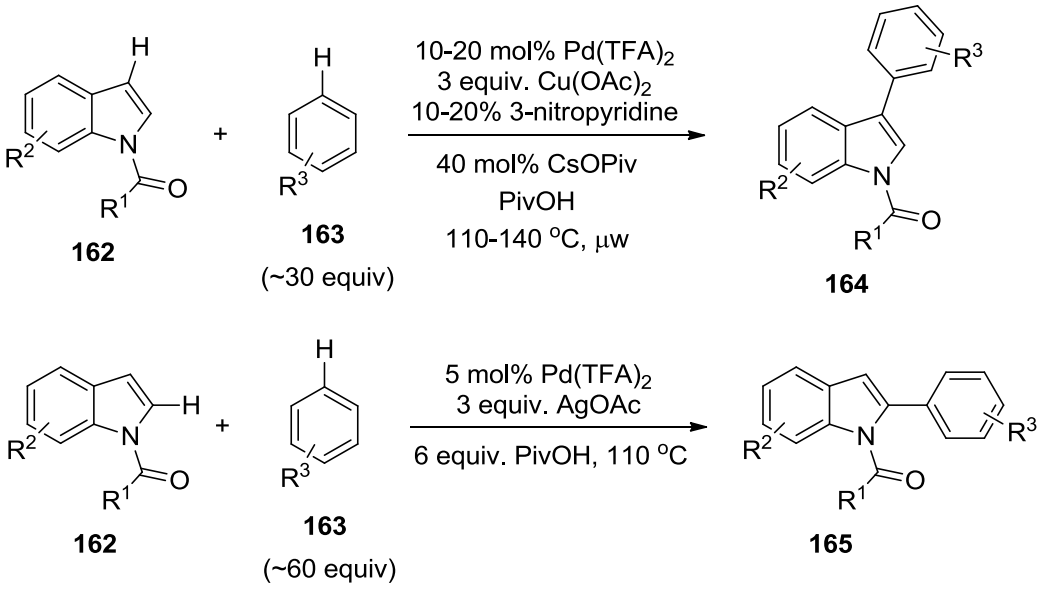


Scheme 42 Pd-catalysed C–H alkenylation and C–H alkynylation.

The cross-coupling reactions of two arene C–H bonds are more challenging in terms of regioselectivity and chemoselectivity, because both coupling partners contain many aromatic C–H bonds that have similar reactivities. While tethers reduce the degree of freedom in intramolecular reactions, the intermolecular reactions between two different arenes could result in mixtures of many regioisomeric products and unwanted homocoupling by-products. Despite these difficulties, a number of oxidative cross-coupling reactions between two simple arenes have been reported in recent years. In these reactions, one of the coupling partners is generally an electron-rich arene or an arene bearing a directing group, and the other, usually a less reactive component, is an unfunctionalised arene that is added in excess. This allows a better control of both the regioselectivity and chemoselectivity in appropriate catalytic conditions.

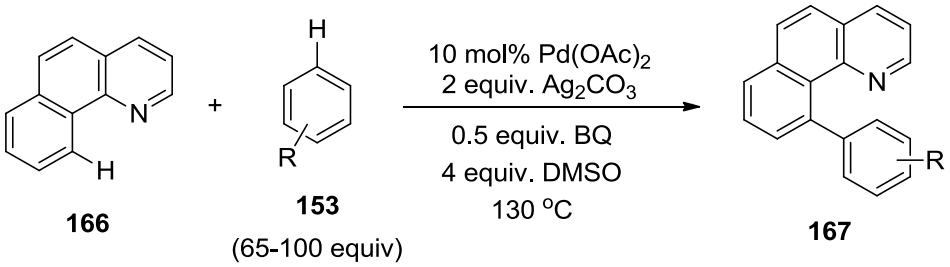
In 2007, Fagnou disclosed two palladium-catalytic systems that gave C2- and C3-selective arylations of indoles **162** with simple arenes **163** (Scheme 43). The initially developed condition using copper(II) acetate as the stoichiometric oxidant led to predominant functionalisation at the C3-position in high regioselectivity.[95] Although conventional heating was effective, microwave heating was employed because of the enhanced reaction rate. The ratio of the coupling partners was important in achieving chemoselective reactions, with a huge excess of arenes **163** resulting in completely selective formation of the oxidative cross-coupling products **164**. No homocoupling by-products from either indoles **162** or arenes **163** were detected. The selectivity of these reactions could be altered in favour of the C2-position when using silver(I) acetate as an

alternative oxidant.[96] It was proposed that mixed Pd-Cu clusters[97] that favour C3 selectivity are formed when excess copper(II) acetate is used. This cluster formation does not take place in the presence of silver(I) acetate, thus selectively giving the C2-arylated products **165**. Similarly, DeBoef showed that C2 and C3 regioselectivity of oxidative cross-coupling reactions of benzofurans could be controlled with the choice of oxidants.[98,99]



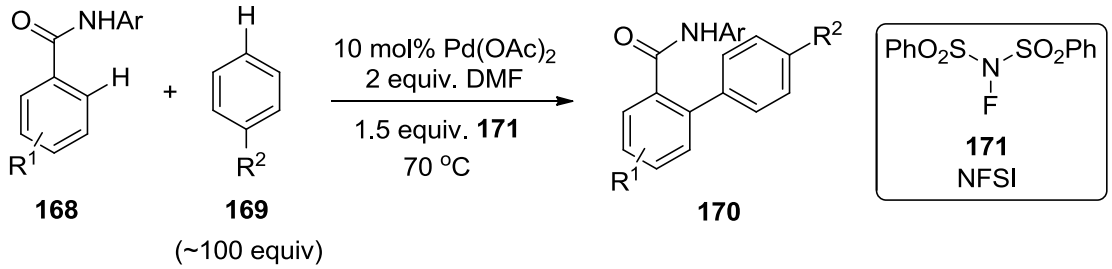
Scheme 43 Pd-catalysed C2- and C3-selective arylations of indoles with simple arenes.

Directing group assisted *ortho*-functionalisation has also been utilised in oxidative cross-coupling reactions with simple arenes. In 2007, Sanford reported the palladium-catalysed oxidative arylation of benzoquinoline **166** that proceeds in a highly chemo- and regioselective manner (Scheme 44).[100] A range of arene coupling partners **153** were reacted using silver(I) carbonate as the external oxidant and DMSO additive to prevent both aggregation and decomposition of Pd^0 complex. The addition of 1,4-benzoquinone was also crucial for obtaining high yields, with the later mechanistic studies suggesting its role as promoting reductive elimination process.[101]



Scheme 44 Pd-catalysed oxidative cross-coupling reactions of benzoquinoline with simple arenes.

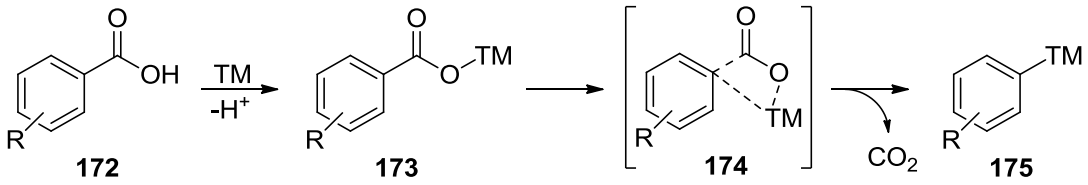
Other substrates such as pyridine *N*-oxides,[102] amides[103] and anilides[104] have also been employed in similar reactions. While the regioselectivity on one coupling partner is well controlled through the use of directing groups in these reactions, it is less so for the other coupling partner. A mixture of regioisomers is generally formed when a simple mono-substituted arene or an unsymmetrical arene is used as the coupling partner. A few protocols that are regioselective on both coupling partners have been recently developed. Yu described a palladium-catalysed oxidative cross-coupling between benzamides **168** and mono-substituted arenes **169** (Scheme 45).[105] The corresponding biaryl products **170** were obtained with excellent *ortho*-selectivity with respect to benzamides **168** and *para*-selectivity with respect to arenes **169**. The use of F^+ reagents play an important role for obtaining the *para*-selectivity of arenes **169** in this reaction, with *N*-fluorobenzenesulfonimide **171** giving the highest yields among those tested. The mechanistic study suggested an electrophilic palladation for the C–H activations, but how F^+ reagents are involved in determining the selectivity was not elucidated.



Scheme 45 Pd-catalysed *para*-selective arylation of mono-substituted arenes.

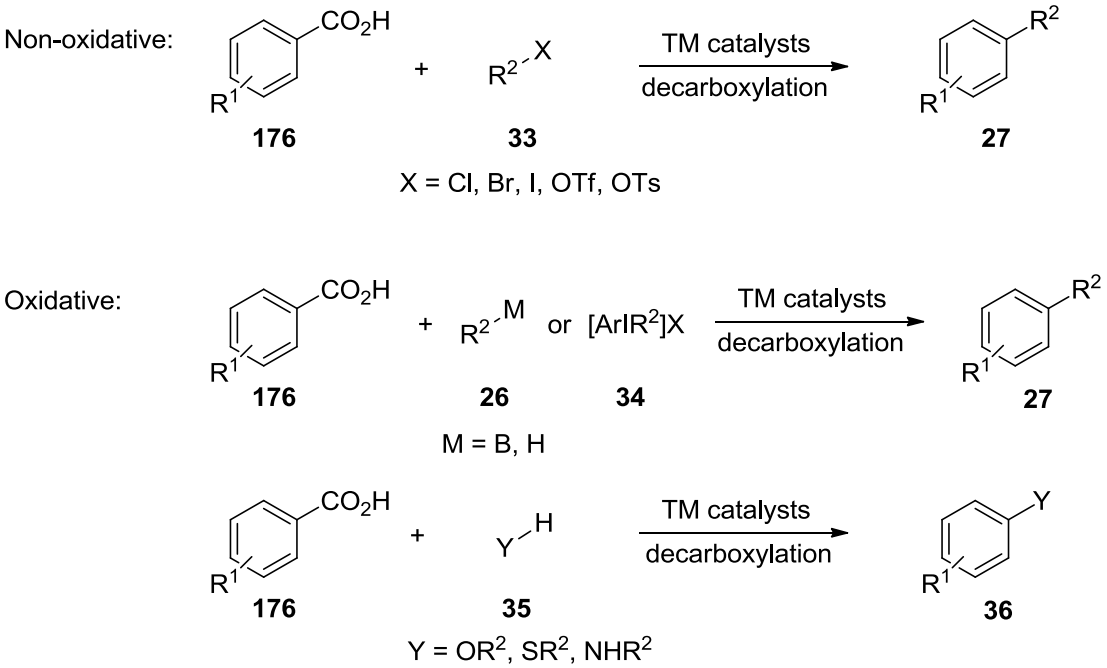
1.3 Decarboxylative functionalisation of aromatic carboxylic acids

In addition to its use as a directing group in C–H activation reactions (Scheme 25-26), carboxylic acid functionality has also been utilised in activating aromatic compounds by means of transition metal-catalysed decarboxylation and *in situ* generation of organometal intermediates **175** (Scheme 46).[106,107,108,109]



Scheme 46 Aromatic functionalisation *via* transition metal-mediated decarboxylation.

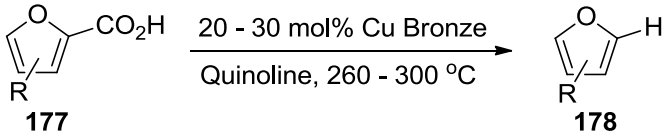
Aromatic carboxylic acids are cheap and readily available starting materials, and carbon dioxide is the only waste generated upon activation. With these advantages, aromatic carboxylic acids have emerged as attractive surrogates of organometallic reagents in transition metal-catalysed cross-coupling reactions (Scheme 47).



Scheme 47 Non-oxidative and oxidative decarboxylative cross-coupling reactions.

The decarboxylative protocols proceed in a manner similar to C–H activation reactions, but with better control of regioselectivity. In the non-oxidative reactions, *in situ* generated organometallic intermediates from aromatic carboxylic acids react with organic halides or pseudohalides *via* Suzuki-type reactions. Bimetallic catalysts are generally employed in these reactions since the activation of carboxylates and C–C bond formations are facilitated separately by two different metals. In the oxidative reactions, two carbon nucleophiles, one originating from carboxylic acids and the other from organometallic reagents, iodonium salts, simple C–H components or unfunctionalised heteroatoms, are coupled with each other in the presence of stoichiometric oxidant.

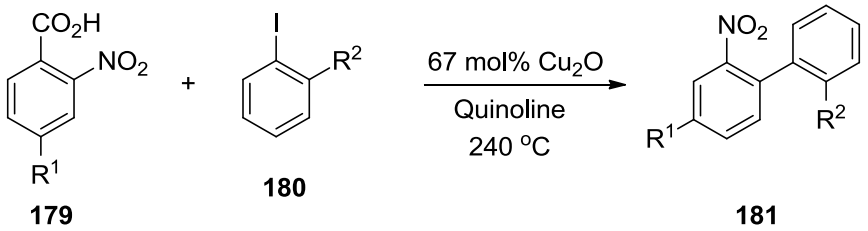
In 1930, Shepard described the first copper-mediated decarboxylation of heteroaromatic carboxylic acids (Scheme 48).[110] A range of halogenated furoic acids **177** were effectively decarboxylated, and the subsequent protonation afforded the corresponding furans **178** in good to excellent yields.



177 **178**

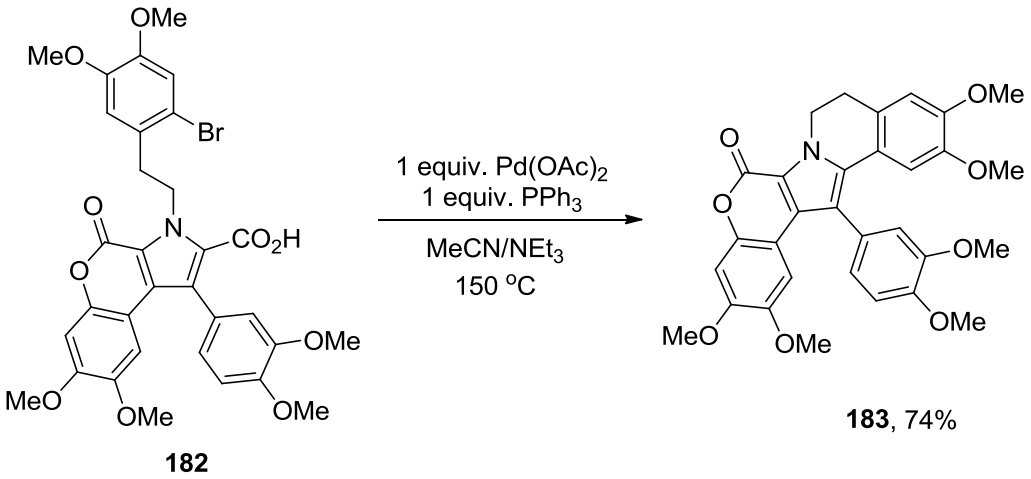
Scheme 48 Cu-mediated protodecarboxylation of furoic acids.

Following this work, in 1966, Nilsson reported the first example that utilised aromatic carboxylic acids in cross-coupling aryl–aryl bond forming reactions (Scheme 49).[111] The author recognised a similarity between the Ullmann reaction and copper-mediated decarboxylation of aromatic carboxylic acids, and proposed a similar organocopper intermediate would be involved in the decarboxylative process. Several *ortho*-nitro benzoic acids **179** were reacted in the presence of a substoichiometric amount of copper(I) oxide, and the resulting aryl-copper intermediates, which in general would be rapidly protonated by surrounding medium to give the corresponding arenes, were captured with excess aryl iodides **180** to give the 2-nitrobiaryl products **181**.



Scheme 49 The first example of decarboxylative aryl–aryl bond formation.

Despite the interesting aspects of this reaction, not much attention had been given to the decarboxylative cross-coupling reactions for long decades. Almost 30 years later, in 1997, Steglich reported the biomimetic synthesis of lamellarin G trimethyl ether **183**, utilising the palladium-mediated decarboxylative cyclisation in the last step of the synthesis (Scheme 50).[112] A Heck-type coupling on the pyrrole unit followed by the decarboxylation was suggested as a plausible mechanism.



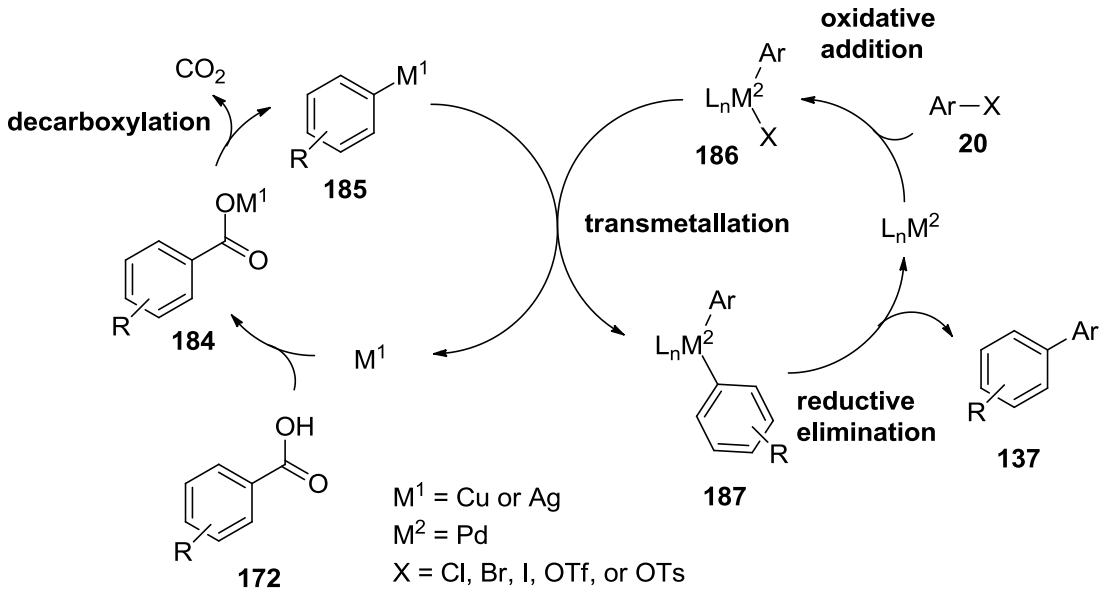
Scheme 50 Synthesis of lamellarin G trimethyl ether *via* Pd-mediated decarboxylative cross-coupling reaction.

This work is a nice example that shows the application of decarboxylative activation in the synthesis of complex molecules, but the reaction is limited by the need of a stoichiometric amount of a palladium catalyst. It is only the last few years that have seen rapid progress in the development of catalytic decarboxylative cross-coupling reactions. The recent advances have identified that various catalytic systems are capable of performing such reactions more efficiently and under milder conditions. A wide range of C–C and C–heteroatom bond forming reactions have been reported.

Decarboxylative arylation reactions, in particular, have been studied extensively, and some of the selected examples of such reactions are given hereafter.

1.3.1 Non-oxidative decarboxylative arylation

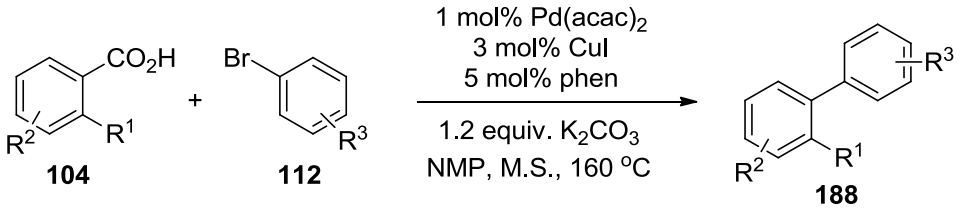
As seen in the earlier examples (Scheme 49-50), both the decarboxylation and coupling process can be promoted by the same metal for certain classes of decarboxylative C–C bond forming reactions, but generally with limited substrate scope. Bimetallic catalysts have been introduced as alternatives, allowing better and more selective reactions through combination of two separate catalytic activations (Scheme 51).



Scheme 51 Decarboxylative cross-coupling reactions catalysed by two metals.

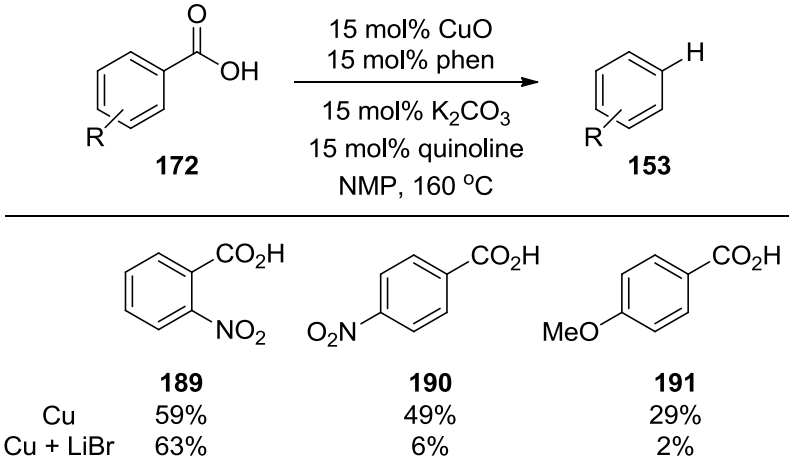
The first metal, typically copper or silver, activates the strongly endothermic decarboxylation process to generate a stable organometallic intermediate **185**. The second metal, predominantly palladium, is responsible for the cross-coupling with an aryl halide or pseudohalide **20** through the well-established catalytic cycle of conventional transition metal reactions. Goossen provided much of the early development of these reactions, focusing on the use of copper/palladium bimetallic catalysts. In 2006, his group reported the first catalytic decarboxylative arylation of benzoic acids **104** with aryl bromides **112** (Scheme 52).[113] A number of benzoic acids

bearing *ortho*-substituents were coupled in the presence of palladium(II) acetylacetonate (1 mol%), copper(I) iodide (3 mol%), 1,10-phenanthroline (5 mol%), potassium carbonate (1.2 equiv.), and 3 Å molecular sieves in *N*-methyl-2-pyrrolidone (NMP) at 160 °C. The addition of the chelating bipyridine ligand was crucial for enhancing the decarboxylation activity of the copper complex.



Scheme 52 Cu/Pd-catalysed decarboxylative cross-coupling reactions of benzoic acids with aryl bromides.

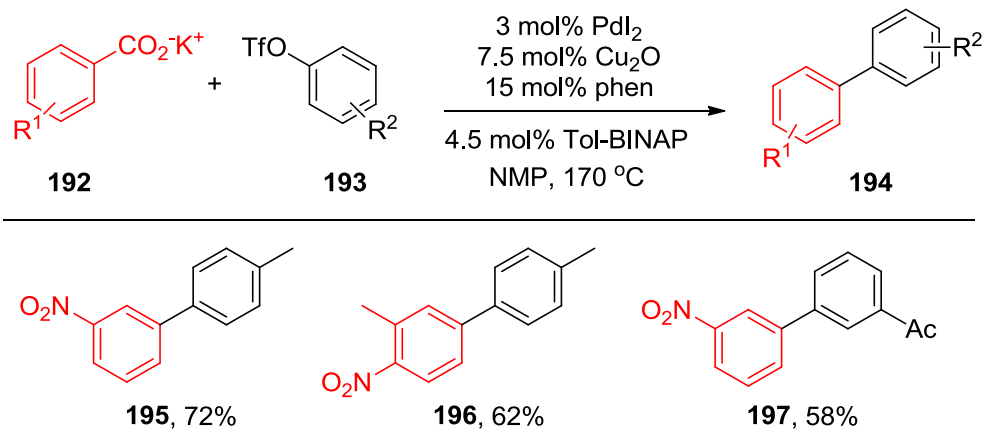
This protocol is highly effective and suitable for a variety of aryl bromides **112**, with both electron-rich and electron-poor electrophiles being successfully reacted with carboxylic acids **104**. However, the reaction is limited only to *ortho*-substituted benzoic acids under the optimised conditions. The decarboxylation step was investigated separately using only a copper catalyst, and it was found that a wide range of aromatic and heteroaromatic carboxylic acids could be protodecarboxylated to give the corresponding arenes. However, added halide ions retarded this process for non-*ortho*-substituted benzoic acids while not affecting the reactions of *ortho*-substituted ones (Scheme 53).



Scheme 53 Effects of halides on copper-catalysed protodecarboxylation.

From these results, the author suggested that the halide ions released from aryl halides in decarboxylative cross-coupling reactions are competitively coordinating to the copper complex, generating inactive copper halide salts. Therefore, a stronger preference of copper for carboxylates over halide ions would be a requirement for achieving a general reaction that is catalytic in both copper and palladium. It was proposed that strongly coordinating *ortho*-substituents would enhance the copper–carboxylate ligation, so that efficient decarboxylative reactions could be achieved with *ortho*-substituted benzoic acids. By contrast, a stoichiometric amount of copper(II) catalyst was needed for the reactions of non-*ortho*-substituted benzoic to afford synthetically useful yields.

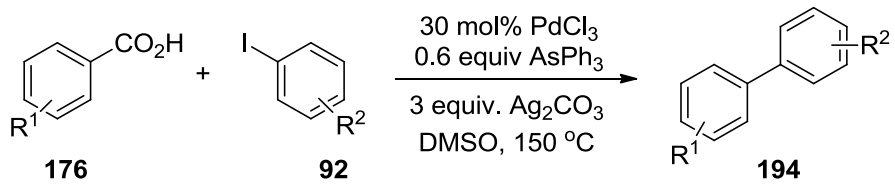
Following this work, Goossen developed a number of other copper/palladium catalytic systems that utilise aryl chlorides,[114] triflates[115] and tosylates[116] as alternative electrophiles. The triflate and tosylate examples are of particular interest since the decarboxylative arylation with these coupling partners obviates the need for an *ortho*-substituent in carboxylate substrates. In these reactions, triflate and tosylate ions are only weakly coordinating to the copper complex, so carboxylates, regardless of their substitution pattern, can successfully compete for the coordination to the copper centre. This avoids the consumption of the copper catalyst in the form of inactive copper salts, thus allowing the decarboxylation to be catalytic in copper. The reaction of aryl triflates **193** was initially studied, and a range of *ortho*-, *meta*- and *para*-substituted aromatic carboxylates **192** were found to react efficiently under the optimised conditions (Scheme 54).[115]



Scheme 54 Cu/Pd-catalysed decarboxylative arylation of benzoic acids with aryl triflates.

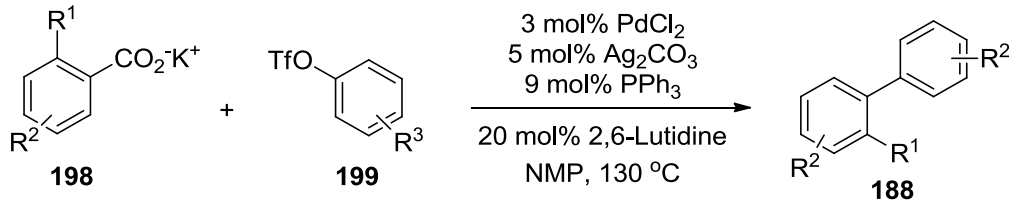
One of the key factors in making this reaction effective was the choice of phosphine ligands. Among those tested, the sterically demanding and moderately electron-rich chelating phosphine ligand Tol-BINAP was found to be ideal for stabilising the palladium complex while maintaining the activity of the copper catalyst. The reaction was later extended to less expensive aryl tosylates, with a slightly modified condition giving satisfactory results for a range of aromatic and heteroaromatic carboxylic acids.[116] The use of XPhos as a ligand was found to be essential for this reaction.

Silver has also been employed in conjunction with palladium for decarboxylative cross-coupling reactions. In 2007, Becht and Wagner reported the first example of silver/palladium-mediated decarboxylative arylation of benzoic acids **176** with aryl iodides **92** (Scheme 55).[117] In this work, the authors suggested the role of silver(I) carbonate as a base, but the later studies by other groups[118,119,120] indicate that it could be acting as an activator for the decarboxylation process.



Scheme 55 The first Ag/Pd system for decarboxylative arylation of benzoic acids with aryl iodides.

This reaction is limited to *ortho*-substituted benzoic acids, and more disadvantages arise from the requirement of high loadings of both the palladium catalyst and silver salt, and also from the use of a toxic arsine ligand. For the analogous reactions, Wu reported a slightly modified condition using BINAP as an alternative ligand.[121] This allowed the reaction to proceed with a lower catalyst loading (10 mol% palladium(II) chloride), but an excess amount of silver(I) carbonate was still required for efficient results. The first example of silver/palladium-based decarboxylative protocols that are catalytic in both metals was reported by Goossen in 2010 (Scheme 56).[122]

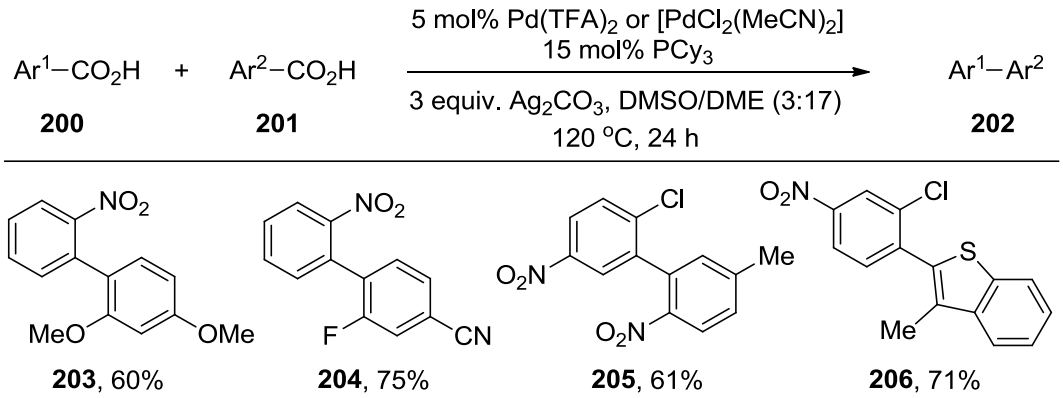


Scheme 56 Ag/Pd-catalysed decarboxylative arylation of aromatic carboxylates and aryl triflates.

In this work, aryl triflates **199** were employed as coupling partners to increase the chance of the silver–carboxylate coordination, so that the decarboxylative process could be catalytic in silver. The use of silver/palladium bimetallic catalyst allowed a number of aromatic carboxylate salts **198** to react very efficiently using relatively inexpensive ligands and at lower temperatures compared to the copper/palladium system (Scheme 54). However, the need of an *ortho*-substituent in aromatic carboxylates **198** is a major limitation of this silver/palladium-based protocol.

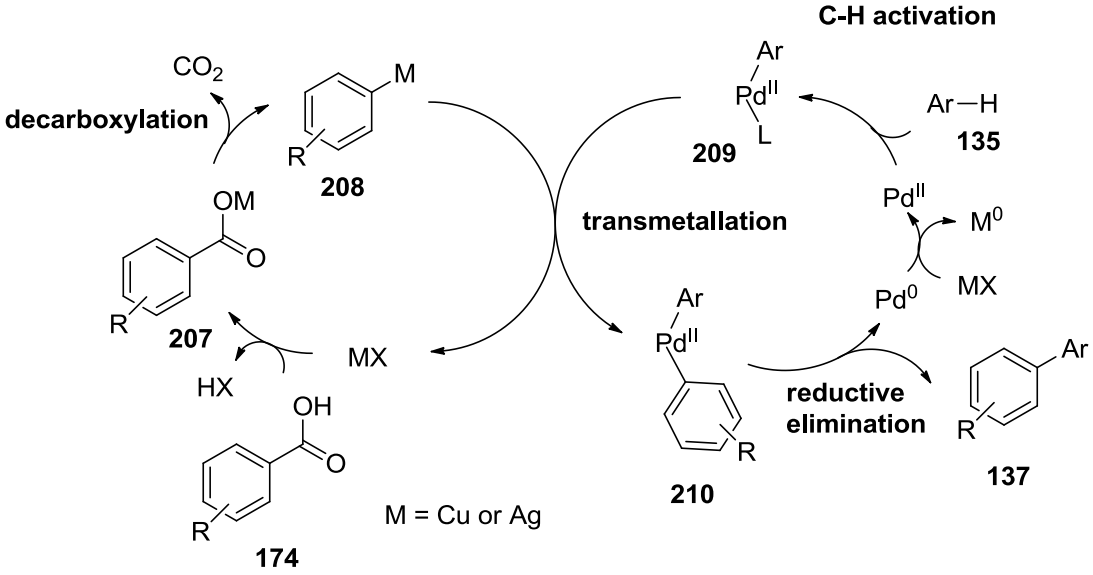
1.3.2 Oxidative decarboxylative arylation

In recent years, a number of oxidative catalytic systems have been developed for decarboxylative aryl–aryl bond forming reactions, allowing aromatic carboxylic acids to react with other nucleophiles such as arylboronic acids[123] and diaryliodonium salts.[124] These reactions, however, suffer from the use of highly functionalised coupling partners. In 2012, Su reported an interesting strategy involving decarboxylative cross-coupling reactions between two different aromatic carboxylic acids (Scheme 57).[125] Under the Pd^{II}/PCy_3 conditions, electronically different or electronically similar substrates **200** and **201** were coupled with each other to afford unsymmetrical biaryl compounds **202** in high yields and with a broad substrate scope. The choices of ligands and solvent systems were important for favouring the desired cross-coupling reaction over the homocoupling and protodecarboxylation side reactions. A dual role of silver, as a catalyst for the decarboxylation process and also as an oxidant for regenerating the active palladium catalyst from the inactive reduced form, was proposed in this reaction.



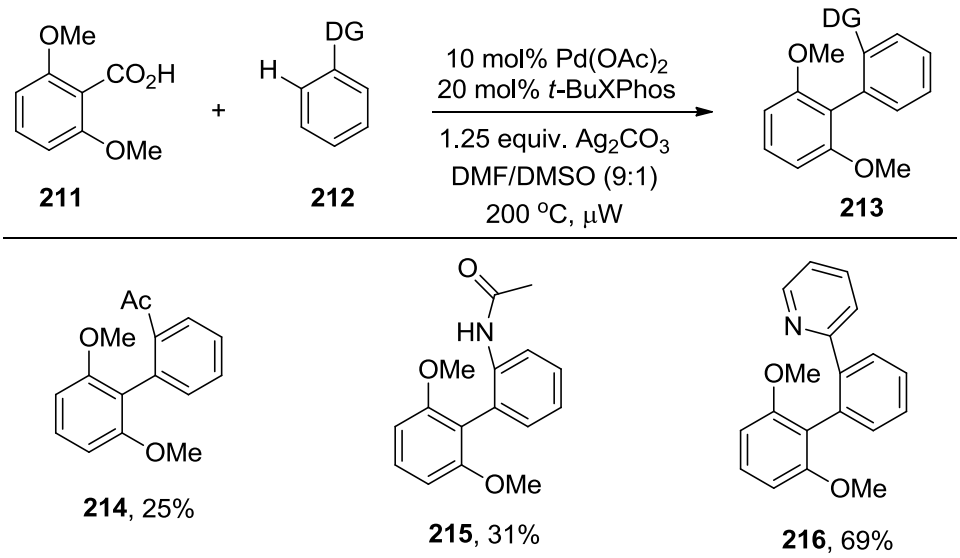
Scheme 57 Ag/Pd-Mediated decarboxylative cross-coupling reaction between two aromatic carboxylic acids.

There has also been much research carried out into the development of decarboxylation/C–H activation strategies where simple arenes are used as coupling partners to aromatic carboxylic acids. This protocol is a nice alternative to the oxidative cross-coupling of two simple arenes, because aromatic carboxylic acids are as versatile and cheap as simple C–H components. In addition to this, better control of regioselectivity can be achieved through decarboxylative activation, and the two coupling partners display different reactivities to allow chemoselective reactions. This in turn prevents the need for an excess amount of one coupling partner, which is one of the main disadvantages seen in C–H/C–H cross-coupling reactions. As in other decarboxylative cross-coupling processes, a bimetallic mechanism is in operation (Scheme 58).



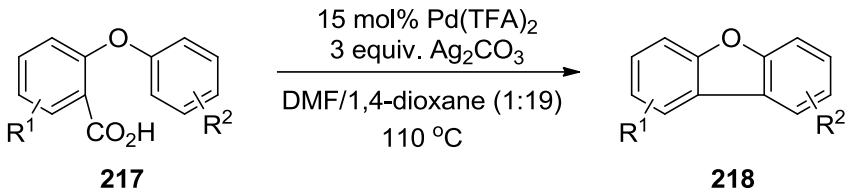
Scheme 58 A bimetallic mechanism of decarboxylative direct C–H arylation.

In 2008, Crabtree reported the first example of decarboxylative direct arylation reactions (Scheme 59).[126] Using palladium(II) acetate (10 mol%), *t*-BuXPhos (20 mol%), silver(I) carbonate (1.25 equiv.) and microwave heating, 2,6-dimethoxybenzoic acid **211** was reacted with arenes bearing a directing group **212** to afford the biaryl products **213** in low yields and with a narrow substrate scope. A large quantity of unwanted 1,3-dimethoxybenzene by-product was generated as a result of the protodecarboxylation side reaction of **211**. Despite these limitations, this work illustrated the possibility of combining two different green activation methods; decarboxylative and C–H activations.



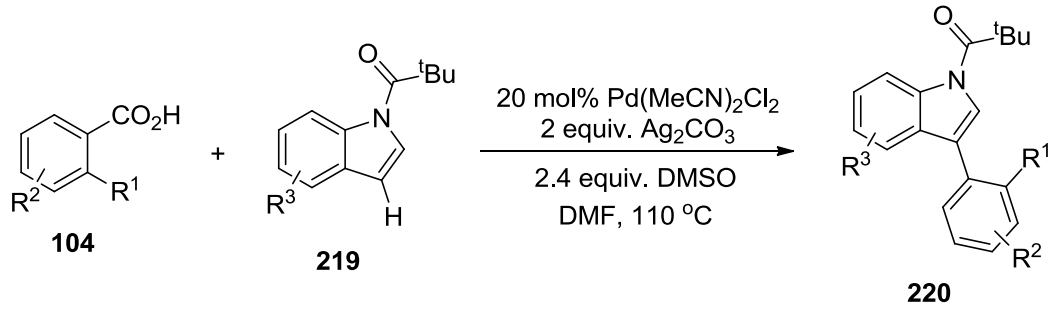
Scheme 59 The first example of decarboxylative direct arylation.

In the same report, an example of an intramolecular decarboxylative arylation of 2-phenoxybenzoic acid was also described, but the reaction was limited by the same disadvantages mentioned above. In 2009, Glorius developed a general palladium-catalysed method for this particular reaction, where dibenzofurans **218** could be formed in much improved yields under milder conditions (Scheme 60).[127] The optimised catalytic system using palladium(II) trifluoroacetate led to an excellent control over the competing protodecarboxylation, allowing a variety of 2-phenoxybenzoic acids **217** with both electron-rich and electron-withdrawing substituents to be tolerated.



Scheme 60 Ag/Pd-mediated intramolecular decarboxylative direct arylation of 2-phenoxybenzoic acids.

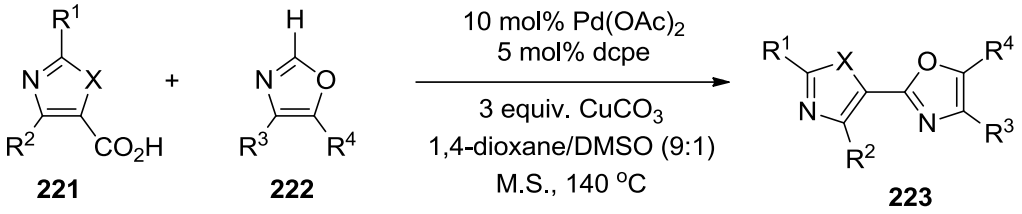
A few other groups have applied this strategy to intermolecular decarboxylative/C–H arylation reactions between aromatic carboxylic acids and electron-rich heteroarenes. Larrosa developed a silver/palladium system that allows the intermolecular coupling of a variety of *ortho*-substituted benzoic acids **104** with *N*-pivaloyl protected indoles **219** (Scheme 61).[128] This protocol is regioselective for the indole moiety, giving almost exclusively the C3-arylated products **220** (>99:1). One of the drawbacks of this method is that the reaction is limited to benzoic acids bearing an electron-withdrawing substituent at the *ortho*-position. Su reported a similar protocol for C2- and C3-selective arylation of *N*-protected indoles.[129] The C2 and C3 regioselectivity in this reaction is governed by the electronic nature of the benzoic acids, with electron-rich and electron-poor substrates giving C2- and C3-arylation respectively.



Scheme 61 C3-arylation of *N*-pivaloylindoles *via* Ag/Pd-mediated decarboxylative direct arylation.

In 2010, the Greaney group reported a decarboxylative C–H arylation of azole compounds, extending the concept to heteroaromatic carboxylic acids (Scheme 62).[130] The principal challenge in this reaction was to avoid the formation of undesired homocoupling products from the oxazole substrates **222**. The use of the sterically hindered bidentate dcpe ligand in combination with copper(II) carbonate as the

decarboxylation catalyst/oxidant/base resulted in highest yields of the cross-coupling products **223** and good selectivity over the side reactions. A range of thiazole- and oxazole-5-carboxylic acids **221** were reacted through decarboxylation. The regiocontrol for oxazoles **222** containing C–H bonds at the C2 and C5-positions (R^4 = H) proved difficult due to their similar reactivities. A substituent at the C5-position was required in order to avoid the complexity of obtaining regioisomers. The C4-position of oxazoles, on the other hand, is known to be less reactive towards C–H activation.



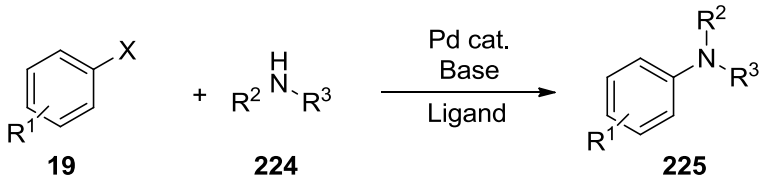
221 **222** **223**

Scheme 62 Biazole synthesis *via* Cu/Pd-mediated decarboxylative C–H arylation.

2 Decarboxylative C–N bond formation of aromatic carboxylic acids

2.1 Introduction and aims

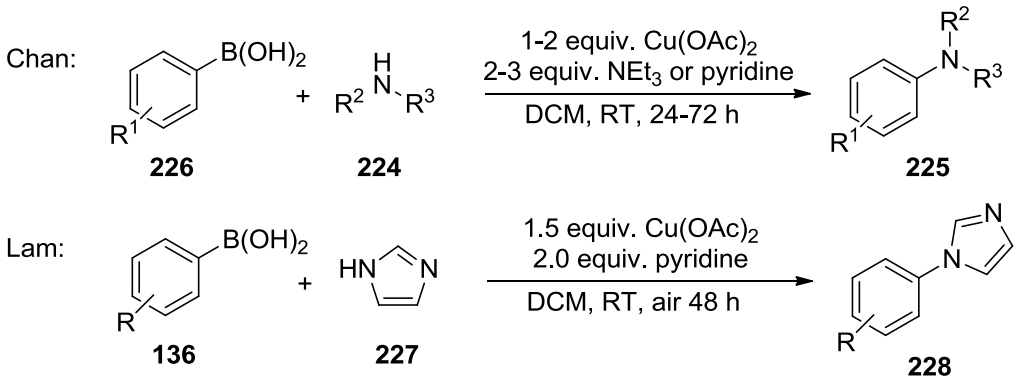
The synthesis of aromatic amines is one of the important reactions in organic synthesis due to their vast presence in many biologically active compounds. With significant advancements made in the last few years, transition metal-catalysed C–N bond forming reactions have become a standard procedure for the introduction of amines into aromatic systems. Among those reported, the palladium-catalysed cross-coupling of amines **224** with aryl halides or pseudohalides **19** is arguably the most widely used method in both industry and academia (Scheme 63).[131,132,133,134]



Scheme 63 The Buchwald-Hartwig amination.

The first example of these types was reported by Migita in 1983, describing the reaction between tin amides and aryl bromides.[135] This work had been unreferenced for a decade, until the groups of Hartwig[136] and Buchwald[137] reported a mechanistic study and an extension of the original work respectively in 1994. A synthetically more useful method using free amines was then developed by both groups in the following year, eliminating the need for toxic and unstable tin reagents.[138,139] Such reaction is now known as the Buchwald-Hartwig amination, which is named after the two scientists for their contributions in the early discoveries. Recent research in this area has focused on the development of new classes of ligands for a wider range of substrates to be used under milder reaction conditions. A variety of sterically hindered mono- and bidentate phosphine ligands have been developed, with recent examples including dialkylbiaryl phosphines such as BrettPhos and RuPhos. These ligands have been shown to generate highly active catalysts for a range of reactions.

Another attractive method for the synthesis of aromatic amines is the Chan-Lam reaction, which is a copper-mediated oxidative coupling of arylboronic acids with N–H containing compounds.[140,141,142] Despite the early discovery of Ullmann condensation reaction (Scheme 2), the use of copper in C–N bond forming reactions had been less favoured compared to the Buchwald-Hartwig amination due to the harsh reaction conditions and limited range of substrate scope. Independent reports by the groups of Chan[143] and Lam[144] in 1998 described improved methods for copper-mediated C–N bond formation with arylboronic acids as the alternative aryl donors (Scheme 64). In these reports, the groups showed that a variety of N–H coupling partners including amines, amides, imides, ureas, carbamates, sulfonamides and *NH*-containing heteroarenes could be successfully arylated at room temperature using a stoichiometric amount of copper(II) acetate and triethylamine or pyridine as a base.

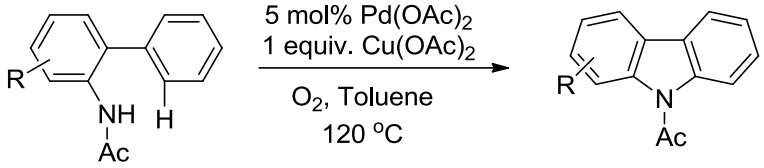


Scheme 64 The first examples of Chan-Lam coupling reactions.

Since these initial findings, significant progress has been made in expanding the scope and applications of this reaction by incorporating different substrates, solvents, reaction temperatures and reaction times, as well as by introducing ligands. These developments led to a new powerful methodology for *N*-arylation reaction. The recent protocols employ an external oxidant, typically molecular oxygen, to allow the reactions to take place catalytically under mild and simple conditions with high tolerance of a wide range of functional groups. In addition, the use of less toxic and less expensive copper is advantageous over the palladium-catalysed methods.

Despite the recent developments offering many advantages, the two C–N bond forming reactions described above are not without limitations. The main disadvantages are

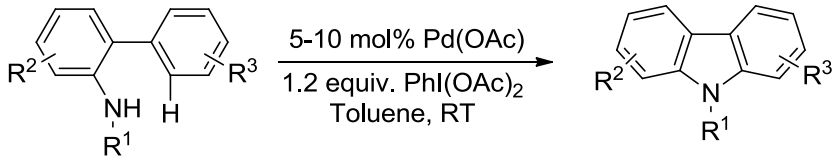
associated with the use of preactivated arylating reagents. With this regard, the C–H and decarboxylative activation methods would provide attractive alternatives for the synthesis of aromatic amines. Recently, a number of palladium-catalysed C–H/N–H coupling reactions have been reported.[145,38] Buchwald provided an early example in 2005, reporting the synthesis of carbazoles **230** *via* palladium-catalysed intramolecular C–H amidation of 2-phenylacetanilides **229** (Scheme 65).[146] In this reaction, an acetyl protecting group on the amine was required to furnish efficient reactions using copper(II) acetate and molecular oxygen as the oxidants.



229 **230**

Scheme 65 The synthesis of carbazoles *via* Pd-catalysed intramolecular C–H amidation.

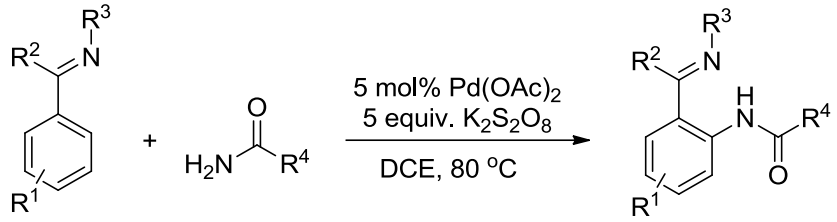
Gaunt developed a milder condition for the similar reaction using iodobenzene diacetate as an alternative oxidant (Scheme 66).[147] Under the optimised conditions, the reaction proceeds efficiently at room temperature, allowing the synthesis of *N*-alkyl and *N*-allylcarbazoles **232** from anilines **231**. The reaction has a broad substrate scope and can also be applied to complex systems, showing its potential applications in natural product synthesis. A Pd^{II}/Pd^{IV} catalytic cycle was proposed for this reaction. The higher oxidation state palladium is believed to facilitate the reaction under mild conditions, giving the distinguishing features compared to the above work. Other groups also reported similar intramolecular C–H/N–H coupling protocols for the synthesis of other heterocycles such as indazoles,[148] indoles[149] and indolines.[150]



231 **232**

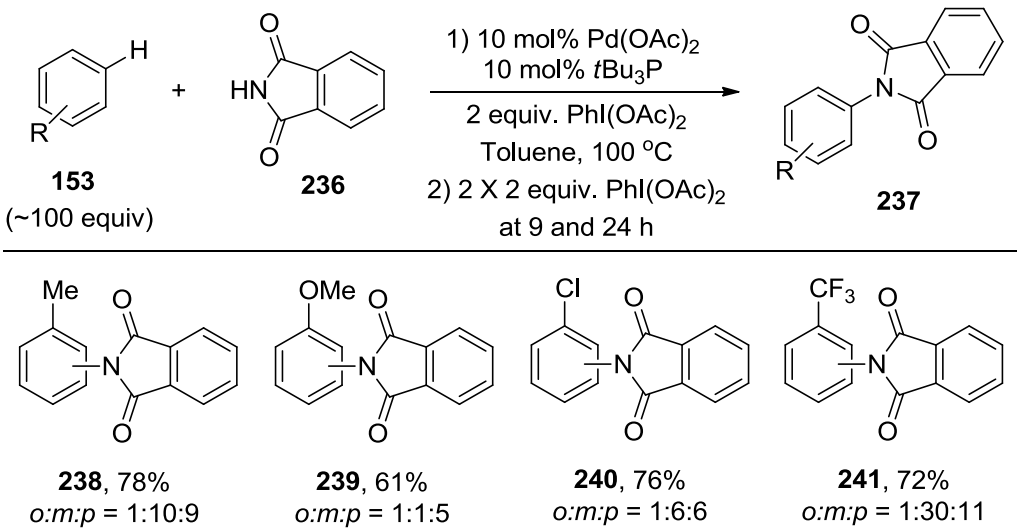
Scheme 66 Room temperature synthesis of carbazoles *via* Pd-catalysed intramolecular C–H amination.

In 2006, Yu and Che reported an intermolecular C–H amidation of simple arenes **233** containing pyridine or oxime ether directing groups (Scheme 67).[151] Using palladium(II) acetate in conjunction with a strong oxidant potassium peroxydisulfate, a number of amides **234**, including carbamates, acetamides, and sulfonamides, were reacted with arenes **233** to afford the *ortho*-amidated products **235** in high yields. Interestingly, this protocol could also be applied to unactivated primary and secondary C(sp^3)–H bonds. The author proposed that the reaction goes through cyclopalladation followed by nitrene insertion into the Pd–C bond.



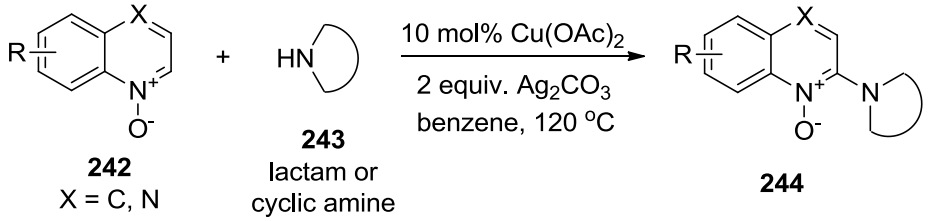
Scheme 67 Pd-catalysed intermolecular C–H amidation of simple arenes containing pyridine or oxime ether directing groups.

More recently, Hartwig reported the palladium-catalysed oxidative amidation of simple arenes **153** with phthalimide **236** (Scheme 68). The use of iodobenzene diacetate as the oxidant was effective to provide the aminated products **237**, with sequential addition of this reagent allowing the reactions to occur in good yields in neat arenes **153**. The regioselectivity of this reaction is controlled by steric effects, favouring the less hindered *meta*- and *para*-positions in general. This observation is distinct from the previously reported C–H activation reactions of similar arenes, where the *ortho*- and *para*-substituted products are predominantly formed. Despite this interesting result, the reaction still suffers from the need of arenes **153** in huge excess, and the selectivity between the *meta*- and *para*-positions can be hardly predicted.



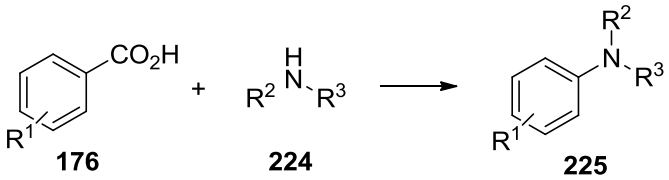
Scheme 68 Pd-catalysed intermolecular C–H amidation of simple arenes lacking a directing group.

Copper catalysts have also been utilised in both intramolecular and intermolecular aromatic C–H/N–H coupling reactions. A number of copper-catalysed protocols have been disclosed for the synthesis of benzimidazoles,[152] pyrido[1,2-α]benzimidazoles,[153] carbazoles[154] and imidazobenzimidazoles,[155] and also for the intermolecular direct C–N bond formation of azoles,[156,157] indoles,[158] 2-arylpyridines[158,159] and polyfluorobenzenes.[160] One very recent example is the reaction of quinoline *N*-oxides **242** with lactams or cyclic amines **243** using a copper catalyst and silver(I) carbonate as the external oxidant (Scheme 69).[161] A variety of 2-aminoquinoline compounds **244** could be synthesised through C2-selective direct amination/amidation of the *N*-oxides **242**.



Scheme 69 Cu-catalysed intermolecular C–H amination/amidation of quinoline *N*-oxides.

As can be seen from the above examples, the C–H activation strategy has proved to be applicable in oxidative C–N bond forming reactions for the synthesis of aromatic amines. The decarboxylative activation, by contrast, has been less utilised for the analogous synthesis, despite its wide use in C–C bond forming reactions. This prompted us to study decarboxylative C–N bond forming reactions of aromatic carboxylic acids. The aim of this project was to harness the synthetic utility of organometallic intermediates generated *in situ* from carboxylic acids and design an optimal condition to react them with nitrogen nucleophiles (Scheme 70). This method would replace the prefunctionalised arylating reagents used in the conventional transition metal-catalysed reactions with inexpensive and widely available carboxylic acids, and would also solve the regioselectivity issue observed in the C–H activation reactions.

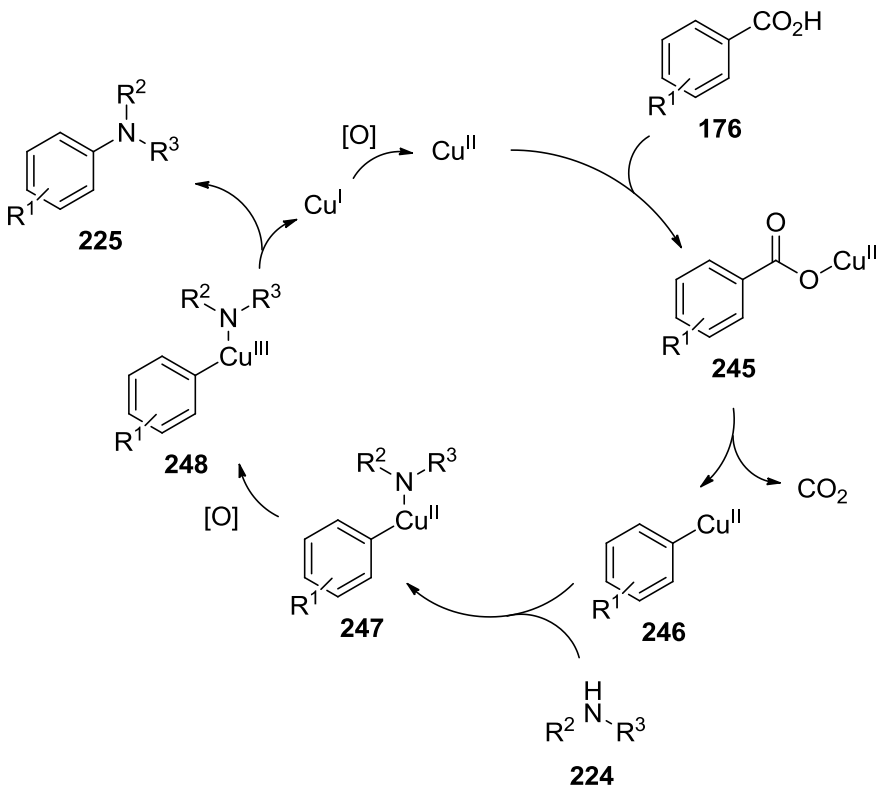


Scheme 70 Decarboxylative C–N bond forming reaction.

2.2 Results and discussion

2.2.1 Copper-catalysed intermolecular decarboxylative C–N bond formation

We initially proposed that both the decarboxylation and C–N bond coupling could be activated by the same metal catalyst. As reviewed in section 1.3, copper has served as an effective catalyst for decarboxylation of aromatic carboxylic acids and been utilised in various decarboxylative cross-coupling reactions. In addition, this metal has also been found active in oxidative C–N bond formation of aryl nucleophiles such as boronic acids (Chan-Lam reaction) and simple aromatic compounds (C–H activation). This led us to envision that the decarboxylative C–N bond formation would be possible through the combination of decarboxylative activation and Chan-Lam reaction (Scheme 71).

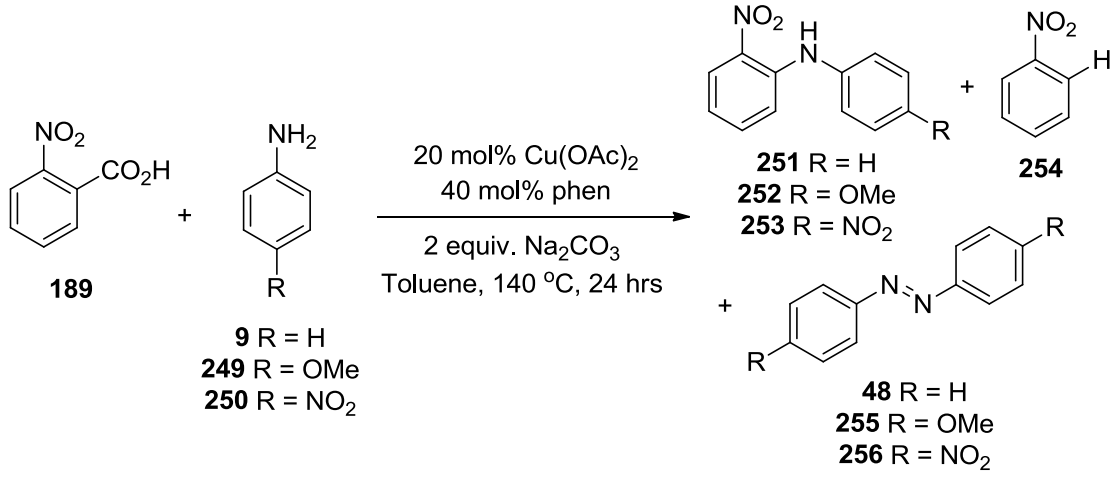


Scheme 71 Proposed reaction pathway for decarboxylative C–N bond forming reaction.

The copper-catalysed decarboxylation of aromatic carboxylic acids **176** would generate the organocopper species **246**, which is equivalent to the intermediate formed by the treatment of arylboronic acids with copper in the Chan-Lam reaction. The rest of the catalytic cycle would then proceed as in the conventional copper-catalysed C–N bond forming reactions. The formation of aryl-Cu^{III} complex **248** has been proposed in many oxidative C–N bond forming reactions, but the reaction may well proceed *via* Cu^{0}/Cu^{II} catalytic cycle.

With the above proposed approach, we started by investigating the reaction of several amines and amides with 2-nitrobenzoic acid **189**. This acid was chosen for the initial investigation due to its well-known reactivity in various copper-catalysed decarboxylative reactions.[106,107] The first attempts were all conducted using copper(II) acetate (20 mol%), 1,10-phenanthroline (40 mol%), sodium carbonate (2 equiv.) in anhydrous toluene under air at 140 °C, and it was found that the aniline derivatives gave the desired C–N coupling products, albeit in poor yields (Table 1).

Table 1 Initial investigation of copper-catalysed decarboxylative Chan-Lam reactions



Entry	R	Product (%)	254 (%)	Diazene compound (%)
1	H	4	16	2
2	OMe	9	17	6
3	NO_2	3	19	0

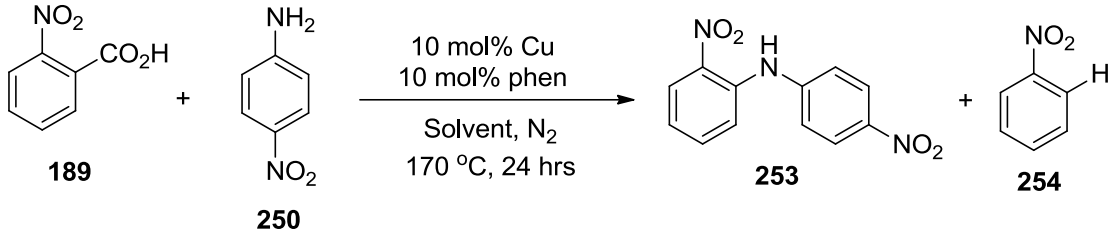
Reaction conditions: Performed on a 0.3 mmol scale with 1.5 equiv. of *o*-nitrobenzoic aicd; Isolated yields.

Several problems arose: First, the decarboxylation of **189** was really poor and failed to reach completion even after an overnight reaction. Second, the formation of undesired by-products from protodecarboxylation of **189** and homocoupling of anilines caused problems, resulting in messy reactions. The protodecarboxylation side reaction (**254**) may be a result of an inefficient reductive elimination step rather leading to protonation of the organocopper intermediate. This can probably be prevented by removing the source of protons or by increasing the efficiency of the reductive elimination. It has been reported that copper in a higher oxidation state (Cu^{III}) performs a better reductive elimination, thus the source of oxidants may play an important role for achieving this. Meanwhile, the homocoupling of anilines was no surprise, with a similar copper-catalysed condition (10 mol% copper (I) bromide, 30 mol% pyridine, toluene, O_2, 60 °C) being already reported for this reaction.[162] With the decarboxylation and cross-coupling taking place on one metal, the selective coordination of the metal to the reactants in an appropriate order is desired for achieving selective reactions. As in other transition metal-catalysed reactions, this can be induced with the use of ligands that can affect the

properties of the metal complexes *via* electronic or steric effects. The formation of undesired aromatic diazene compounds (**48**, **255**-**256**) can also be avoided by reducing the rate of oxidative homocoupling of anilines. The kinetic experiments by Jiao illustrated such reactions with electron-donating substituents reacted faster than those with electron-withdrawing substituents.[162] This agreed with our initial findings above, where the diazene by-products **48** and **255** were obtained in 2 % and 6 % yields respectively from the neutral **9** and electron-donating **249** substrates, while the electron-withdrawing substrate **250** did not give the corresponding homocoupling compound **256**. Although the reaction of **250** resulted in the lowest yield of the desired C–N coupling product **253** (3 %), it was decided to utilise this substrate for the optimisation studies so that the potential confusion of mixtures could be obviated.

The decarboxylation of 2-nitrobenzoic acid **189** is a crucial activation step to access the carbon nucleophile for the C–N bond formation, so conditions to improve this step were next sought. The copper-catalysed decarboxylation of **189** has been described in various transformations. Goossen developed a general protocol (5 mol% copper(I) oxide, 10 mol% 1,10-phenanthroline, NMP/quinoline (3:1), 170 °C, under N_2) for the protodecarboxylation of non-activated aromatic carboxylic acids including **189**.[163] Using this condition as a starting point, several copper salts and solvents were examined for the reaction of **189** with 4-nitroaniline **250** (Table 2). It was hoped that an efficient decarboxylation could be achieved under the protodecarboxylation conditions, and that the subsequent C–N bond formation could be improved through modifications of the reaction conditions. Unfortunately, the results were disappointing, immediately revealing that the decarboxylation process is significantly affected by the presence of the aniline coupling partner. Otherwise efficient Goossen's conditions gave a poor conversion of **189** to only 31 % of nitrobenzene by-product **254** and no desired product **253** (Entry 1). The use of different copper salts or solvents had no notable effects (Entries 2-5), with only the conditions similar to our initial experiments giving an isolable yield of **253** along with **254** as the main product.

Table 2 Initial screening of copper-catalysed decarboxylative amination



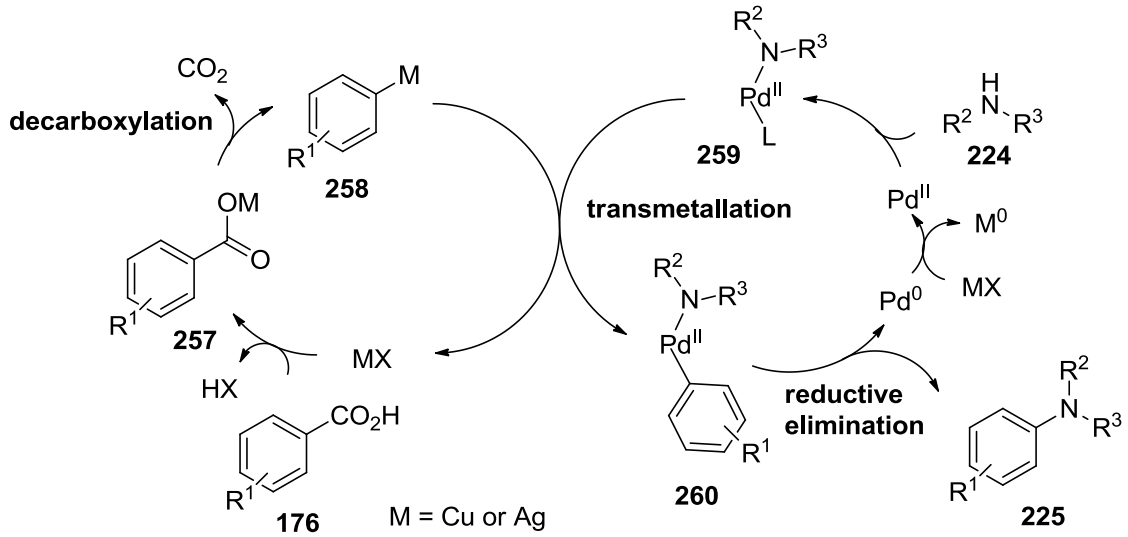
Entry	Cu	Solvent	Product (%)	254 (%)
1	Cu_2O	NMP/quinoline (3:1)	0	31
2	CuI	NMP/quinoline (3:1)	0	28
3	$Cu(OAc)_2$	NMP/quinoline (3:1)	0	17
4	Cu_2O	DMSO	0	30
5	Cu_2O	Toluene	0	15
6[a]	Cu_2O	Toluene	0	18
7[a]	$Cu(OAc)_2$	Toluene	4	20

Reaction conditions: Performed on a 0.3 mmol scale with 1.5 equiv. of *o*-nitrobenzoic aicd; Isolated yields. [a] In the presence of Na_2CO_3 (2 equiv.) and under O_2 atmosphere.

This reaction proceeds *via* an open catalytic cycle, needing a source of oxidants to keep the copper complex in its active oxidation state. Molecular oxygen has been widely utilised as the oxidant in the Chan-Lam reaction, but this reaction was not much affected when performed under oxygen atmosphere (Entries 6-7). It was thought that the poor decarboxylation in the presence of **250** would be due to the strong coordination of the nitrogen nucleophile to the copper complex, which would in turn reduce the electrophilicity of copper and interfere with its coordination to carboxylate. A preferential coordination of the carboxylate substrate to copper would be desired for an efficient decarboxylation to take place.

2.2.2 Copper/palladium-catalysed intermolecular decarboxylative C–N bond formation

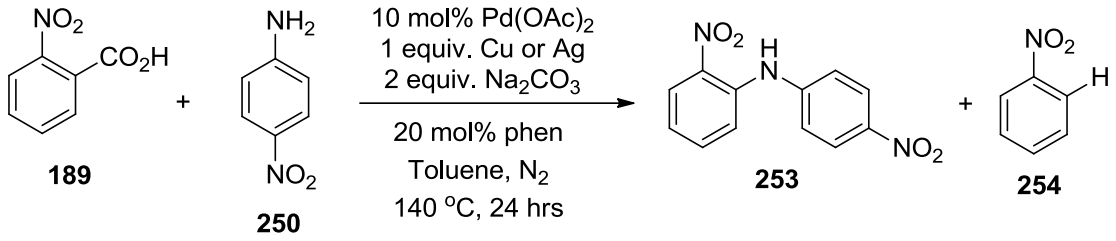
Another approach to solve the issue of inefficient decarboxylation in the decarboxylative C–N bond formation would be to use bimetallic catalysts (Scheme 72). As mentioned earlier in section 1.3.2, palladium has been utilised in conjunction with stoichiometric copper or silver sources in various oxidative C–C bond formations between aromatic carboxylic acids and carbon nucleophiles. We envisioned that similar conditions could be applied to the decarboxylative C–N bond forming reactions with nitrogen nucleophiles. Under the palladium-based bimetallic system, palladium would facilitate the reductive elimination step for C–N bond formation, while copper or silver would activate the decarboxylation. The second metal (copper or silver) also acts as an external oxidant and base, therefore, would be needed in stoichiometric or excess amounts. This would increase the chance of metal–carboxylate coordination, and as a result, would improve the decarboxylation step.



Scheme 72 A bimetallic system for decarboxylative amination.

Using 10 mol% palladium(II) acetate, 20 mol% 1,10-phenanthroline and 2 equivalent sodium carbonate in anhydrous toluene at 140 °C under N_2 atmosphere, it was decided to investigate different copper and silver sources to see how this would affect the reaction (Table 3).

Table 3 Investigation of Pd/Cu and Pd/Ag bimetallic catalysts for decarboxylative amination



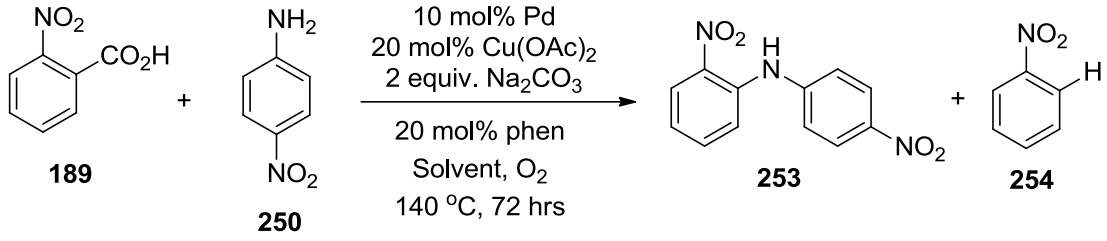
Entry	Cu	Product (%)	254 (%)
1	CuOAc	0	22
2	CuBr	0	29
3	Cu_2O	0	33
4	$Cu(OAc)_2$	24	30
5	$CuBr_2$	2	12
6	$CuSO_4$	3	15
7	$Cu(acac)_2$	19	21
8	AgOAc	17	51
9	Ag_2CO_3	12	48
10[a]	$Cu(OAc)_2$	25	34
11[b]	$Cu(OAc)_2$	6	14
12[b,c]	$Cu(OAc)_2$	12	19
13[b,c,d]	$Cu(OAc)_2$	30	34
14[b,c,d,e]	$Cu(OAc)_2$	28	37
15[b,c,d,f]	$Cu(OAc)_2$	22	25

Reaction conditions: Performed on a 0.3 mmol scale with 1.5 equiv. of *o*-nitrobenzoic aicd; Isolated yields. [a] 2 equiv. of $Cu(OAc)_2$. [b] 20 mol% $Cu(OAc)_2$. [c] Under O_2 atmosphere. [d] Reactions for 72 hours. [e] Reactions for 120 hours. [f] Addition of molecular sieves (100 mg).

Compared to the copper-only conditions, better decarboxylation of 2-nitrobenzoic acid **189** could be achieved in general although the reaction did not go to completion. Copper (I) sources were ineffective in producing the desired C–N coupling product **253**, giving only the protodecarboxylation by-product **254** (Entries 1-3). The use of copper(II) acetate led to a much improved reaction, yielding 24% of **253** and 30% of **254** (Entry 4). Other copper (II) sources were less effective (Entries 5-7). The use of silver (I) sources gave relatively efficient decarboxylation, but the poor subsequent C–N coupling resulted in the generation of **254** as the major product (Entries 8-9). The reaction was not affected by an increased amount of copper(II) acetate (Entry 10). The use of catalytic copper(II) acetate led to a poorer conversion (Entry 11), but this could be improved by (i) performing the reaction under an oxygen atmosphere (Entry 12), and (ii) leaving the reaction to run for a longer period of time (30% of **253**) (Entries 13-14). It is believed that molecular oxygen may act as a co-oxidant to regenerate active forms of metal catalysts, allowing the reaction to be catalytic in both palladium and copper. Despite the improvements, the reactions still suffered from the generation of undesired protodecarboxylation by-product **254**. It was thought that the formation of **254** could be reduced by removing the source of protons, but the reaction under anhydrous conditions using molecular sieves gave a similar result (Entry 15). We reasoned that this may be due to the inefficient C–N coupling process resulting in the unwanted side reaction.

With the aim of improving this, palladium sources were next investigated using catalytic copper(II) acetate (20 mol%) under an oxygen atmosphere (Table 4). Despite the longer reaction time required (3 days), catalytic conditions were chosen for their many beneficial aspects. Unfortunately, other palladium sources hardly affected the reaction, giving similar yields of **253** and **254** (Entries 1-5). This indicated that the activity of the palladium catalyst would need to be enhanced by other reaction parameters. A brief solvent screen confirmed that toluene was, in fact, the best reaction solvent, with the use of some of the common solvents resulting in more formation of **254** as the main product (Entries 6-9).

Table 4 Investigation of the effect of palladium catalysts



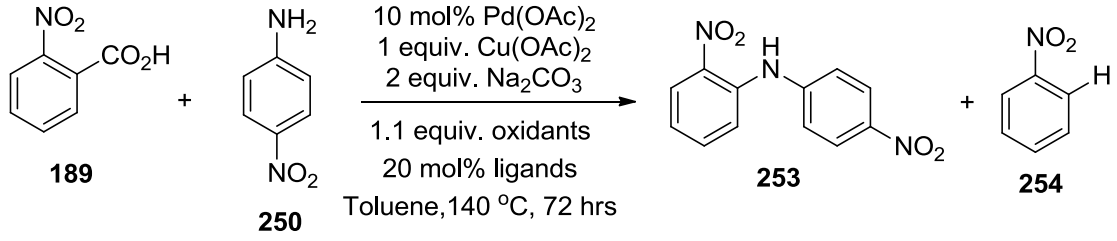
Entry	Pd	Solvent	Product (%)	254 (%)
1	$PdCl_2(dppb)$	Toluene	29	27
2	$PdCl_2(bpy)_2$	Toluene	30	33
3	$PdCl_2(PhCN)_2$	Toluene	25	26
4	(IPr)Pd(allyl)Cl	Toluene	27	32
5	$Pd(dba)_2$	Toluene	26	30
6	$Pd(OAc)_2$	DMF	11	32
7	$Pd(OAc)_2$	DMA	15	39
8	$Pd(OAc)_2$	DMSO	14	45
9	$Pd(OAc)_2$	NMP	11	41

Reaction conditions: Performed on a 0.3 mmol scale with 1.5 equiv. of *o*-nitrobenzoic aicd; Isolated yields.

We next investigated a number of oxidants and ligands to see if these could improve the activity of palladium for the C–N bond coupling (Table 5). The results were, however, discouraging, with the change of either oxidant or ligand leading to poorer conversion. The presence of TEMPO, pyridine *N*-oxide, $PhI(OAc)_2$ or 1,4-benzoquinone as the oxidant worsened the decarboxylation process, mainly giving back unreacted starting materials (Entries 1-4). Similarly, changing to other nitrogen-based ligands resulted in poor yields of the product (Entries 5-8). Other aromatic carboxylic acids (2-methoxy-, 4-methoxy-, 2-methyl-, 4-methyl-, 4-nitro-, 3-trifluoromethyl- and 3,4-dimethoxybenzoic acid) and other nitrogen nucleophiles (morpholine, 2-oxazolidinone, N-methylbenzamide, phthalimide, pivalamide, indole and imidazole) were also reacted using the best condition found (Table 3, Entry 13), but neither decarboxylation nor C–N coupling occurred with such substrates. This may be because those carboxylic acids are

less reactive toward decarboxylation compared to **189**, and the C–N coupling under the reaction condition may be highly substrate dependent.

Table 5 Investigation of the effect of oxidants and ligands

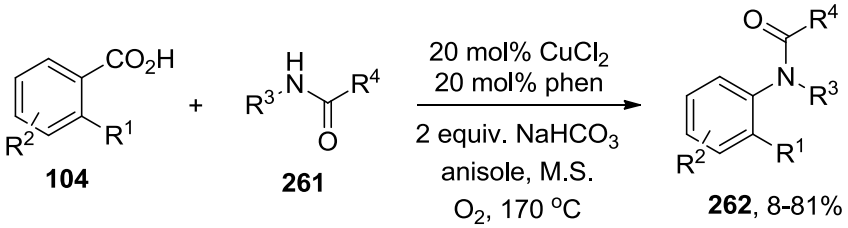


Entry	Oxidant	Ligand	Product (%)	254 (%)
1	TEMPO	1,10-phenanthroline	22	15
2	Pyridine *N*-oxide	1,10-phenanthroline	19	21
3	$PhI(OAc)_2$	1,10-phenanthroline	0	0
4	1,4-benzoquinone	1,10-phenanthroline	0	6
5	O_2	2,2'-bipyridine	15	24
6	O_2	2,2'-diamino-1,1'-binaphthalene	9	8
7	O_2	1,2-diaminocyclohexane	0	11
8	O_2	pyridine	14	12

Reaction conditions: Performed on a 0.3 mmol scale with 1.5 equiv. of *o*-nitrobenzoic aicd; Isolated yields.

In 2012 while our decarboxylative C–N coupling work was on hold, Patel and Mainolfi reported the copper-catalysed decarboxylative C–N coupling of aromatic carboxylic acids **104** with amides **261** (Scheme 73).[164] This reaction works in the same pathway as our initial ideas, utilising a simple copper catalytic system to achieve the decarboxylative activation and subsequent Chan-Lam reaction. The use of copper(II) chloride as the catalyst had a significant effect to afford the desired C–N coupling products **262** in good yields and high selectivity. However, a very forcing condition is required for the decarboxylative activation, and the reaction is also limited to benzoic

acids bearing an electron-withdrawing substituent at the *ortho*-position and to a narrow range of nitrogen nucleophiles.



Scheme 73 Cu-catalysed decarboxylative amidation of aromatic carboxylic acids.

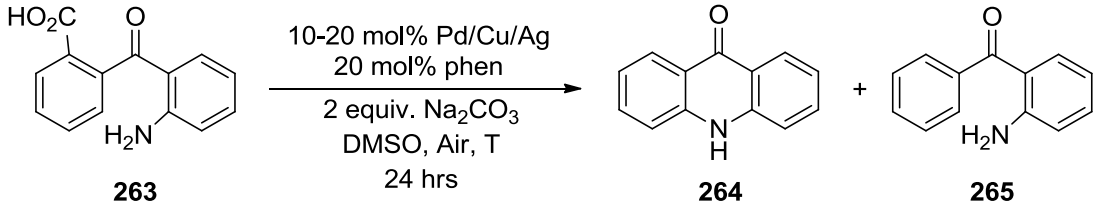
We believe these limitations can be improved with the use of bimetallic catalysts, and further optimisation studies will be the subject of future work. What have not been investigated in our work are other types of ligands. We looked at only a small number of nitrogen-based ligands because of their efficiency in stabilising the copper complex for the decarboxylation of aromatic carboxylic acids. However, palladium-catalysed C–N bond formation is typically facilitated with the use of phosphine ligands. As described in section 1.3.1, Goossen used the combination of both nitrogen- and phosphine-based ligands for the copper/palladium-catalysed decarboxylative arylation of aryl triflates (Scheme 54)[115] and tosylates.[116] In addition to 1,10-phenanthroline as the ligand for the stabilisation of the copper complex, phosphine ligands were employed for facilitating the palladium-catalysed C–C bond formation. Similar conditions with the addition of an external oxidant can probably be applied to improve our decarboxylative C–N bond forming reactions. It would be crucial to find a phosphine ligand that could stabilise the palladium catalyst while maintaining the decarboxylation activity of the copper catalyst.

2.2.3 Copper/silver/palladium-catalysed intramolecular decarboxylative C–N bond formation

In the intermolecular decarboxylative C-N formation, we reasoned that the poor reaction was due to the strong coordination of the nitrogen nucleophile to the copper complex interfering with its coordination to carboxylate, thus resulting in inefficient decarboxylation. Also, the reaction suffered from the formation of undesired protodecarboxylation by-product. While further investigation would be required in

order to improve the intermolecular reaction, we envisaged that these problems could be eliminated in an intramolecular reaction. In such a reaction system, the two functional groups, carboxylate and amine, would be in place for selective bindings to the active metal centres, hence, more efficient decarboxylation and less side reactions should be obtained. We began our investigation by studying the reaction of 2-(2'-aminobenzoyl) benzoic acid **263**, which has two aromatic rings tethered by a carbonyl functionality (Table 6).

Table 6 Investigation of the intramolecular decarboxylative amination



263 **264** **265**

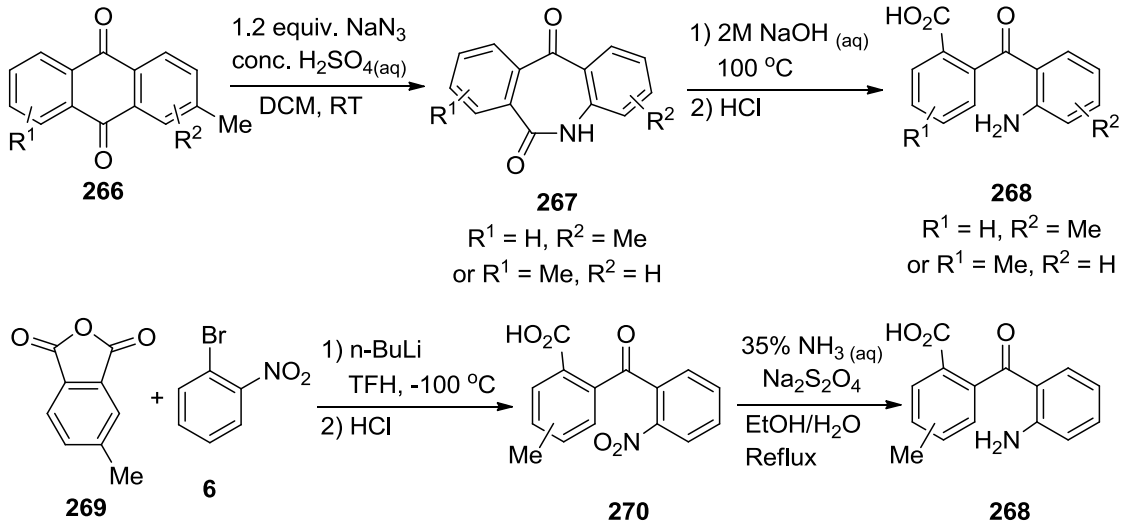
Entry	Pd/Cu/Ag (mol%)	T (°C)	Product (%)[a]	265 (%)[b]
1	$Cu(OAc)_2$ (20)	120	8	0
2	$Pd(OAc)_2$ (10), $Cu(OAc)_2$ (20)	120	15	0
3	Ag_2CO_3 (10), $Cu(OAc)_2$ (20)	120	14	0
4	$Pd(OAc)_2$ (10), Ag_2CO_3 (20)	120	6	<1
5	$Pd(OAc)_2$ (10), $Cu(OAc)_2$ (20), Ag_2CO_3 (20)	120	34	<1
6	$Pd(OAc)_2$ (10), $Cu(OAc)_2$ (20), Ag_2CO_3 (20)	150	53	<1
7[c]	$Pd(OAc)_2$ (10), $Cu(OAc)_2$ (20), Ag_2CO_3 (20)	150	50	<1
8[d]	$Pd(OAc)_2$ (10), $Cu(OAc)_2$ (20), Ag_2CO_3 (20)	150	83	<1

Reaction conditions: Performed on a 0.3 mmol scale in DMSO (3 ml); [a] Isolated yields. [b] Formation of protodecarboxylation by-product detected by LC/MS analysis, but negligible to be isolated. [c] Under nitrogen atmosphere. [d] Under oxygen atmosphere.

The copper-only system was first studied in the presence of 20 mol% of 1,10-phenanthroline and 2 equivalent of sodium carbonate in DMSO at 120 °C. We were pleased to obtain the desired acridone product **264** in 8% yield, and more importantly, no protodecarboxylation by-product **265** was formed (Entry 1). Most of the starting

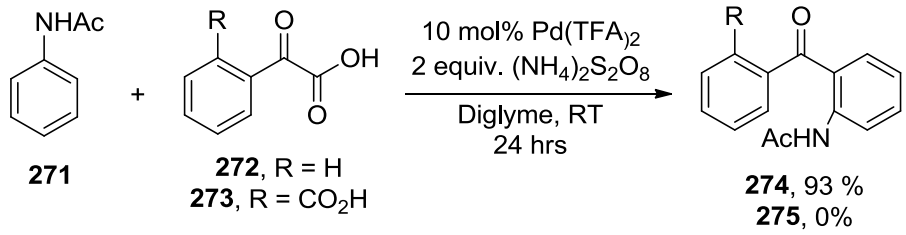
material **263** was recovered unreacted. The addition of either palladium(II) acetate (Entry 2) or silver(I) carbonate (Entry 3) to the copper system improved the reaction, but the silver/palladium-system (Entry 4) was less efficient with a minor formation of **265**. The trimetallic catalytic system of copper/silver/palladium gave the product **264** in a 38% yield (Entry 5), and the reaction was further improved when conducted at higher temperatures (Entry 6). A nitrogen atmosphere had no significant effect on the outcome of the reaction (Entry 7), whereas an oxygen atmosphere increased the yield of **264** to 83% (Entry 8). This indicated that the oxygen molecule can act as a co-oxidant in this reaction, regenerating the active catalysts from their reduced forms. The exact roles of each metal catalyst are unclear, and investigations would need to be made in order to understand how these metals are involved in the catalytic cycle.

We next wished to study the substrate scope using the optimised trimetallic conditions, but the preparation of the starting material proved difficult. Two methods that we initially considered were the Schmidt reaction of anthraquinone followed by hydrolysis of the resulting amide and the reaction of phthalic anhydride with 2-nitroaryllithium reagents followed by reduction of the nitro functional group (Scheme 74). Unfortunately, these reactions suffer from the low regioselectivity and low yields, and both employ hazardous reagents. The reaction of **266** with sodium azide lead to a complex mixture of many regioisomers of **267**, and each isomer could not be isolated in a pure form either by column chromatography or recrystallisation. Similarly, the reaction between **269** and **6** gave two inseparable regioisomers of **270**.



Scheme 74 Proposed methods for the preparation of (2-aminoaroyl)benzoic acids.

In 2010, Ge reported a room temperature palladium-catalysed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids (Scheme 75).[165] This reaction provides efficient access to *ortho*-acyl acetanilides such as *N*-(2-benzoylphenyl)acetamide **274** under mild conditions. It was hoped that 2-(2-acetamidobenzoyl)benzoic acid **275** could be obtained by applying this reaction condition to 2-(carboxycarbonyl)benzoic acid **273**. However, these conditions were ineffective for the substrate bearing a carboxylic acid functional group at the *ortho*-position. The presence of another carboxylic acid moiety may interfere with the selective binding of palladium to α-oxocarboxylate, thus deactivating its decarboxylation process. An alternative pathway would need to be considered for the general synthesis of 2-(2'-aminoaroyl)benzoic acid derivatives.



Scheme 75 Pd-catalysed decarboxylative *ortho*-acylation of acetanilides.

2.3 Conclusions

In conclusion, the decarboxylative C–N cross-coupling reactions between aromatic carboxylic acids and anilines have been investigated. Copper-only and copper/palladium bimetallic catalytic systems have been employed to study the intermolecular decarboxylative amination of 2-nitrobenzoic acid with aniline derivatives. The latter system has been found more effective, affording the diarylamine product and nitrobenzene by-product in similar moderate yields (~30%). Further research is necessary to find an ideal catalytic system that can improve the decarboxylation and subsequent C–N coupling processes, and that can avoid the unwanted protodecarboxylation side reaction.

Copper/silver/palladium trimetallic systems have been found efficient for the intramolecular decarboxylative amination of 2-(2'-aminobenzoyl)benzoic acid,

affording the acridone product in a 83% yield. The reaction was performed under an oxygen atmosphere using palladium(II) acetate (10 mol%), copper(II) acetate (20 mol%), silver(I) carbonate (20 mol%), 1,10-phenanthroline (20 mol%) and sodium carbonate (2 equiv.) in DMSO at 150 ℃. General methods for the synthesis of starting materials would need to be developed for a study of substrate scope and limitations of this reaction.

3 Silver-catalysed decarboxylative radical arylation of simple arenes

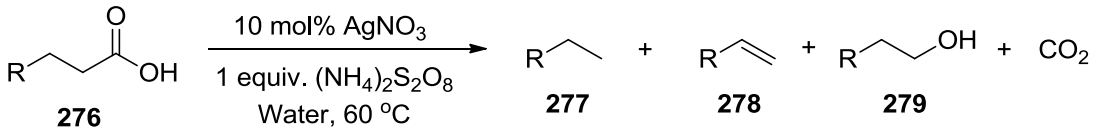
3.1 Introduction and aims

The decarboxylative C–H arylation protocol for the synthesis of biaryls benefits from the superb versatility and low cost of both carboxylic acid and simple arene starting materials.[106,107] In addition, these compounds are usually non-toxic, stable to air, easy to handle, and generate minimal waste. Despite the many advantages this method offers, transition metal-catalysed decarboxylative activation has a major challenge in its substrate scope, with reactions generally being limited to *ortho*-substituted benzoic acids and heteroaromatic carboxylic acids (section 1.3). The mechanistic study by Su and Lin suggests that an *ortho*-substituent produces a steric effect that destabilises the aromatic carboxylate complex, reducing the activation barrier for the decarboxylation process.[166] The coordination effect is the second factor that reduces the reaction energy barrier by stabilising the decarboxylation transition states. As a consequence, *ortho*-substituted benzoic acids could be employed in various decarboxylative transformations under relatively mild conditions. On the other hand, *meta*- and *para*-substituents do not affect the energy barrier for the decarboxylation, hence, more forcing conditions are required for the activation.

During our studies towards decarboxylative C–N bond formation (chapter 2), we have also experienced the difficulty associated with the transition metal-catalysed decarboxylation of aromatic carboxylic acids. The presence of amine reactants significantly retarded the decarboxylation process, and 2-nitrobenzoic acid **189** was the only substrate that resulted in conversion of the starting benzoic acid. In addition to these problems, the oxidative decarboxylative reactions also suffer from the need of metal oxidants, typically copper or silver, in stoichiometric amount.

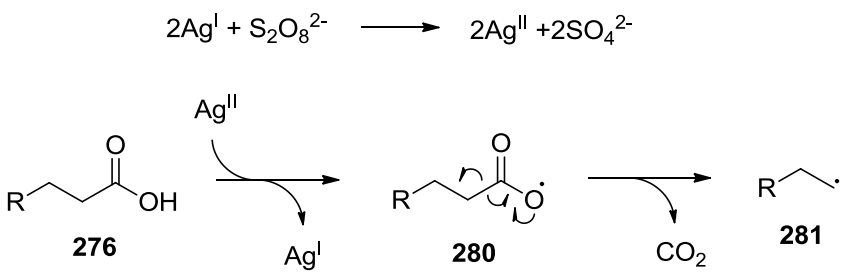
These drawbacks in current decarboxylative methodologies prompted us to investigate alternative approaches, with a view to fully exploiting the potential of carboxylic acid derivatives in aromatic functionalisation. We were interested in examining oxidative decarboxylation in this context, using radical-generating conditions. Kochi, in his

seminal work in 1970, described the oxidative decarboxylation of aliphatic carboxylic acids **276** (Scheme 76).[167] Using catalytic silver(I) nitrate and stoichiometric ammonium peroxydisulfate in aqueous solution at 60 °C, the protodecarboxylation product **277** was obtained as the major product along with alkene **278** and alcohol **279**. It was suggested that the latter two products were derived from the carbonium intermediates that could be formed *via* oxidation of alkyl radicals.



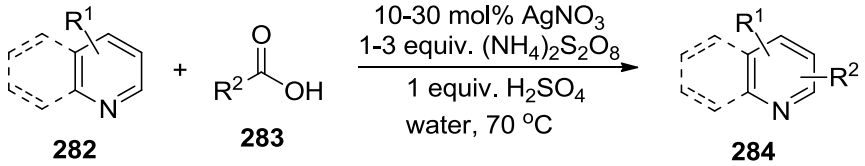
Scheme 76 Oxidative decarboxylation of alkyl carboxylic acids.

The peroxydisulfate ion, $S_2O_8^{2-}$, is a stronge oxidising agent, with its standard redox potential of +2.01 V.[168] Thermal,[169] photochemical,[170] radiolytic,[171] or redox[167] decomposition of $S_2O_8^{2-}$ provides the radical anion $SO_4^{-}\cdot$, which is a very effective electron-transfer oxidising agent. In the above oxidative decarboxylation work, Kochi showed that the presence of silver(I) salt accelerates the decomposition of $S_2O_8^{2-}$ and the subsequent decarboxylation of carboxylic acids **276**. A silver(II) species can be detected by ESR and absorption spectral technique when silver(I) nitrate is treated with ammonium peroxydisulfate, but not when the reaction is performed in the presence of the carboxylic acid. These observations indicate the involvement of silver(II) species as the reactive intermediate directly responsible for the decarboxylation of carboxylic acids **276** (Scheme 77). The oxidation of **276** with *in situ* generated silver(II) leads to the formation of carboxylate radical **280** and regenerate silver(I). The extrusion of carbon dioxide from the unstable intermediate **280** then affords the alkyl radical **281**.



Scheme 77 Proposed mechanism for the oxidative decarboxylation.

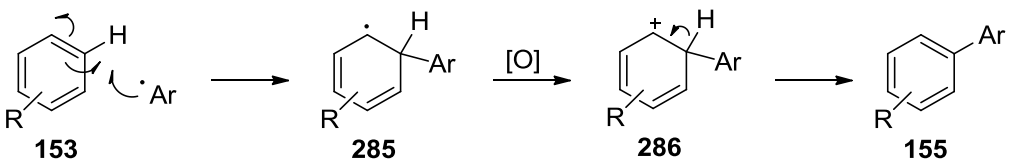
Minisci utilised this chemistry in the development of radical substitution reaction of alkyl radicals with electron-deficient heteroarenes.[172] The first example of the Minisci reaction was reported in 1971, which described the reaction of heteroarenes **282** with alkyl carboxylic acids **283** using the similar conditions of that employed by Kochi (Scheme 78).[173] Various primary, secondary and tertiary alkyl radicals could be generated from the corresponding acids, and the subsequent radical alkylation proceeds under mild conditions to give the product **284** in good yields and with predictable selectivity. The substitution was favoured at the positions of high reactivity toward nucleophiles (*ortho* and *para* to the heteroatom) and at the sterically less hindered positions.



Scheme 78 The first example of the Minisci reaction.

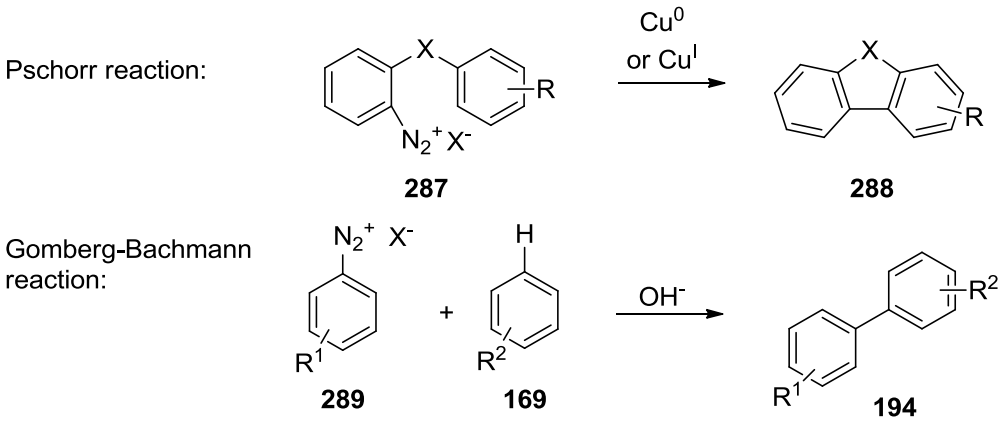
The combination of silver(I) and peroxydisulfate salts has been exploited for the generation of alkyl radicals from alkyl carboxylic acids, but has not been applied for aryl radical generation. The limited access to aryl radicals under such conditions is thought to be due to slow extrusion of CO_2 from aryl carboxylate radical.[174] The aim of the project discussed in this chapter was to develop a general oxidative decarboxylation method for the generation of aryl radicals, and to use the system for C(aryl)–C(aryl) bond forming reactions.

The radical C–H arylation of simple arenes is well precedented in literature.[175,176] This reaction proceeds *via* radical addition to arenes **153** and oxidation of the resulting cyclohexadienyl radical complex **285** into the cationic complex **286** followed by deprotonation/rearomatisation to give the product **155** (Scheme 79).



Scheme 79 Radical C–H arylation of simple arenes.

The use of aryl diazonium salts as the source of aryl radicals was dominant in the early examples. Two classical reactions are the Pschorr cyclisation and the Gomberg-Bachmann reaction (Scheme 80). In 1896, Pschorr first reported the formation of biaryl tricyclic compounds *via* radical cyclisation using aryl diazonium salts.[177] Gomberg and Bachmann then developed an intermolecular variation of the former reaction in 1924.[178] This reaction involves a single electron redox process: the reduction of diazonium salts to generate aryl radicals and the oxidation of the cyclohexadienyl radical intermediate. Transition metals such as copper have been utilised as the redox catalyst in this reaction.

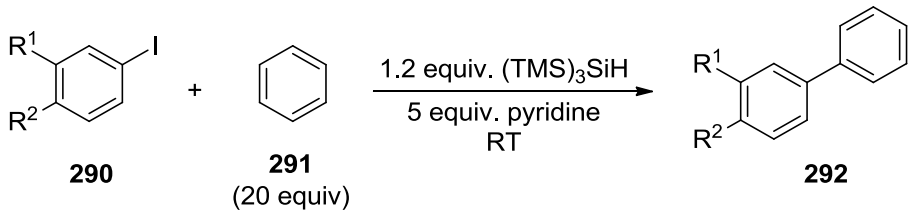


Scheme 80 The Pschorr cyclisation and the Gomberg-Bachmann reaction.

The original procedures offered wide substrate scope, but suffered from low yields of the C–C coupling products, mainly due to the side reactions resulting from diazonium salts.[177,178] The development of phase-transfer reactions allowed stable aryldiazonium salts to be used in organic solvents, thus avoiding some of the side reactions implicated in the reaction.[179] As a result, good to high yields of the arylated products could be obtained with a large variety of substrates at ambient temperatures. Despite these advancements, a large excess of aromatic substrate and the preparation of unstable (often dangerously explosive) diazonium salts are normally required.

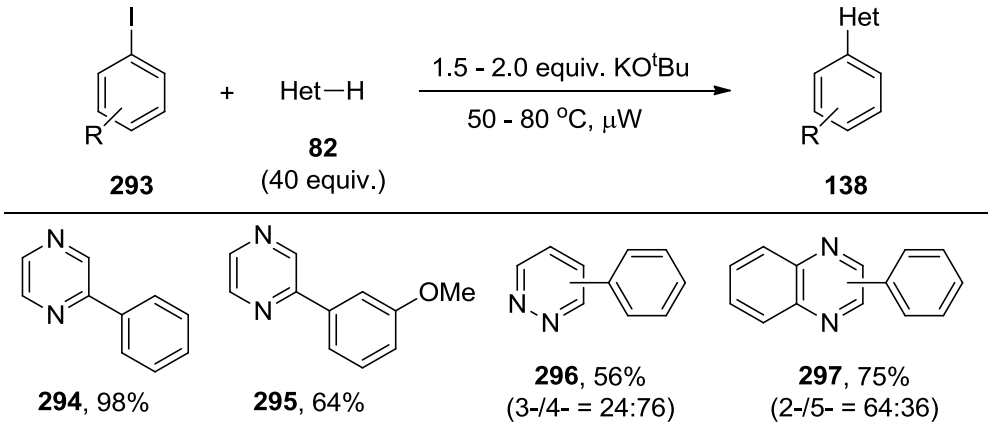
There are a number of other aryl radical sources utilised in radical arylation reactions. One of the protocols involves the generation of aryl radicals from aryl halides under reducing conditions using reagents such as tributyltin hydride or tris(trimethylsilyl)silicon hydride.[180] In 2006, Curran reported an intermolecular homolytic arylation of benzene **291** with aryl iodides **290** (Scheme 81).[181] High yields

of arylated products **292** could be achieved using non-degassed **291** in excess, in the presence of tris(trimethylsilyl)silicon hydride and prydine. It was proposed that molecular oxygen present in the non-degassed solvent provides a rapid and productive path for the oxidative rearomatisation of the cyclohexadienyl radical intermediate, allowing the reactions to be carried under milder conditions.



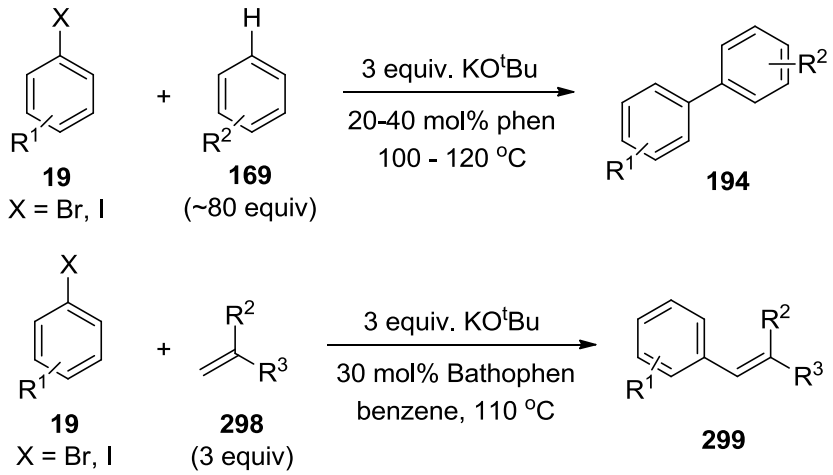
Scheme 81 Tris(trimethylsilyl)silicon hydride-mediated intermolecular homolytic arylation of benzene with aryl iodides.

More recently, *tert*-butoxide salts have been utilised as efficient mediators for the generation of aryl radicals from halides.[182,183] In 2008, Itami reported a potassium *tert*-butoxide-promoted coupling of electron-deficient heteroarenes **82** with aryl iodides **293** under microwave heating conditions (Scheme 82).[184] The reaction was initially attempted using the previously reported iridium-based conditions,[185] but it was soon found that potassium *tert*-butoxide as the sole reagent could promote the reaction to the same extent. A range of control experiments indicated that *tert*-butoxide promotes the generation of an aryl radical *via* single electron transfer. The subsequent homolytic C–C bond formation gives the arylated product **138**.



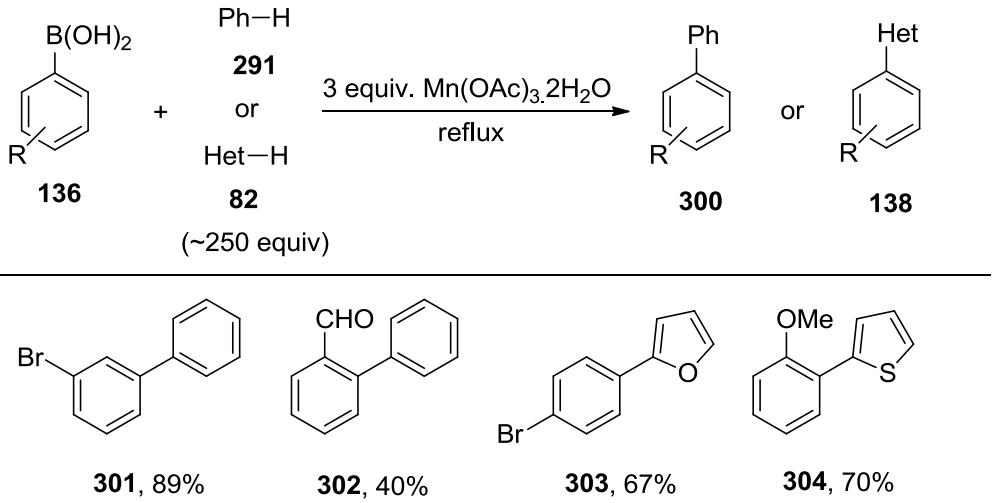
Scheme 82 KO^{t}Bu-promoted homolytic arylation of electron-deficient heteroarenes.

A few other groups have since shown that the scope of this reaction can be extended with the use of diamine catalysts.[182] For examples, Shi reported radical arylations of simple arenes **169** (Gomberg-Bachmann-type reaction)[186] and of polysubstituted alkenes **298** (Meerwein-type reaction)[187] with aryl halides **19**, using potassium *tert*-butoxide and phenanthroline-type ligands (Scheme 83). It was proposed that the latter two reagents form a reactive radical precursor, which promotes the generation of aryl radicals *via* single electron transfer to aryl halides **19**. In 2012, Chen and Ong disclosed EPR spectroscopic evidence further supporting the single electron transfer mechanism for these types of C(aryl)–C(aryl) bond forming reactions.[188]



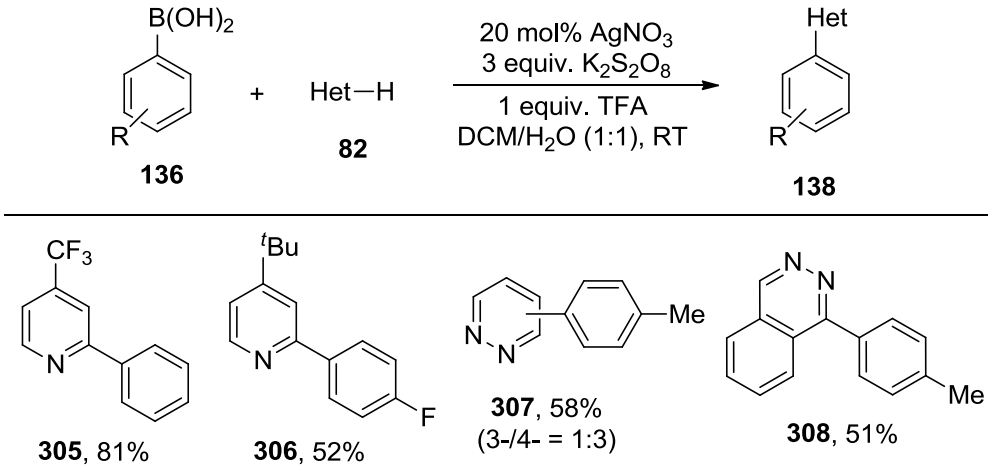
Scheme 83 KO^{t}Bu-Promoted homolytic arylation of simple arenes and of alkenes.

Arylboronic acids have also been utilised as aryl radical precursors under oxidising conditions.[176] In 2003, Demir reported the manganese(III) acetate-promoted radical arylation of aromatic solvents **82** and **291** (furan, thiophene and benzene) with arylboronic acids **136** (Scheme 84).[189] Manganese(III) acetate, a single electron oxidant, was found to be effective for oxidising arylboronic acids **136** to aryl radicals, affording the biaryl products **138** or **300** in high yields and good selectivity. Although the scope with respect to arene coupling partners was not broadly studied, a variety of arylboronic acids were found to be well-tolerated in this reaction. A major drawback of this protocol is the need of arene coupling partners in huge excess.



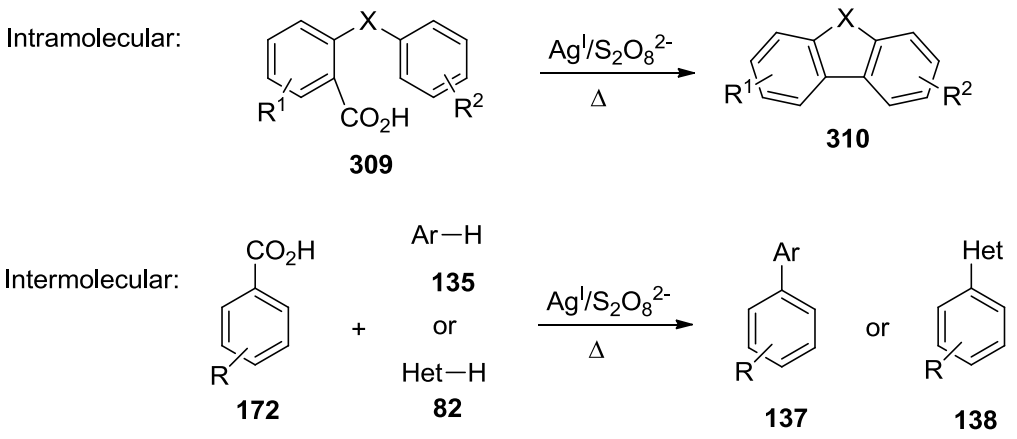
Scheme 84 $Mn(OAc)_3$-mediated homolytic arylation of simple (hetero)arenes with arylboronic acids as the radical source.

More recently, Baran developed a borono-Minisci reaction, utilising Kochi's silver(II) conditions to generate aryl radicals from arylboronic acids **136** (Scheme 85).[190] Under the optimised conditions of catalytic silver(I) nitrate (10 mol%) and stoichiometric potassium peroxydisulfate (3 equiv.), a wide range of arylboronic acids **136** could be directly combined with protonated electron-deficient heteroarenes **82** at room temperature. This reaction also proved general for several classes of heteroarenes **82** of varying substitution, with pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, and phthalazine all successfully giving arylated products **138** in moderate to excellent yields. Similar conditions have also been applied to arylation of quinones[191] and to intramolecular radical substitution reaction.[192]



Scheme 85 Ag^{II}-catalysed homolytic arylation of electron-deficient heteroarenes.

As discussed, significant advancements have been made in the area of radical arylation. A large number of protocols using new aryl radical precursors have been reported over the past years.[176,182] Aryl halides and arylboronic acids, in particular, have offered many advantages in terms of mildness of conditions, generality and product yields. However, the use of such preactivated aromatic compounds is still disadvantageous due to the costs and efforts required for their preparation, and the waste generated during these reactions. In this regard, aromatic carboxylic acids would be attractive alternatives as a source of aryl radicals. We envisioned that silver(II) conditions could facilitate the difficult oxidative decarboxylation of aromatic carboxylic acids, and that this chemistry could be used in intra- or intermolecular radical arylations (Scheme 86). Our work in this area is discussed hereafter in this chapter.

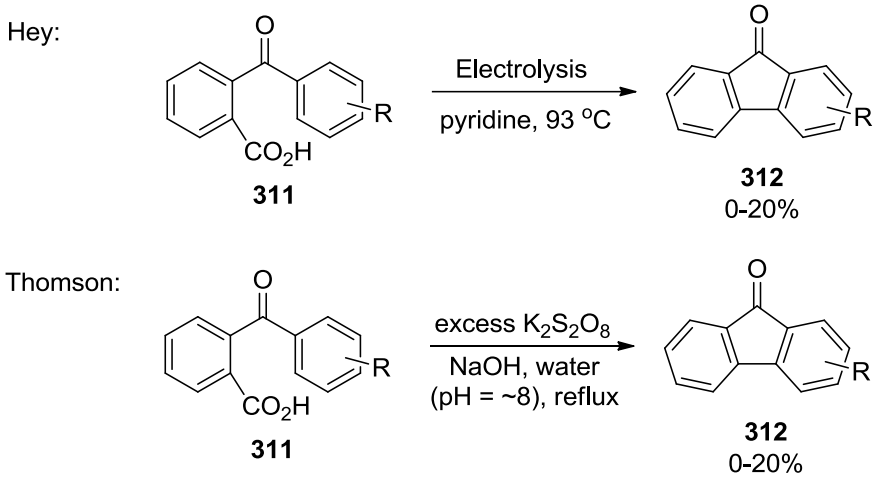


Scheme 86 Decarboxylative C–C bond forming reaction *via* aryl radical intermediates.

3.2 Results and discussion

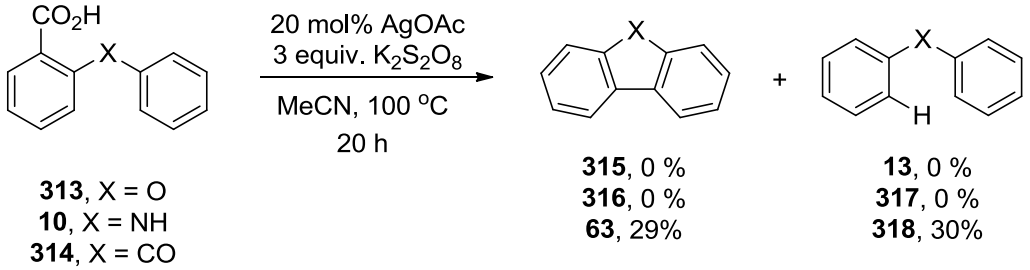
3.2.1 Intramolecular decarboxylative C–H arylation under radical conditions

With significant success achieved in radical cyclisation reactions over the past decades, it was decided to first study the decarboxylative arylation in intramolecular reactions.[193] In 1962, Bunyan and Hey reported a synthesis of fluorenones **312** *via* electrolysis of 2-benzoylbenzoic acids **311**.[194] Shortly after, Russell and Thompson showed that the same reaction could be achieved by simple treatment of benzoylbenzoic acids **311** with potassium peroxydisulfate (Scheme 87).[195]



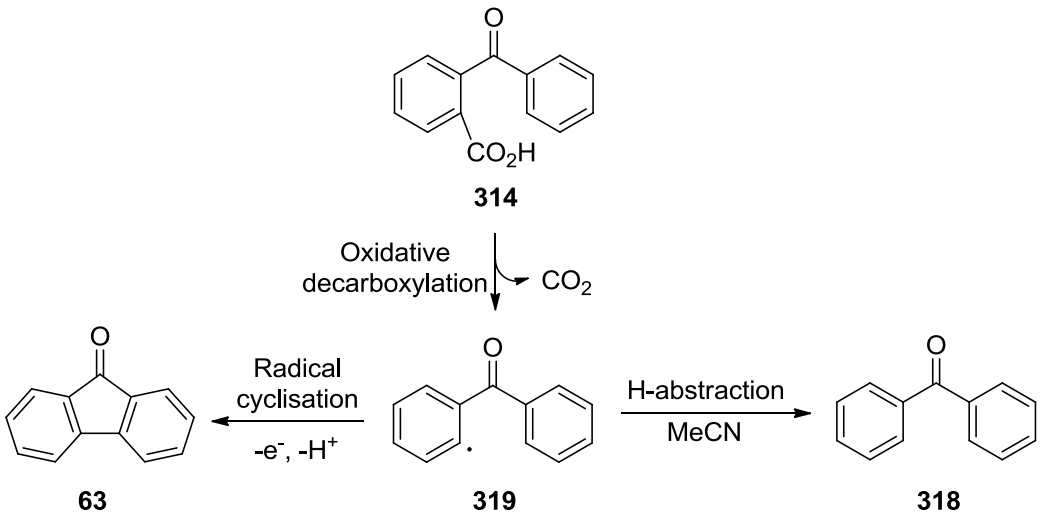
Scheme 87 Fluorenone synthesis *via* oxidative radical cyclisation of 2-benzoylbenzoic acids.

In both of these reactions, an oxidative decarboxylation mechanism was suggested, which involves the generation of aryl radicals followed by radical cyclisation. The latter example is particularly useful because peroxydisulfate is employed as a sole oxidant to affect the product formation. However, the oxidative decarboxylation process in both reactions is very inefficient, affording the cyclisation products **312** in poor yields (<20%). It was discussed earlier that the presence of a silver(I) catalyst accelerates the decomposition of peroxydisulfate and the subsequent decarboxylation of alkyl carboxylic acids,[167] and we believed that this could improve the reaction of aromatic carboxylic acids as well. In our initial investigations, three *ortho*-substituted benzoic acids **313**, **10** and **314** were treated under the radical condition of silver(I) acetate and potassium peroxydisulfate in refluxing acetonitrile at 100 °C. (Scheme 88).



Scheme 88 Initial investigation into intramolecular decarboxylative radical arylation.

2-Phenoxybenzoic acid **313**, which has been reported as a good substrate for the decarboxylative intramolecular arylation under conventional palladium/silver-mediated C–H activation conditions,[127] and 2-(phenylamino)benzoic acid **10** did not undergo the oxidative decarboxylation reaction, only affording recovered starting materials. Encouragingly, 2-benzoylbenzoic acid **314**, the substrate utilised in the previously reported oxidative radical cyclisation reactions (Scheme 87), gave a 29% yield of the desired fluorenone **63** along with the protodecarboxylation by-product benzophenone **318** in 30% yield. Almost a full conversion of **314** was achieved, suggesting that the low yield of **63** was mainly due to the unwanted protodecarboxylation side reaction. This by-product formation was thought to occur *via* hydrogen atom abstraction of the acetonitrile solvent by the aryl radical intermediate **319**, which is generated *in situ* by oxidative decarboxylation of **314** (Scheme 89). The radical cyclisation is in competition with this side reaction, hence, would need to be relatively much faster in order to favour the desired product formation.

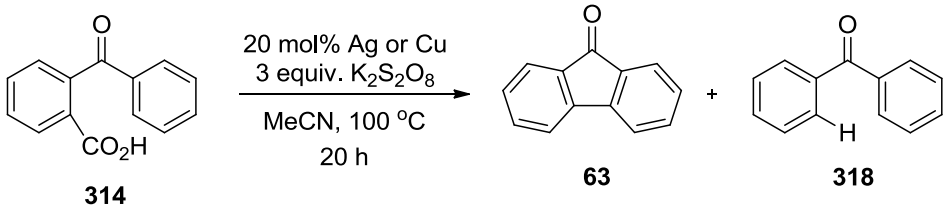


Scheme 89 Proposed pathways to the cyclisation product and protodecarboxylation by-product.

A variety of silver and copper catalysts were first examined to see if these could improve the reaction yield (Table 7). Similar yields of **63** and **318** were obtained with all other silver(I) catalysts (Entries 1-8), with the exception of silver(I) triflate (Entry 9), where less efficient decarboxylation was achieved with some of the starting material **314** being recovered. Copper catalysts were found to be ineffective for the oxidative decarboxylation, failing to produce neither **63** nor **318** (Entries 10-14). These results

indicated that silver is greatly involved in the initial oxidation and decarboxylation of the carboxylic acid functionality, but the nature of its counter ions does not influence the subsequent radical cyclisation. Silver(I) acetate was used for further investigations due to its low cost and better efficiency in this reaction.

Table 7 Investigation of the effect of metal catalysts



314 **63** **318**

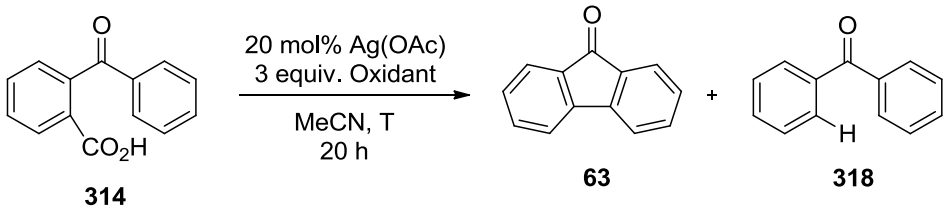
Entry	Ag or Cu	Product (%)	318 (%)
1	$AgNO_3$	24	29
2	AgF	26	29
3	Ag_2O	26	27
4	AgI	28	30
5	AgTFA	22	28
6	Ag_2CO_3	29	27
7	Ag_2SO_4	28	28
8	Ag_3PO_4	27	24
9	AgOTf	15	11
10	CuCl	0	0
11	CuI	0	0
12	$CuBr_2$	0	0
13	$Cu(OAc)_2$	0	0
14	$CuCO_3.Cu(OH)_2$	0	0

Reaction conditions: Performed on a 0.3 mmol scale; Isolated yields.

The effects of other reaction parameters, such as oxidant and reaction temperature, were next investigated (Table 8). Among those oxidants examined (Entries 1-5), ammonium

peroxydisulfate was also found to be effective for the oxidative decarboxylation of **314**, giving a similar result to when potassium peroxydisulfate was employed (Entry 5). Lowering the temperature to 80 ℃ led to a poor conversion (Entry 6). The reaction at 120 ℃ gave a slightly improved yield of **63**, but no improvement in reducing the side reaction was observed (Entry 7). A lower loading of the silver catalyst resulted in a negative effect (Entry 8). The addition of palladium(II) acetate, which has been widely utilised in transition metal-catalysed cross-coupling reactions, was not effective in improving the yield of **63** (Entry 9).

Table 8 Investigation of the effect of oxidants and reaction temperatures

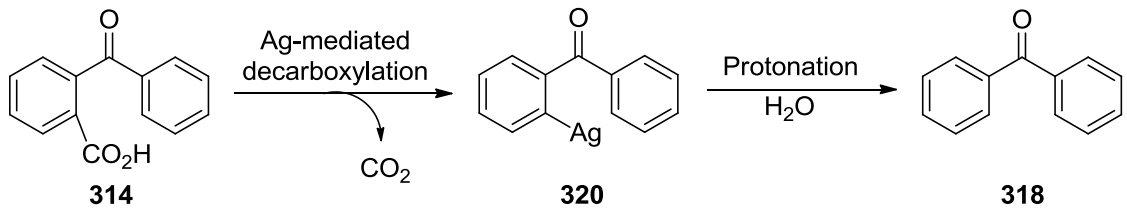


314 **63** **318**

Entry	Oxidant	T (°C)	Product (%)[a]	Ratio 63:318[b]
1	-	100	0	-
2	O_2	100	0	-
3	$Ce(SO_4)_2$	100	0	-
4	$PhI(OAc)_2$	100	0	-
5	$(NH_4)_2S_2O_8$	100	26	1:1.2
6	$K_2S_2O_8$	80	<5[c]	-
7	$K_2S_2O_8$	120	31	1:1.2
8[d]	$K_2S_2O_8$	100	6	1:1.2
9[e]	$K_2S_2O_8$	100	27	1:1.2
10[f]	$K_2S_2O_8$	100	15	1:1.2

Reaction conditions: Performed on a 0.3 mmol scale. [a] Isolated yields. [b] Ratio determined by ^1H NMR integration of crude. [c] Yields estimated by LC/MS. [d] 10% Ag(OAc). [e] Addition of 10 mol% $Pd(OAc)_2$. [f] Reaction under anhydrous condition: addition of 4Å M.S. in distilled/dry MeCN under N_2 (1 atm).

Goossen[118] and Larrosa[120] have independently shown that silver can catalyse the protodecarboxylation of aromatic carboxylic acids and suggested that the reaction goes *via* the formation of organosilver intermediates. Likewise, the possibility of *in situ* generation of **320** could not be excluded, which would produce **318** by protonation with moisture in the solvent (Scheme 90). Removal of moisture should minimise the side reaction if this pathway is in operation. The reaction was repeated under extremely anhydrous conditions, however, both **63** and **318** were still obtained in the same ratio and in poorer yields (Entry 10). This suggested that the reaction would be more likely to proceed *via* a radical pathway.



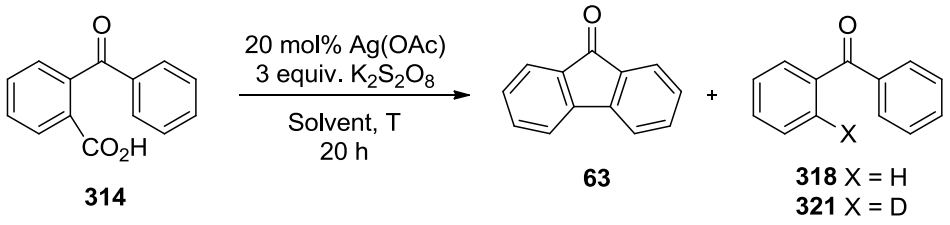
314 **320** **318**

Scheme 90 A possible pathway for the formation of the protodecarboxylation by-product.

It is known that acetonitrile is a good hydrogen atom donor for radical abstraction,[196] and this prompted us to conduct a broad screening of solvents with the aim of finding better solvents that would suppress the unproductive hydrogen atom transfer pathway. Unfortunately, the decarboxylation proved highly specific to acetonitrile, with little desired reaction taking place in any other solvents (chloroform, tetrachloromethane, 1,2-dichloroethane, 1-chlorobutane, TFA, 1,1,2,2-tetrafluoroethane, ethyl acetate, vinyl acetate, chlorobenzene, trifluorotoluene, trifluorotoluene/water (1:1), benzene, toluene, *p*-xylene, mesitylene, cyclohexane, triethylamine, 1,2-dimethoxyethane, THF, 1,4-dioxane, nitromethane, water, acetone, pyridine, di(ethylene glycol), DMSO, DMA, DMF and NMP). The oxidative decarboxylation becomes very inefficient in these solvents, making it very difficult to improve the product formation while avoiding the undesired side reaction. Product **63** could be exclusively formed in some of the solvents tested, but in very low yields (<5%) due to the poor decarboxylation with most of the starting material **314** being recovered.

Slightly better decarboxylation could be achieved in other nitrile solvents, such as propionitrile and isobutyronitrile, but the larger number of hydrogens in these solvents resulted in the increase of the ratio of the by-product formation to the product (Table 9, Entries 1-2). The use of benzonitrile as the solvent resulted in the exclusive formation of **63** in a very low yield (Entry 3). The protodecarboxylation side reaction is avoided probably because Ar–H bonds are difficult to break homolytically. However, the reaction in such a solvent gave poor decarboxylation. The use of deuterated acetonitrile afforded the desired fluorenone **63** in a good yield with only a minor amount of deuterodecarboxylation by-product **321** (Entry 4). It appears that the hydrogen atom abstraction of the aryl radical intermediate **319** (Scheme 89) from deuterated acetonitrile is much slower due to the stronger C–D bond. This enables the radical cyclisation to take place favourably, giving **63** in a 69% yield. Isolation of the deuterated benzophenone **321** as a side product confirmed that the solvent was acting as a hydrogen atom donor.

Table 9 Investigation of the effect of oxidants and reaction temperatures



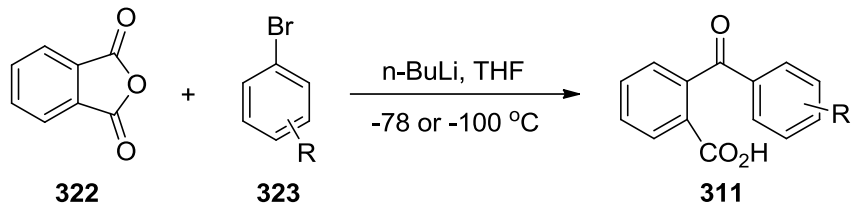
314 **63** **318** X = H **321** X = D

Entry	Solvent	T (°C)	Product (%)[a]	Ratio 63:318 or 63:321[b]
1	EtCN	100	14	1:3.3
2	^{i}PrCN	100	8	1:3.6
3	PhCN	100	3	1:0
4	d_3-MeCN	100	69	9:1[c]
5[d]	d_3-MeCN	100	45	9:1[c]
6[d]	d_3-MeCN	130	76	9:1[c]

Reaction conditions: Performed on a 0.3 mmol scale. [a] Isolated yields. [b] Ratio determined by NMR integration. [c] The by-product is deuterodecarboxylation product **321**. [d] Microwave heating for 1 hour.

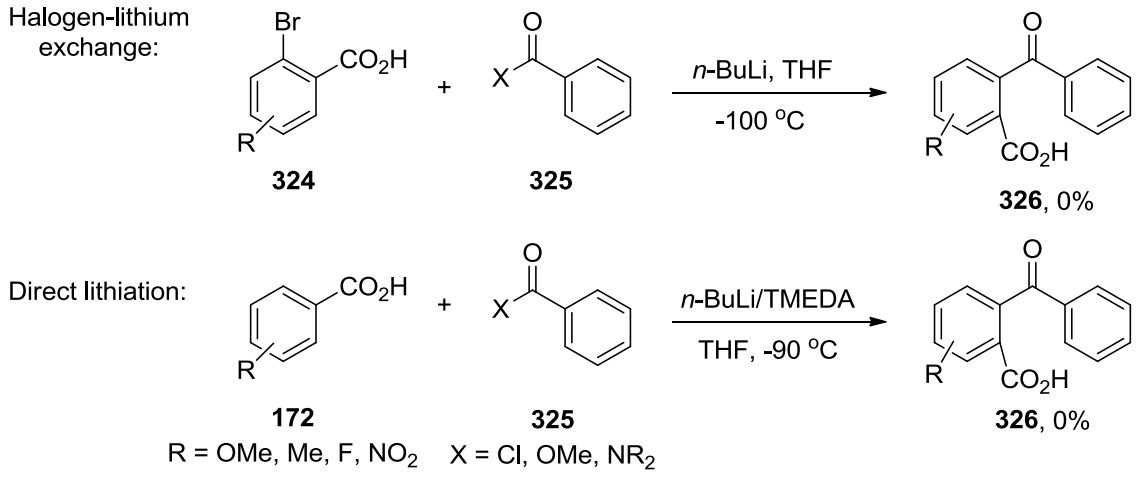
In organic synthesis, the use of deuterated solvents is not desirable due to their costs and availability. Unfortunately, the oxidative decarboxylation of 2-benzoylbenzoic acid **314** was found to be highly specific to acetonitrile, and the unwanted side reaction could be reduced only in deuterated solvent. Although not desired, it was decided to explore the deuterated acetonitrile conditions further and establish the substrate scope, using final optimised conditions of microwave irradiation at 130 °C (Entry 6).

The 2-aroylbenzoic acid starting materials **311** were purchased from commercial suppliers or prepared according to the literature procedure of Parham and Piccirilli (Scheme 91).[197] A range of **311** bearing substituents on the aroyl ring were easily accessed in one step *via* ring opening of phthalic anhydride **322** with aryl lithiums generated from the treatment of aryl bromides **323** with *n*-butyllithium.



Scheme 91 Preparation of 2-aroylbenzoic acid starting materials bearing substituents on the aroyl ring.

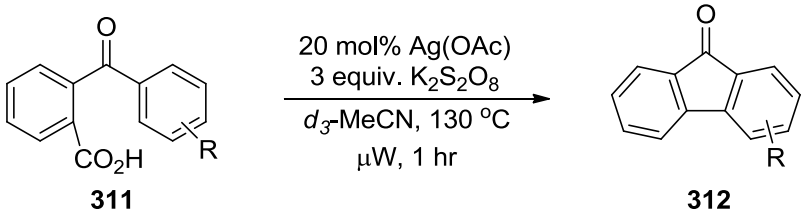
The same procedure could not be employed for the synthesis of 2-aroylbenzoic acids **326** bearing substituents on the benzoate ring (LHS ring) due to poor regioselectivity of the reaction. Alternatively, similar reactions between *ortho*-lithiated benzoic acids and aroyl electrophiles **321** were attempted using halogen-lithium exchange and direct *ortho*-lithiation methods (Scheme 92),[198] however, these strategies were also unsuccessful for the preparation of aroylbenzoic acids **326**. Due to the difficulty of making these substrates, the functional group tolerance only on the aroyl ring was investigated.

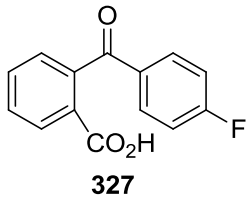
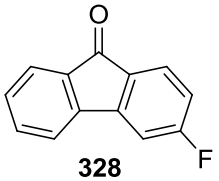
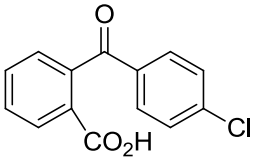
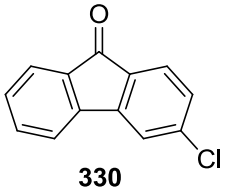
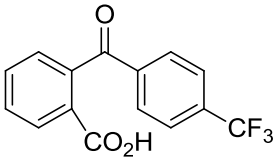
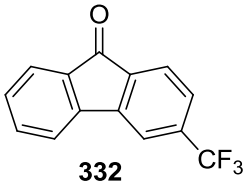
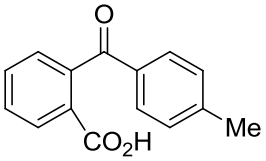
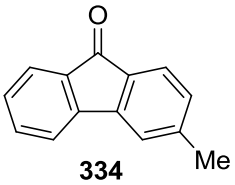
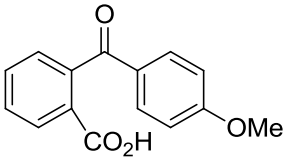
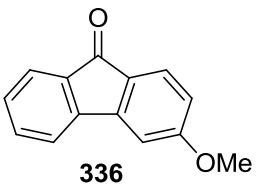


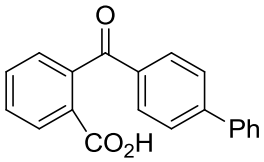
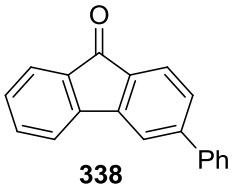
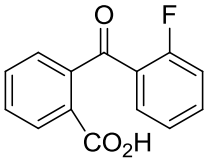
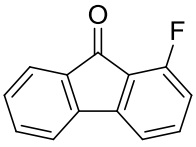
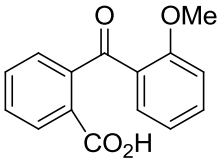
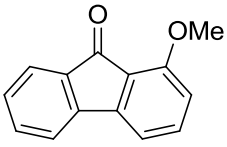
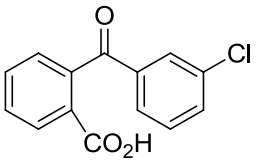
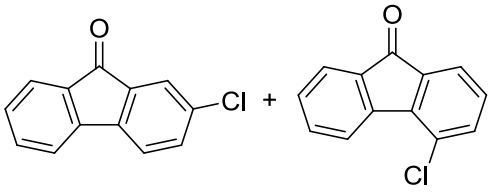
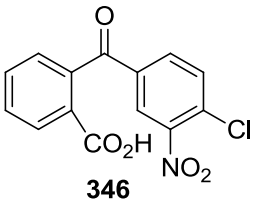
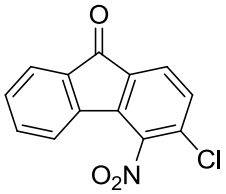
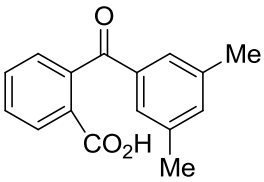
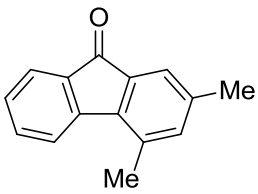
Scheme 92 Attempts for the synthesis of 2-aroylbenzoic acids bearing substituents on the benzoate ring.

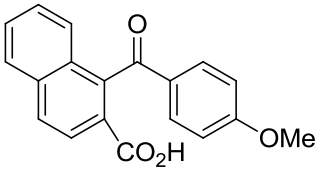
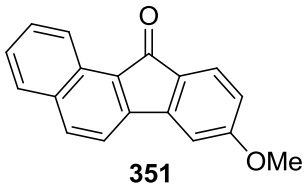
Various 2-aroylbenzoic acids **311** were converted to the corresponding fluorenones **312** under the optimised conditions (Table 10). The cyclisation was successful onto a series of *para*-substituted aromatics. Electron-withdrawing groups on the 4-position (fluoro, chloro and trifluoromethyl) of the aroyl ring were all tolerated well, affording the fluorenone products **328**, **330** and **332** in good yields (Entries 1-3), whereas the more electron rich substituents (4-methoxy and 4-methyl) afforded moderate yields of fluorenones **334** and **336** (Entries 4-5). Aryl radicals generated under the silver-catalysed decarboxylative conditions may have a nucleophilic character, thus leading to better reactions with electron-deficient substrates. Similar results were observed in the previously reported borono-Pschorr reaction, where the substrates bearing electron-withdrawing substituents resulted in better yields of the fluorenone products.[192] A 4-phenyl group was also well-tolerated, producing **338** in 65% yield (Entry 6). There was little difference in yield when the substituent was placed in the *ortho*-position for fluoro (Entry 7) and methyl (Entry 8) relative to their *para*-congeners.

Table 10 Scope of intramolecular decarboxylative radical arylation for the synthesis of fluorenones



Entry	SM	Product	Yield (%)
1	 **327**	 **328**	70
2	 **329**	 **330**	84
3	 **331**	 **332**	77
4	 **333**	 **334**	46
5	 **335**	 **336**	58

Entry	SM	Product	Yield (%)
6	 **337**	 **338**	65
7	 **339**	 **340**	69
8	 **341**	 **342**	51
9	 **343**	 **344** **345**	70[a]
10	 **346**	 **347**	56[b]
11	 **348**	 **349**	45

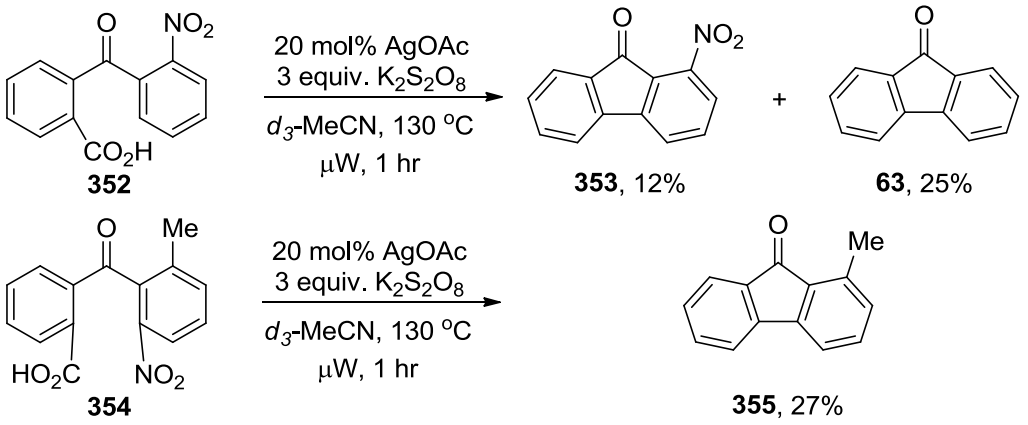
Entry	SM	Product	Yield (%)
12	 **350**	 **351**	31[c]

Reaction conditions: Performed on a 0.3 mmol scale, d_3-MeCN (2.0 mL), microwave heating at 130 °C for 1 hr; Isolated yields. [a] Inseparable mixture; **344**:**345** = 1:1.4. [b] Isolated yield of the major regioisomer. The other isomer could not be isolated in a pure form. [c] Reaction for 2 hrs; Second addition of AgOAc (20 mol%) and $K_2S_2O_8$ (3 equiv.) after 1 hr.

We next examined *meta*-substituted aromatics in the form of 3-chloro (Entry 9), 3-nitro-4-chloro (Entry 10) and 3,5-dimethyl **343**, **346** and **348** (Entry 11) substrates. The former proceeded in good yield (70%) with little regioselectivity between the two isomers. The result for the 3-chloro compound **343** is in line with typical Pschorr cyclisation of *meta*-substituted arenes, which rarely show regioselectivity in the free radical aromatic substitution step.[199] The 3-nitro-4-chloro compound **346**, by contrast, was unusual in this regard, cycling successfully to a major regioisomer **347**, with only small amounts of the minor isomer arising from cyclisation *para* to the nitro group. The 3,5-dimethyl substituted **348** substrate cyclised in a moderate yield (45%) to **349**. Benzofluorenone **351** was formed in a low yield (31%) from the corresponding 2-naphthoic acid **350** (Entry 12). The decarboxylation with such a substrate was very inefficient even with the second additions of silver(I) acetate and potassium peroxydisulfate, suggesting that the oxidative radical method is less compatible with the electron-rich naphthyl system.

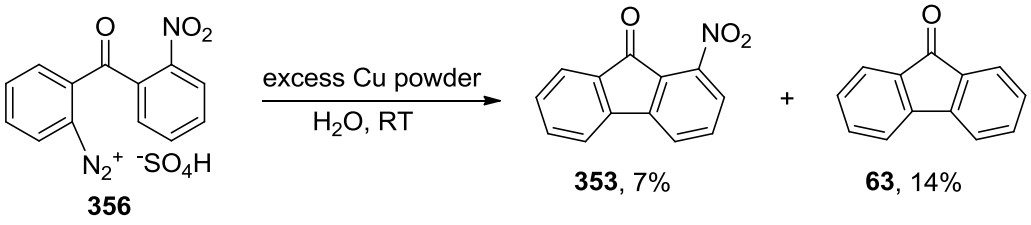
In addition, an interesting side product was observed on exposure of 2-nitro substrate **352** to the reaction conditions, with a small amount of fluorenone **63** being isolated along with the expected 2-nitrofluorenone **353** (Scheme 93). Given the stability of the nitro group to the reaction conditions (Table 10, Entry 10), and the lack of any deuterium incorporation in **63**, it is unlikely that the formation of **63** arises from denitration of **353**. To investigate the reaction further, we prepared the 2-methyl-6-nitro

substrate **354** and observed cyclisation to **355** in a 27% yield under the reaction conditions.



Scheme 93 Intramolecular decarboxylative radical arylation of *o*-nitro substrates.

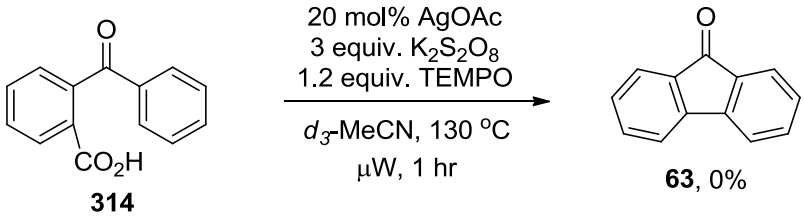
This denitrative decarboxylative cross-coupling likely proceeds *via* direct *ipso*-substitution of the nitro group with loss of NO_2.[200] A similar reaction can be found in the classical Pschorr reaction reported by Hey and Mulley in 1952, where the analogous diazonium salt **356** undergoes radical cyclisation to produce both **353** and **63** (Scheme 94).[201] As in our decarboxylative reaction, the *ipso*-substitution is more facile than the direct substitution, resulting in a more favourable formation of **63** over **353**. This evidence supports a radical mechanism for our decarboxylative cyclisation reactions. A number of other reports have also shown that nitro substituents can be replaced by radical reactants in aromatic substitution reactions.[202]



Scheme 94 The Pschorr cyclisation of *o*-nitro substrates.

To prove further that the oxidative decarboxylation of 2-aroylbenzoic acids proceeds *via* a radical mechanism, a control experiment was carried out using TEMPO as a radical scavenger (Scheme 95). It was soon found that the addition of 1.2 equivalent TEMPO to the background reaction blocked the decarboxylation step, resulting in a 0% conversion of the starting material. This result is consistent with the reaction mechanism *via* aryl

radical generation from oxidative decarboxylation and subsequent intramolecular radical C–H arylation (Scheme 89).

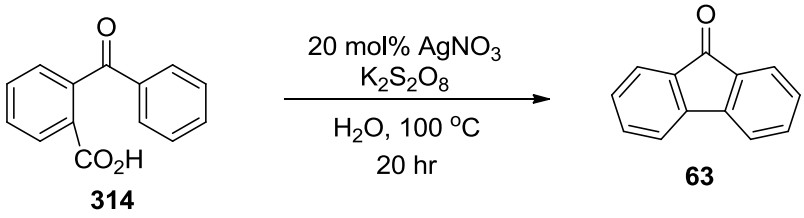


Scheme 95 Control experiment in the presence of TEMPO.

Finally, our oxidative radical conditions enabled decarboxylative arylation of substrates that were resistant to conventional palladium/silver co-catalysis. The advantages of our method over the reported protocols include; 1) no need of an expensive palladium catalyst, 2) a lower loading of a silver salt, and 3) lower temperatures employed. The requirement of a deuterated solvent, however, is a current limitation of this methodology.

The role of acetonitrile as the solvent is not fully understood, but the slow addition experiments under aqueous conditions indicate that a slow introduction of peroxydisulfate into the reaction medium may be an important factor for efficient decarboxylation (Table 11).

Table 11 Investigation into aqueous reaction conditions



Entry	$K_2S_2O_8$	Addition	63 (%)
1	3 equiv.	Normal condition	0
2	~0.65 equiv.	Slow addition of saturated aqueous solution of $K_2S_2O_8$ (1 ml) over 10 hr	14
3	~1.95 equiv.	Slow addition of saturated aqueous solution of $K_2S_2O_8$ (3 ml) over 10 hr	19

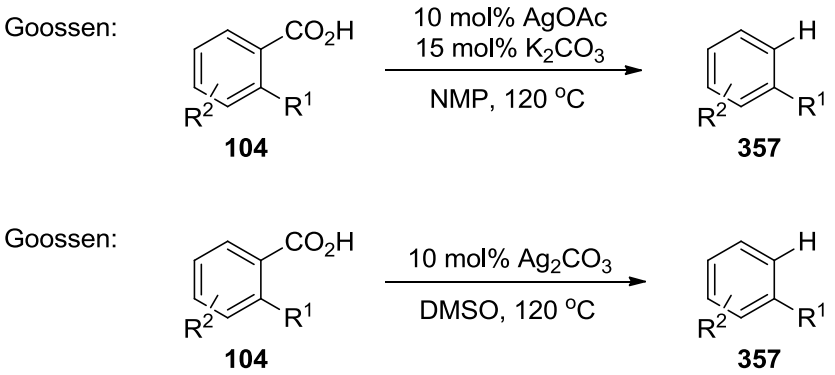
Reaction conditions: Performed on a 0.3 mmol scale; Yield determined by NMR analysis.

No product could be formed in water (Entry 1), but low yields of **63** could be exclusively obtained when potassium peroxydisulfate was added slowly in aqueous solution (Entries 2-3). Potassium peroxydisulfate is only sparingly soluble in acetonitrile, and this may allow a slow introduction of the oxidant into the reaction to give efficient decarboxylation. Further investigations would need to be made in order to fully understand and improve the reaction. Investigating water as the solvent would be interesting since this obviates the formation of undesired protodecarboxylation by-product, and also provides benefits as a low-cost green solvent.

3.2.2 Protodecarboxylation of benzoic acids under radical conditions

Protodecarboxylation is important in synthesis that uses a carboxylate to direct aromatic functionalisation, but do not require the acid group in the final molecule.[61] Moreover, the loss of CO_2 is a key step in any decarboxylative coupling reaction, and studying this step using protodecarboxylation as a model system has been a productive avenue for catalyst design and refinement.

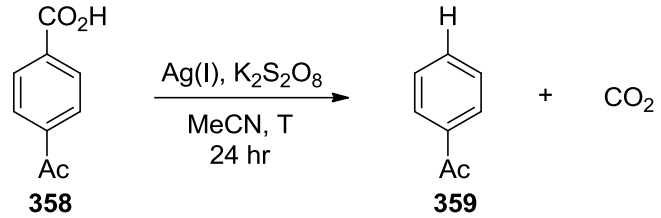
In 2007, Goossen reported copper-catalysed protodecarboxylation reactions of benzoic acids, but this protocol is limited by the need of extremely high temperatures and an expensive ligand for activating the catalyst.[163] In 2009, the same group[118] and Larrosa[119,120] independently developed ligand-free silver-catalysed protodecarboxylation reactions which proceed at lower temperatures. Good substrate scope for heteroaromatic carboxylic acids was obtained, but benzoic acids required an *ortho*-substituent for the reactions to proceed (Scheme 96). This requirement of an *ortho*-substituent, frequently a heteroatom, for decarboxylation of benzoic acids is a significant restriction. Therefore, we were interested in applying our silver(II)-catalysed radical approach to protodecarboxylation with the aim of expanding the scope beyond *ortho*-substituted benzoic acids.[203]



Scheme 96 Ag-Catalysed protodecarboxylation of *ortho*-substituted benzoic acids.

We selected the *para*-substituted 4-acetylbenzoic acid **358** as a model substrate and screened conditions using the combination of silver(I) salts and potassium peroxydisulfate in acetonitrile (Table 12). We were pleased to find that the reaction was productive using 20 mol% of silver(I) acetate with excess potassium peroxydisulfate (3 equiv.) at 100 °C, providing a good conversion to acetophenone **359** in 71% NMR yield (Entry 1). Raising the reaction temperature to 120 °C gave a similar yield of **359** (Entry 2). Increasing the catalyst loading was counterproductive (Entry 3), but increasing the amount of potassium peroxydisulfate was beneficial (Entry 4) providing 84% ^{1}H NMR yield and 78% isolated yield of **359**. The reaction was effective for a variety of silver salts, with sulfate, carbonate, oxide and trifluoroacetate all giving similar results (Entries 5-8). Silver halides, triflate and nitrate were found to be poor catalysts for this reaction (Entries 9-12). The reaction time could be reduced using microwave heating at 130 °C, with little loss in yield (Entry 13).

Table 12 Reaction optimisation of Ag-catalysed protodecarboxylation under radical conditions



Entry	Ag^{I} catalyst	Catalyst Loading (mol%)	$K_2S_2O_8$ (equiv.)	T (°C)	Yield (%)[a]
1	AgOAc	20	3	100	71
2	AgOAc	20	3	120	69
3	AgOAc	40	3	100	45
4	AgOAc	20	5	100	84 (78[b])
5	Ag_2SO_4	10	5	100	81
6	Ag_2CO_3	10	5	100	67
7	Ag_2O	10	5	100	68
8	Ag(TFA)	20	5	100	75
9	Ag(OTf)	20	5	100	<10
10	AgI	20	5	100	<10
11	AgF	20	5	100	32
12	$AgNO_3$	20	5	100	40
13[c]	AgOAc	20	5	130	77

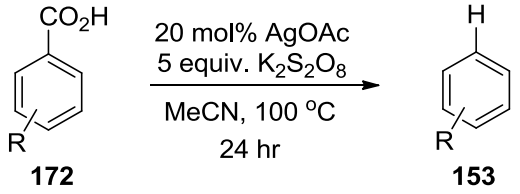
Reactions were performed on a 0.3 mmol scale. [a] Yield determined by ^{1}H NMR analysis using nitromethane as an internal standard. [b] Isolated yields. [c] Microwave heating for 1 hr.

With optimised conditions in hands, we examined a variety of functionalised aromatic carboxylic acids to investigate the scope of the reaction (Table 13). For products with low volatilities, yields were determined by ^{1}H NMR analysis using nitromethane as an internal standard.

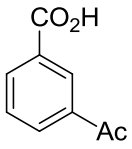
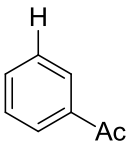
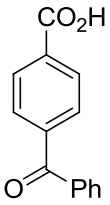
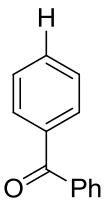
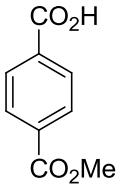
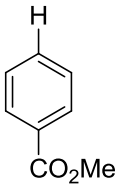
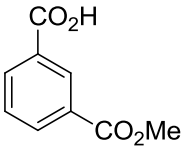
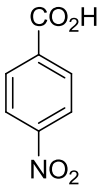
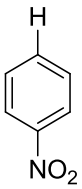
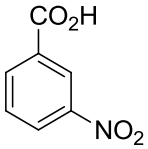
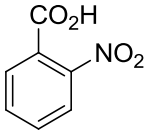
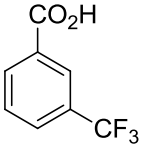
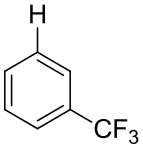
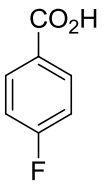
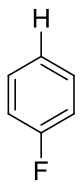
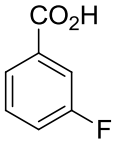
Effective protodecarboxylation was observed for a wide substrate range of *ortho*-, *meta*- and *para*-substituted benzoic acids. Good to excellent yields were obtained for ketones **360** and **361** (Entries 1-2), esters **362** and **364** (Entries 3-4), nitro **190**, **365** and **189** (Entries 5-7), trifluoromethyl **366** (Entry 8), fluoro **368** and **370** (Entries 9-10) and bromo **371** (Entry 11) substituted compounds. 4-Iodobenzoic acid **372** was an exception, giving a poor yield probably due to deiodination side reactions (Entry 12).[204] Disubstituted benzoic acids **373**, **374** and **376** were also good substrates for the reaction (Entries 13-15), although the 3,5-difluoro substrate **378** was poorly converted to the corresponding protodecarboxylation product **379** (Entry 16). Benzoic acid **380** (Entry 17) itself also underwent protodecarboxylation to benzene **291**, indicating that electron-withdrawing groups are not a requirement for the reaction. This result is particularly interesting considering that the parent acid has been absent as a substrate in previously reported transition metal-catalysed decarboxylative transformations.

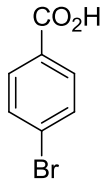
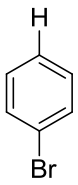
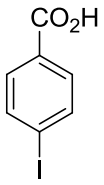
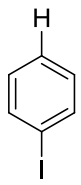
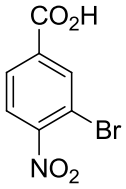
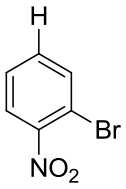
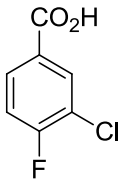
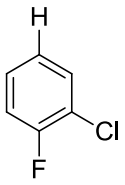
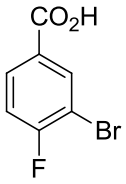
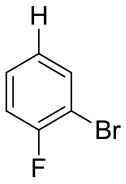
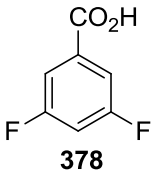
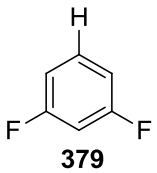
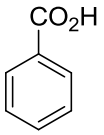
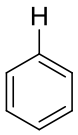
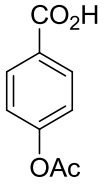
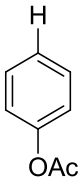
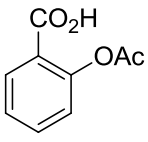
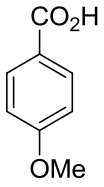
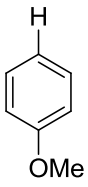
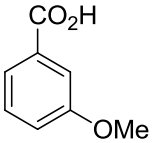
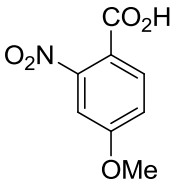
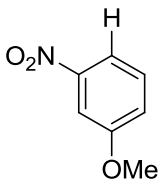
Electron rich benzoic acids were less effective substrates for protodecarboxylation. 4-Acetoxy **381** (Entry 18), 2-acetoxy **383** (Entry 19) and 4-methoxy **191** (Entry 20) substrates afforded only low yields of the protodecarboxylation products **382** and **384**. The non-conjugated 3-methoxybenzoic acid **385** is slightly better, producing anisole **384** in 45% yield (Entry 21). The deactivating effect of simple π–donors on loss of CO_2 from aromatic carboxylate radical is known, with 4-methoxy benzoate radical undergoing decarboxylation six times slower than the parent benzoate radical in carbon tetrachloride.[205] This deactivation could be partially ameliorated with electron-withdrawing groups, with the substrate **386** undergoing protodecarboxylation to afford **387** in a 58% yield.

Table 13 Scope of silver-catalysed protodecarboxylation under radical conditions



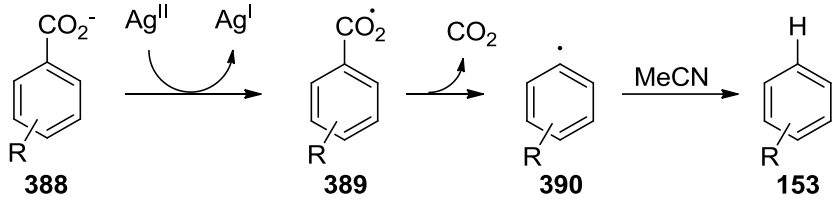
172 **153**

	SM	Product	Yield (%)[a]		SM	Product	Yield (%)[a]
1	 **360**	 **359**	63	2	 **361**	 **318**	75
3	 **362**	 **363**	82	4	 **364**	**363**	81
5[b]	 **190**	 **254**	61	6[b]	 **365**	**254**	54
7	 **189**	**254**	84	8	 **366**	 **367**	68[c]
9	 **368**	 **369**	64[c]	10	 **370**	**369**	57[c]

	SM	Product	Yield (%)[a]		SM	Product	Yield (%)[a]
11	 **371**	 **11**	67[c]	12	 **372**	 **17**	40[c]
13	 **373**	 **6**	43	14	 **374**	 **375**	74[c]
15	 **376**	 **377**	75[c]	16	 **378**	 **379**	39[c]
17	 **380**	 **291**	52[c]	18	 **381**	 **382**	25
19	 **383**	**382**	31	20	 **191**	 **384**	34[c]
21	 **385**	**384**	45[c]	22	 **386**	 **387**	58

Reaction conditions: Performed on a 0.3 mmol scale. [a] Isolated yields. [b] 40 mol% AgOAc was used. [c] Yields determined by ^{1}H NMR analysis using nitromethane as an internal standard.

The addition of TEMPO as a radical scavenger shuts down the otherwise efficient protodecarboxylation, which again demonstrates that a radical mechanism is likely operative in this reaction. A possible mechanism is that silver(II) oxidises carboxylate **388** to the radical **389**, which could afford the aryl radical **390** after loss of CO_2. This radical can then be effectively trapped through hydrogen atom transfer from the acetonitrile solvent to give the protodecarboxylation product **153** (Scheme 97).



Scheme 97 A proposed mechanism for the $Ag^{II}/K_2S_2O_8$-mediated protodecarboxylation of aromatic carboxylic acids.

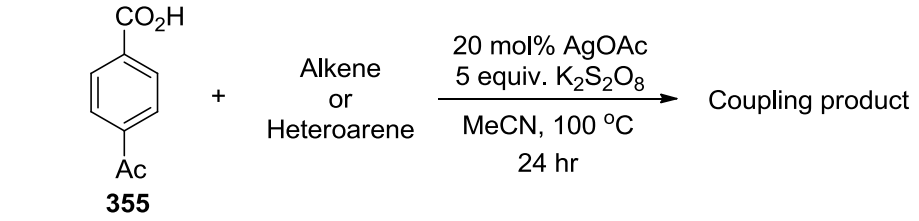
This newly developed protodecarboxylation method uses a cheap inorganic oxidant and catalytic amounts of silver under simple reaction conditions. The substrate scope is substantially expanded from existing methods for decarboxylation of benzoic acids. More importantly, a mild protocol for the generation of aryl radicals is provided, which uses cheap and widely available carboxylic acids as the radical source. Applications of this chemistry in radical reactions would potentially provide many advantages over conventional methods.

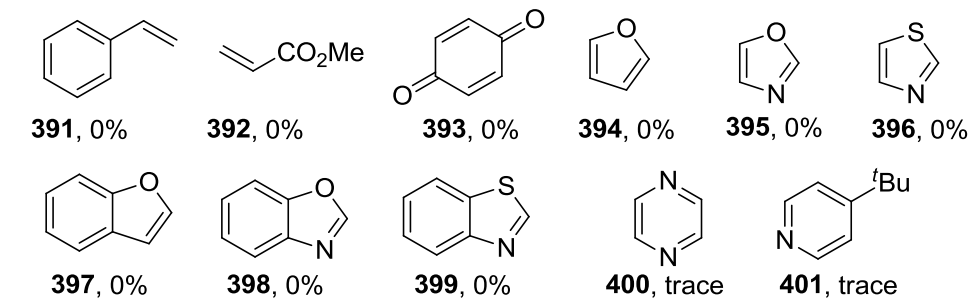
3.2.3 Intermolecular decarboxylative C–H arylation under radical conditions

As discussed earlier in section 3.1, addition of aryl radicals to various radicalophiles is well-known in a number of classical named reactions such as the Gomberg-Bachmann (addition to arenes), Minisci (electron-deficient heteroarenes) and Meerwein (alkenes) reactions. We have shown that benzoic acids can be oxidatively decarboxylated to aryl radicals using $Ag^{I}/K_2S_2O_8$ systems, and envisioned that such a protocol could be utilised in intermolecular radical addition reactions.

In our initial investigations, 4-acetylbenzoic acid **358**, a good substrate for oxidative decarboxylation, was reacted with a number of arenes and alkenes under the radical generating condition using silver(I) acetate and potassium peroxydisulfate (Table 14), and the product formation was monitored by LC/MS analysis.

Table 14 Initial investigation of silver-catalysed intermolecular decarboxylative radical arylation

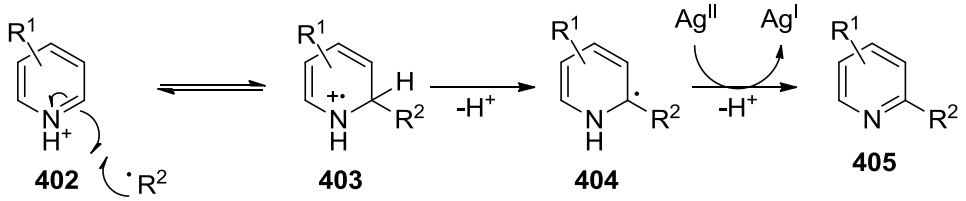




Reaction conditions: Performed on a 0.3 mmol scale; Reactions were monitored by LC/MS.

Unfortunately, no productive results were obtained for any of the alkenes (**391**-**393**) or electron-rich arenes (**394**-**399**) when reacted under such conditions. The oxidative decarboxylation becomes inefficient when these coupling partners are present in the reaction, giving most of unreacted starting materials. Increasing the loading of the silver catalyst improved the decarboxylation, but the unwanted protodecarboxylation by-product was formed as the sole product. The reactions of electron-poor heteroarenes (**400**-**401**) experienced similar problems, although coupling products were observed in low yields by LC/MS analysis. This supports our earlier hypothesis that aryl radicals generated under the silver-catalysed decarboxylative conditions may have a nucleophilic character, and thus react better with electron-deficient substrates. The reactivity of 4-(*tert*-butyl)pyridine **401** for radical arylation is well-established in Baran's borono-Minisci reaction,[190] and it was decided to use this substrate for our further optimisation studies.

Extensive studies by Minisci showed that azines are better radicalophiles in their protonated forms.[172] Mechanistically, it was proposed that the initial radical addition to azines is a reversible process (Scheme 98). In their protonated forms **402**, the resulting radical cation intermediate **403** would favour the loss of α-proton to give the strongly nucleophilic radical **404**, which undergoes oxidation and rearomatisation to give the arylation product **405**. As a result, the effects of the reversibility are minimised, giving an increased reactivity for the C–C bond formation.



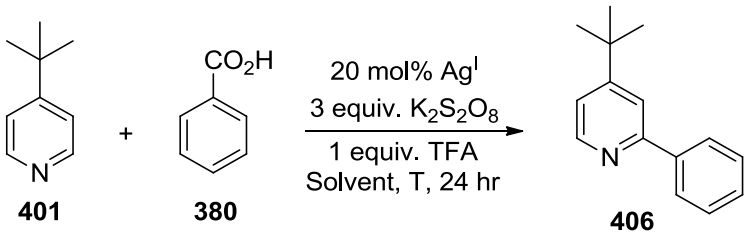
Scheme 98 Mechanism of the Minisci reaction.

The intermolecular decarboxylative radical arylation of **401** was, therefore, further optimised under acidic conditions. Trifluoroacetic acid, which has been utilised in the borono-Minisci reaction, was chosen as the acid source. A series of conditions for the reaction with unsubstituted benzoic acid **380** were investigated, varying the silver catalyst, solvent and temperature (Table 15). Although aromatic carboxylic acids with electron-withdrawing substituents are more prone to decarboxylation, the unsubstituted substrate was elected for our optimisation studies since unsubstituted phenyl radical possesses increased reactivity toward electron-deficient heteroarenes.

To our delight, the initial reaction condition using silver(I) nitrate (20 mol%), potassium peroxydisulfate (3 equiv.), trifluoroacetic acid (1 equiv.) in refluxing acetonitrile at 100 ℃ gave the desired phenylated product **406** in a 10% yield (Entry 1). The LC/MS analysis indicated that there was still a significant quantity of the acid starting material remaining unreacted, and the formation of protodecarboxylation by-product **291** was also confirmed by crude ^{1}H NMR and TLC analysis. Attempts were made to improve this using different silver sources (Entry 2-3), but lower yields of **406** were obtained. The reaction at the slightly elevated temperature of 120 ℃ was also ineffective (Entry 4). As found in the intramolecular reaction (section 3.2.1), other solvents were

inefficient for decarboxylation of **380** (Entry 5). The reaction in water unexpectedly gave **406** in a 7 % yield (Entry 6).

Table 15 Reaction optimisation of Ag-catalysed decarboxylative arylation of 4-(*tert*-butyl)pyridine



401 380 406

Entry	Ag^I catalyst	Solvent	T (°C)	Yield (%)
1	$AgNO_3$	MeCN	100	10
2	Ag_2CO_3	MeCN	100	7
3	AgOAc	MeCN	100	8
4	$AgNO_3$	MeCN	120	10
5	$AgNO_3$	Solvent[a]	100	0
6	$AgNO_3$	H_2O	100	7
7	$AgNO_3$	MeCN/H_2O (1:1)	100	15
8	-	MeCN/H_2O (1:1)	100	8
9	$AgNO_3$	MeCN/H_2O (2:1)	100	5
10	$AgNO_3$	MeCN/H_2O (1:2)	100	6
11[b]	$AgNO_3$	MeCN/H_2O (1:1)	100	22
12[b,c]	$AgNO_3$	MeCN/H_2O (1:1)	100	20

Reaction conditions: Performed on a 0.3 mmol scale; Isolated yields. [a] Solvent: chloroform, 1,2-dichloroethane, benzene, toluene, 1,4-dioxane, DMSO and DMF. [b] A second addition of $AgNO_3$ (20 mol%) and $K_2S_2O_8$. [c] Reactions were run for 40 hr.

The slow addition experiments during the investigation of intramolecular decarboxylative reactions showed that slow incorporation of the peroxydisulfate oxidant into the reaction medium might be important for efficient decarboxylation (Table 11). A 1:1 mixture of acetonitrile and water was employed to control the solubility of potassium peroxydisulfate, and this resulted in a slightly improved yield of **406** (Entry 7). In this solvent system, the product could be formed even in the absence of the silver catalyst, but in a poorer yield (Entry 8). Changing the composition of the solvent mixture also led to poorer reaction yields (Entries 9-10). After 10 hours of reaction, the same amounts of silver(I) nitrate and potassium peroxydisulfate were additionally added in order to react remaining starting material **380** (Entry 11). This gave an improved reaction to produce **406** in 22% yield, but the conversion was still poor with a large quantity of **380** still remaining unreacted. A slow reaction was suspected, but longer reaction times gave no improvement upon the product yield (Entry 12).

The reaction under above conditions suffers from poor decarboxylation of **380** and also from the formation of protodecarboxylation by-product **291**. Alternative reaction systems will need to be developed to improve the decarboxylation and subsequent coupling reactions of the resulting aryl radicals while avoiding the side reaction. This will be the subject of future work in the Greaney group.

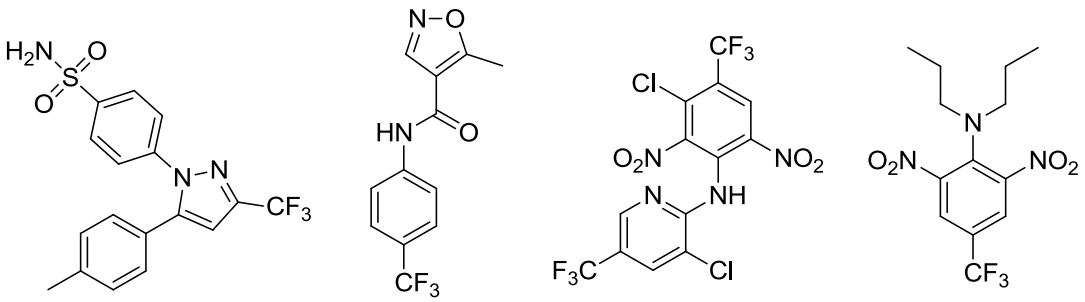
3.3 Conclusions

In conclusions, a novel decarboxylative radical cyclisation reaction has been developed for the synthesis of fluorenones. By using catalytic silver(I) acetate (20 mol%) and stoichiometric potassium peroxydisulfate (3 equiv.) to promote a radical pathway, a class of aroyl benzoic acids that are not productive in Pd/Cu or Pd/Ag catalytic decarboxylative arylations can undergo decarboxylative radical cyclisation to give fluorenones in good yields (31-84%). The reaction demonstrates that aroyl benzoic acids can be used as radical precursors for radical arylation, a transformation previously confined to alkyl carboxylic acids. The requirement of expensive d_3-MeCN as the reaction solvent is a current limitation.

The oxidative radical process has also been applied to the protodecarboxylation of benzoic acids. The substrate scope of this key reaction has been substantially expanded to *m*eta- and *para*-substituted benzoic acids, from existing methods that were limited to *ortho*-substituted substrates. Various arenes have been obtained using catalytic silver(I) acetate (20 mol%) and stoichiometric potassium peroxydisulfate (5 equiv.) in acetonitrile. Applications of this chemistry have also been investigated in intermolecular radical arylation of electron-deficient heteroarenes, but the current limitations are that decarboxylation of aromatic carboxylic acids become inefficient when heteroarene coupling partners are present and that unwanted protodecarboxylation side reaction occurs.

4 Direct trifluoromethylation of simple arenes and heteroarenes

The carbon–fluorine (C–F) bond is highly polarised due to the large electronegativity differences between the two atoms. This electrostatic nature of the C–F bond leads to strong polar interactions with other dipoles, and incorporation of fluorine or fluorine-containing functional groups into organic molecules consequently influences molecular properties such as bioavailability, lipophilicity and metabolic stability. The trifluoromethyl (CF_3) group is one of the most important classes of such functionalities. In 1927, Lehman first investigated the biological activity of CF_3-containing compounds, examining a number of benzotrifluorides to study how these compounds affect the central nervous system of frogs.[206] The importance of the CF_3 group has since been realised in various biologically active compounds.[207] Those bearing the CF_3 group on aromatic rings are particularly numerous and important. Indeed, a considerable number of pharmaceuticals and agrochemicals contain one or more CF_3 groups attached to aromatic rings (Figure 5).

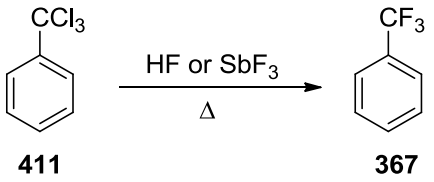


407 Celecoxib (NSAID) **408** Leflunomide (DMARD) **409** Fluazinam (Fungicide) **410** Trifluralin (Herbicide)

Figure 5 Pharmaceuticals and agrochemicals containing the CF_3 group.

Synthetic methods for trifluoromethylation of aromatic and heteroaromatic compounds are thus critical to the discovery of new molecules of high value. Trifluoromethylated aromatic compounds were first prepared by Swarts in 1898.[208] In his original work, Swarts demonstrated that benzotrichloride **411** could be fluorinated with antimony fluoride to give benzotrifluoride **367** (Scheme 99). In the 1930s, two industrial groups discovered that hydrogen fluoride could be successfully employed as an alternative

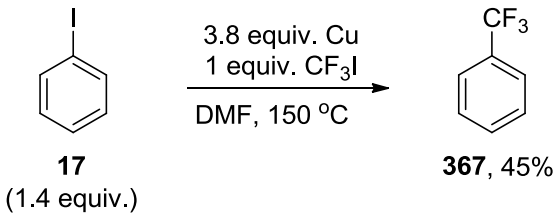
fluorinating reagent.[209,210] The latter methods have been widely utilised in industry for large scale manufacture of trifluoromethylated aromatic compounds.



Scheme 99 Fluorination of benzotrichloride to benzotrifluoride (Swarts reaction).

The Swarts reaction uses stoichiometric quantities of inexpensive but hazardous fluorinating reagents, and generates superstoichiometric amounts of chloride and antimony waste. In addition, benzotrichloride starting materials may also need to be prepared, requiring additional synthetic steps and thus generating more waste. This protocol is thus neither atom economical nor environmentally benign.

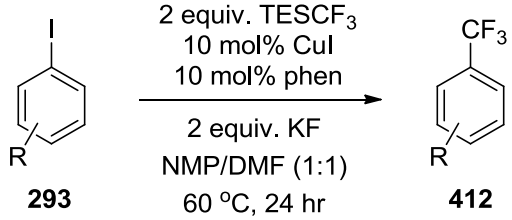
With significant developments made in recent years, transition metal-catalysed cross-coupling reactions have become one of the most used protocols for the introduction of the CF_3 group into aromatic rings.[211,212,213] The first example of this type of Ar–CF_3 bond forming reaction was reported in 1969 by McLoughlin and Thrower (Scheme 100).[214] Benzotrifluoride **367** was obtained in 45% yield by reacting iodobenzene **17** with trifluoroiodomethane in the presence of copper bronze. *In situ* generation of a trifluoromethyl copper (CF_3Cu) complex was proposed, which would then reductively couple with **17**.



Scheme 100 The first example of transition metal-mediated trifluoromethylation of aryl iodides.

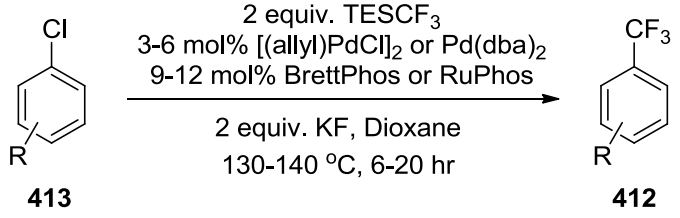
This work initiated research towards the use of transition metal catalysis in trifluoromethylation of aromatic compounds. Several modifications to the reaction

conditions and reagents have since been reported. In 2009, Amii reported the first catalytic procedure using the nucleophilic trifluoromethylating reagent, triethyl(trifluoromethyl)silane (Scheme 101).[215] Aryl iodides **293** were successfully converted to benzotrifluorides **412** in the presence of catalytic amounts of copper (I) iodide (10 mol%) and 1,10-phenanthroline (10 mol%). It was proposed that the diamine ligand stabilises the copper complex, enabling fast ligand exchange with the trifluoromethyl anion (CF_3^-) released from $TESCF_3$/KF. The resulting trifluoromethylcopper complex would undergo oxidative addition with **293** followed by reductive elimination to complete the catalytic cycle.



Scheme 101 The first example of Cu-catalysed Ar–CF_3 bond forming reactions.

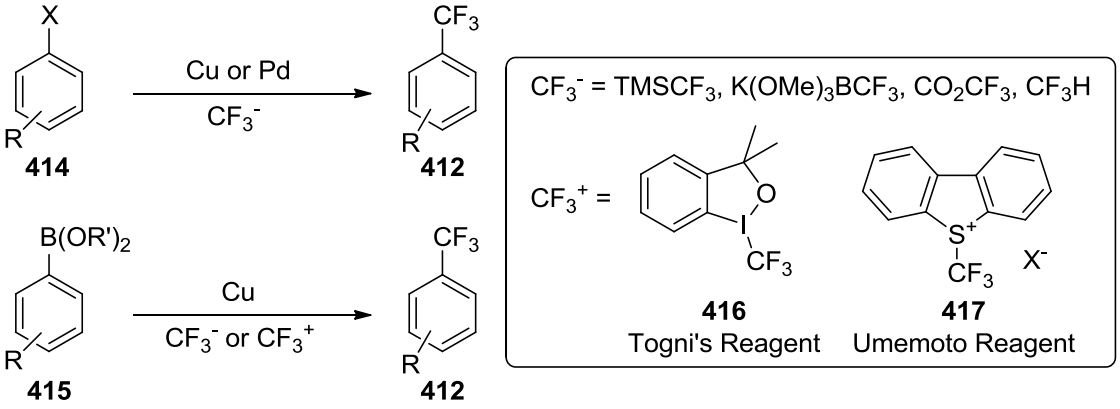
In 2010, Buchwald developed the first palladium-catalysed Ar–CF_3 bond forming reaction (Scheme 102).[216] A range of aryl chlorides **413** could be efficiently converted to their trifluoromethylated analogues **412** when reacted with triethyl(trifluoromethyl)silane in the presence of either [allylpalladium (II) chloride] or [bis(dibenzylideneacetone)palladium (0)]. The use of a sterically large monodentate phosphine ligand (BrettPhos or RuPhos) facilitates the otherwise unfavourable Ar–CF_3 bond forming reductive elimination from the Pd^{II} centre, allowing the reaction to proceed with high functional group tolerance.



Scheme 102 The first example of Pd-catalysed Ar–CF_3 bond forming reactions.

More recently, several alternative methods have been developed using other nucleophilic or electrophilic trifluoromethylating reagents (Scheme 103).[213] The scope

has been broadened not only to other halides but also to boronic acids and esters, providing mild reactions for the synthesis of trifluoromethylated aromatic rings.



Scheme 103 Recent developments in transition metal-catalysed trifluoromethylation of functionalised aromatic compounds.

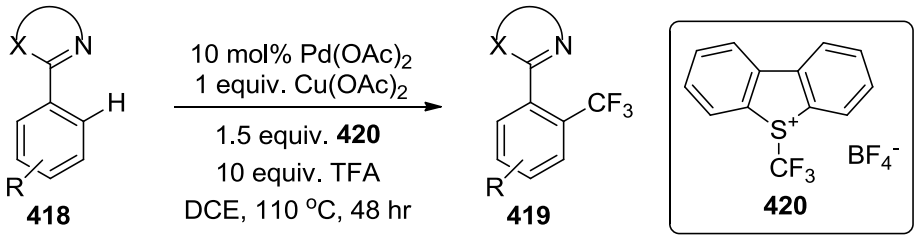
Despite the development of these powerful methods, the previous transition metal-catalysed reactions remain limited by the use of preactivated aromatic compounds. A desirable alternative approach would be *via* directly accessing C–H bonds of simple aromatic compounds. The use of unfunctionalised arenes would provide a rapid and more atom economical synthetic route for the preparation of CF_3-containing arenes and heteroarenes.

4.1 Silver-catalysed radical trifluoromethylation of simple arenes and heteroarenes using $TMSCF_3$ as a trifluoromethylating radical source

4.1.1 Introduction and aims

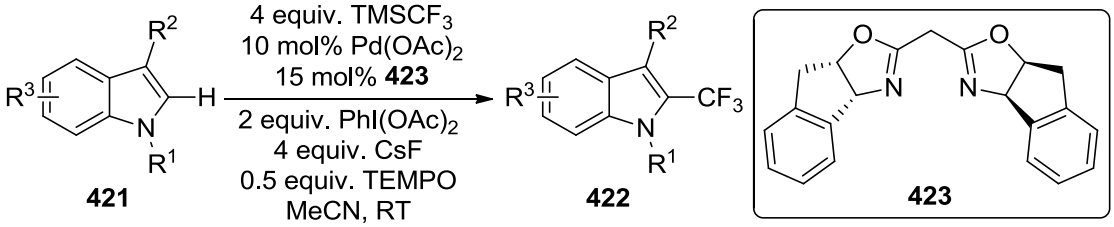
Recently, a number of C–H activation methods have been reported for the direct trifluoromethylation of aromatic C–H bonds.[217] In 2010, Yu developed a palladium-catalysed *ortho*-selective trifluoromethylation of arenes through directing group assisted functionalisation (Scheme 104).[218] (Trifluoromethyl)dibenzothiophenium tetrafluoroborate **420** (Umemoto's reagent) was employed as the CF_3 source and *N*-heteroarenes (pyridine, pyrimidine, 1-methyl-1*H*-imidazole and thiazole) as the

directing groups. The use of trifluoroacetic acid was found to be crucial for successful Ar–CF_3 bond formation, and copper (II) acetate was found to be effective for enhancing the catalytic turnover. The same group also showed that amides[219] and amines[220] could be used as alternative directing groups under slightly modified conditions.



Scheme 104 Pd-catalysed trifluoromethylation of arenes through directing group assisted C–H activation.

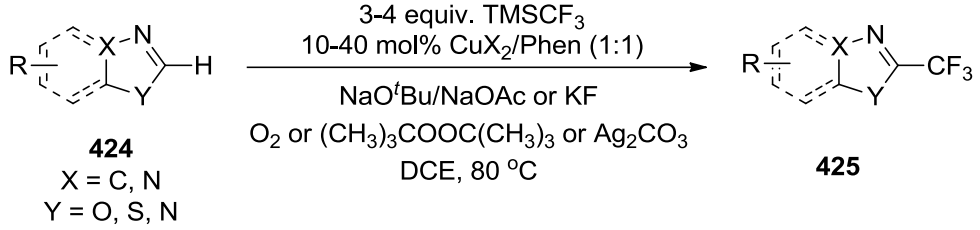
In 2011, Liu reported a palladium-catalysed C2-trifluoromethylation of 1,3-substituted indoles **421** (Scheme 105).[221] The reaction proceeds at room temperature using trimethyl(trifluoromethyl)silane as the CF_3 source and iodobenzene diacetate as the oxidant, affording the trifluoromethylated indoles **422** in good yields. A small amount of side-product containing the CF_3 group on the benzene ring was formed in their initial investigation. This could be inhibited with the addition of a radical scavenger, TEMPO, indicating that the side reaction might occur through a radical process. Mechanistically, it was proposed that highly reactive Pd^{IV} complexes would be generated under the oxidative conditions, which would then lead to favourable reductive elimination for Ar–CF_3 bond formation (Pd^{II}/Pd^{IV} catalytic cycle). Addition of the bidentate nitrogen ligand **423** was also found to be beneficial to the reaction.



Scheme 105 Pd-catalysed C–H trifluoromethylation of 1,3-substituted indoles.

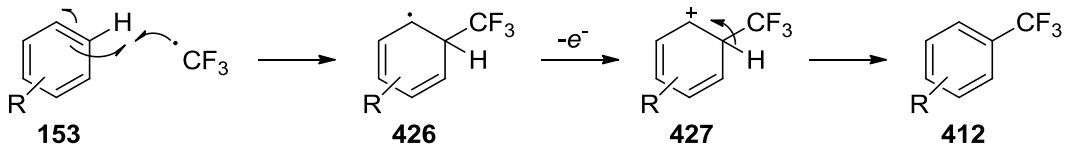
More recently, Qing developed a copper-catalysed protocol for the direct trifluoromethylation of heteroarenes **424** with trimethyl(trifluoromethyl)silane (Scheme

106).[222] Using a number of different sets of oxidative conditions, 1,3,4-oxadiazoles, benzoxazoles, benzothiazoles, benzoimidazoles and indoles could be converted to the corresponding trifluoromethylated products **425** with high functional group tolerance. The mechanistic investigations indicated that a Cu^{I}/Cu^{III} catalytic cycle occurs *via* generation of a $CF_3Cu^{I}L_n$ complex as the key intermediate.



Scheme 106 Cu-Catalysed C–H trifluoromethylation of heteroarenes.

The C–H activation methods are advantageous due to the low cost and versatility of unfunctionalised arenes. However, such methods are limited either to substrates bearing a directing group or to certain classes of heteroarenes. The use of very expensive CF_3^+ reagents in some protocols is also undesirable. A more common approach for C–H trifluoromethylation of aromatic compounds is *via* radical aromatic substitution with the CF_3 radical.[223] The fluorine atom in the CF_3 radical is inductively electron-withdrawing, making the radical centre very electrophilic and reactive towards radical aromatic substitution (Scheme 107). The capture of the CF_3 radical with arene **153** is followed by oxidation of the radical intermediate **426** and rearomatisation of the resulting cation **427** to give the trifluoromethylated product **412**. Due to its electrophilic nature, the CF_3 radical generally reacts more readily with electron-rich arenes and heteroarenes.

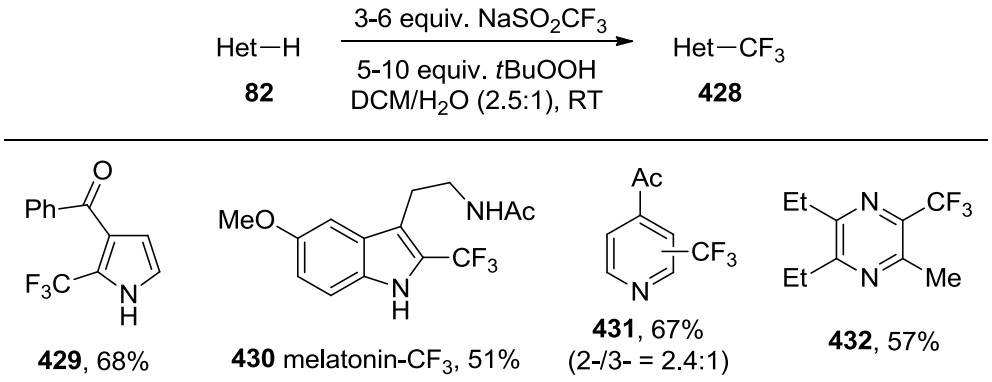


Scheme 107 Radical C–H trifluoromethylation of aromatic compounds.

Early studies utilised gaseous trifluoromethyl halides as the CF_3 radical source, but recent developments have seen the use of more stable and easily handled reagents as alternatives. Langlois first demonstrated that sodium trifluoromethanesulfinate ($NaSO_2CF_3$) can be used to generate the CF_3 radical under oxidising conditions using a

copper catalyst and a stoichiometric amount *tert*-butyl peroxide.[224] The *tert*-butoxide radical is believed to react with $CF_3SO_2^-$ to provide the $CF_3SO_2\cdot$ radical, which then homolytically cleaves to release SO_2 and the CF_3 radical. A number of electron-rich arenes were reported to react with the CF_3 radical generated under these conditions.

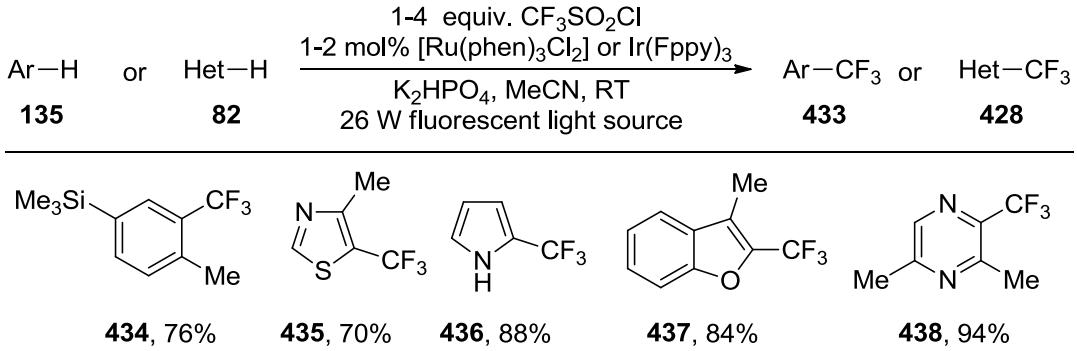
Recently, Baran showed that CF_3 radical formation from sodium trifluoromethanesulfinate can be effective even with no added transition metal catalysts.[225] Various heteroarenes **82** could be conveniently trifluoromethylated using *tert*-butyl peroxide as the oxidant in a biphasic solvent system of dichloromethane and water at room temperature (Scheme 108). The trifluoromethylation products **428** were obtained in good yields and with high functional group tolerance. Surprisingly, this reaction was successful not only with electron-rich heteroarenes (**429**-**430**), but also with electron-deficient substrates (**431**-**432**). Although addition of transition metal was not required for a productive reaction, it was proposed that trace metals found in sodium trifluoromethanesulfinate could be responsible for reaction initiation. More recently, the same group showed that the reaction could be improved by using zinc trifluoromethanesulfinate ($Zn(SO_2CF_3)_2$) as an alternative.[226]



Scheme 108 Radical trifluoromethylation of heteroarenes using $NaSO_2CF_3$.

MacMillan developed an interesting photoredox-based protocol that allows for the facile trifluoromethylation of arenes **135** and heteroarenes **82** at room temperature (Scheme 109).[227] Exposure of the simple aromatic compounds to a household 26 W fluorescent light source in the presence of trifluoromethylsulfonyl chloride, either $[Ru(phen)_3Cl_2]$ or $Ir(Fppy)_3$, and base, enabled trifluoromethylation with excellent efficiency and a broad substrate scope. It is the high energy excited complex ($*Ru^{II}$ or $*Ir^{III}$) which reduces

CF_3SO_2Cl *via* single electron transfer to give the CF_3 radical with the release of SO_2 and Cl^-.

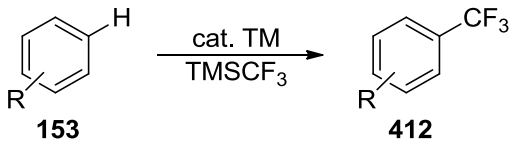


Scheme 109 Photoredox-based C–H trifluoromethylation of arenes and heteroarenes.

The particular value of the above two protocols was highlighted by the trifluoromethylation of complicated biologically active molecules under mild reaction conditions. These methods allow straightforward access to drug analogues through late-stage functionalisation, and therefore, should find broad utility in drug discovery research.

Despite these ground-breaking developments, there is still great demand for the development of catalytic C–H trifluoromethylation methods that function under mild and simple conditions. One of the limitations found in the above methods is the use of reagents that are difficult to handle. For example, trifluoromethylsulfonyl chloride utilised in the photoredox reaction is a low-boiling liquid and is moisture sensitive. As a result, purification of the reagent is occasionally required in prior to use.

Trimethyl(trifluoromethyl)silane, often referred to as Ruppert's reagent, is a commonly used reagent for a wide range of trifluoromethylation reactions. This reagent is relatively inexpensive, commercially available and air-stable, thus allowing easy handling and simple reaction setup. Our aim was to employ this reagent for the development of a new catalytic method for simple and mild C–H trifluoromethylation of aromatic compounds (Scheme 110). Our efforts and results in this study will be discussed.



153 412

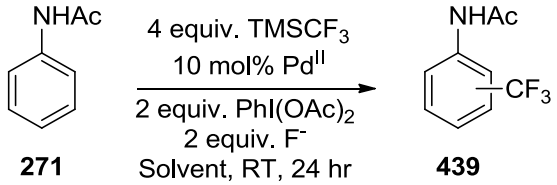
Scheme 110 Transition metal-catalysed trifluoromethylation of aromatic C–H bonds using $TMSCF_3$ as the CF_3 source.

4.1.2 Results and discussion

Our initial investigation was based on the reaction of acetanilide **271** with trimethyl(trifluoromethyl)silane (Table 16). It was thought that an *ortho*-selective trifluoromethylation of **271** could be achieved *via* directing group assisted C–H activation using similar palladium-catalysed conditions to Liu's indole trifluoromethylation protocol (Scheme 105).[221]

However, the results immediately revealed that the reaction is neither efficient nor regioselective, resulting in a mixture of all three possible isomers in poor yields. The Liu's conditions using palladium(II) acetate gave only a 5% combined NMR yield of *ortho*-, *meta*- and *para*-trifluoromethylated products (Entry 1). The use of palladium (II) trifluoroacetate, which has been successfully utilised in room temperature *ortho*-selective C–H activation of **271**,[165] had no significant effects on the outcome of our reaction (Entry 2). Reactions in other solvents were less productive (Entries 3-5). Surprisingly, the reaction in the absence of any transition-metal catalysts still gave the desired products in a similar yield (Entry 6). Other fluoride sources were investigated (Entries 7-9), and it was found that silver (I) fluoride gives the best result, improving the yield to 13% (Entry 9).

Table 16 Initial investigation of aromatic C–H trifluoromethylation using $TMSCF_3$ as the CF_3 source



271 439

Entry	Pd catalyst	F^- source	Solvent	Yield (%)[a]
1	$Pd(OAc)_2$	CsF	MeCN	5
2	$Pd(TFA)_2$	CsF	MeCN	4
3	$Pd(OAc)_2$	CsF	Diglyme	0
4	$Pd(OAc)_2$	CsF	DCM	1
5	$Pd(OAc)_2$	CsF	DCE	4
6	-	CsF	MeCN	7
7	-	KF	MeCN	7
8	-	$(NH_4)F$	MeCN	3
9	-	AgF	MeCN	13

Reaction conditions: Performed on a 0.3 mmol scale; [a] Combined yields of three regioisomers determined by ^{19}F NMR using 4-fluoroanisole as the internal standard; ratios not determined.

From the above results, it was suspected that the reaction may occur *via* radical trifluoromethylation, which may be catalysed in the presence of silver (I) source. There have been few reports of silver-mediated trifluoromethylation using trimethyl(trifluoromethyl)silane as the CF_3 source. In 2011, Sanford reported a C–H trifluoromethylation of simple aromatic compounds **153** using excess amounts of silver (I) triflate and potassium fluoride (Scheme 111).[228] Trimethyl(trifluoromethyl)silane was employed as the limiting reactant in this reaction, and an excess **153** was needed to obtain synthetically useful yields of trifluoromethylated aromatic compounds **412**. The author proposed that the reaction proceeds *via* the formation of the CF_3 radical from a $AgCF_3$ intermediate, which then participates in a radical aromatic substitution reaction.

Scheme 111 Ag-mediated C–H trifluoromethylation of aromatic compounds.

In 2012, Bräse reported a silver-mediated *ortho*-selective trifluoromethylation of aromatic triazenes **440** (Scheme 112).[229] Unlike the above reaction, this reaction was proposed to occur *via* C–H activation with *in situ* generated $AgCF_3$, which explains the high *ortho*-selectivity. A variety of *ortho*-trifluoromethyl triazenes **441** were obtained in good yields with broad functional group tolerance. The triazene moiety can be converted into various functional groups, such as halides, azide, nitrile and phenol, making this protocol attractive for the synthesis of *ortho*-functionalised benzotrifluorides.

Scheme 112 Ag-mediated *ortho*-C–H trifluoromethylation of aromatic triazenes.

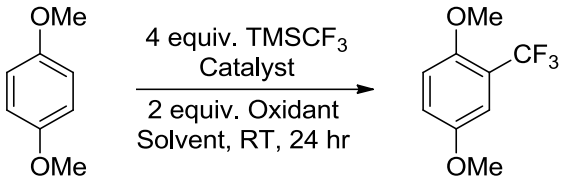
Although these silver-mediated reactions provided alternative approaches for direct trifluoromethylation of aromatic C–H bonds, the development of milder, and more importantly, catalytic reactions would be desirable. The redox catalysis of silver, comprising one electron steps between 0, +1, +2 and +3 oxidation states, has been scarcely exploited in synthesis relative to other late transition metals.[230] It was envisioned that the use of oxidative conditions could offer productive catalytic pathways for a silver-based trifluoromethylation.

To avoid the confusion of a mixture of regioisomers, the further optimisation studies were carried out using 1,4-dimethoxybenzene **442** as the substrate (Table 17).[231] For efficient screening of reaction conditions, yields were determined by ^{19}F NMR analysis

by using 4-fluoroanisole as the internal standard, and some of the isolated yields were compared for accuracy.

Beginning with the best results from the initial investigation in Table 16, the desired trifluoromethylated product **443** was obtained in 26% NMR yield (Entry 1). The reaction proved sensitive to solvent choice, with other common solvents producing no desired product (Entry 2). DMSO proved more effective than acetonitrile, probably due to better solubility of both silver and the hypervalent iodine oxidant in such a solvent, affording **443** in a 51% conversion (Entry 3). Fluoride was not a requirement, with silver(I) acetate and silver(I) carbonate being similarly effective (Entries 4-5). The reaction in the absence of any catalysts produced a low conversion to **443**, suggesting that iodobenzene diacetate alone is moderately effective (Entry 6). Other metal sources were also investigated, but were found to be counterproductive, resulting in poorer yields of **443** (Entries 7-9). Alternative oxidants were found to be less effective (Entries 10-12). The use of bis(*tert*-butylcarbonyloxy)iodobenzene gave a slightly lower yield (Entry 10), while bis(trifluoroacetoxy)iodobenzene dramatically decreased the yield (Entry 11). Potassium peroxydisulfate, an oxidant used in our silver-catalysed decarboxylative reactions,[193,203] produced only 20% of **443** (Entry 12). The reaction in the absence of any oxidants was inefficient in forming the CF_3 radical, with only the arene starting material **442** being recovered unreacted (Entry 13). The reaction could be slightly improved when the silver catalyst was slowly added into the stirring mixture of the rest of the reactants and reagents, instead of everything being mixed together at once (Entry 14). Crucially, catalytic amounts of silver(I) fluoride proved equally effective (Entries 15-19). The use of 25 mol% of the silver catalyst gave as good a result as the stoichiometric reaction (Entry 15). The yield drops to 46% when the loading of silver(I) fluoride is lowered to 10 mol% (Entry 16). Further loading of silver(I) fluoride and iodobenzene diacetate had only a little effect on the reaction, affording **443** in a 58% yield (Entry 17). It was also found that 2 equivalent of trimethyl(trifluoromethyl)silane was enough to achieve a good conversion (Entry 18). Finally, the use of the more stable triethyl(trifluoromethyl)silane reagent lead to a marginal improvement, giving **443** in a 60% yield (Entry 19).

Table 17 Optimisation studies of silver-catalysed aromatic C–H trifluoromethylation



442 **443**

Entry	Catalyst (equiv.)	Oxidant	Solvent	Yield (%)[a]
1	AgF (1.0)	$PhI(OAc)_2$	MeCN	26
2	AgF (1.0)	$PhI(OAc)_2$	Solvent[b]	0
3	AgF (1.0)	$PhI(OAc)_2$	DMSO	51
4	AgOAc (1.0)	$PhI(OAc)_2$	DMSO	44
5	Ag_2CO_3 (0.5)	$PhI(OAc)_2$	DMSO	48
6	-	$PhI(OAc)_2$	DMSO	26
7	CuI (1.0)	$PhI(OAc)_2$	DMSO	5
8	$ZnCl_2$ (1.0)	$PhI(OAc)_2$	DMSO	8
9	$FeCl_2$ (1.0)	$PhI(OAc)_2$	DMSO	11
10	AgF (1.0)	$PhI(OPiv)_2$	DMSO	41
11	AgF (1.0)	$PhI(TFA)_2$	DMSO	5
12	AgF (1.0)	$K_2S_2O_8$	DMSO	20
13	AgF (1.0)	-	DMSO	0
14[c]	AgF (1.0)	$PhI(OAc)_2$	DMSO	58
15[c]	AgF (0.25)	$PhI(OAc)_2$	DMSO	55
16[c]	AgF (0.1)	$PhI(OAc)_2$	DMSO	46
17[c,d]	AgF (0.25)	$PhI(OAc)_2$	DMSO	58
18[c,e]	AgF (0.25)	$PhI(OAc)_2$	DMSO	55 (58[f])
19[c,g]	AgF (0.25)	$PhI(OAc)_2$	DMSO	60

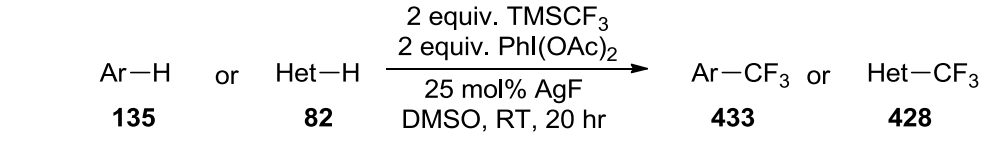
Reaction conditions: Performed on a 0.3 mmol scale in DMSO (1 ml). [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] THF, 1,4-dioxane, MeOH,

$(CF_3)_2CH_2OH$, DCE, DCM. [c] Slow addition of AgF to the stirring mixture of **442**, $TMSCF_3$ and $PhI(OAc)_2$ in DMSO. [d] Second addition of AgF (25 mol%) and $PhI(OAc)_2$ (2 equiv.) after 4 hr. [e] 2 equiv. of $TMSCF_3$. [f] Isolated yields. [g] $TESCF_3$ (2 equiv.) instead of $TMSCF_3$.

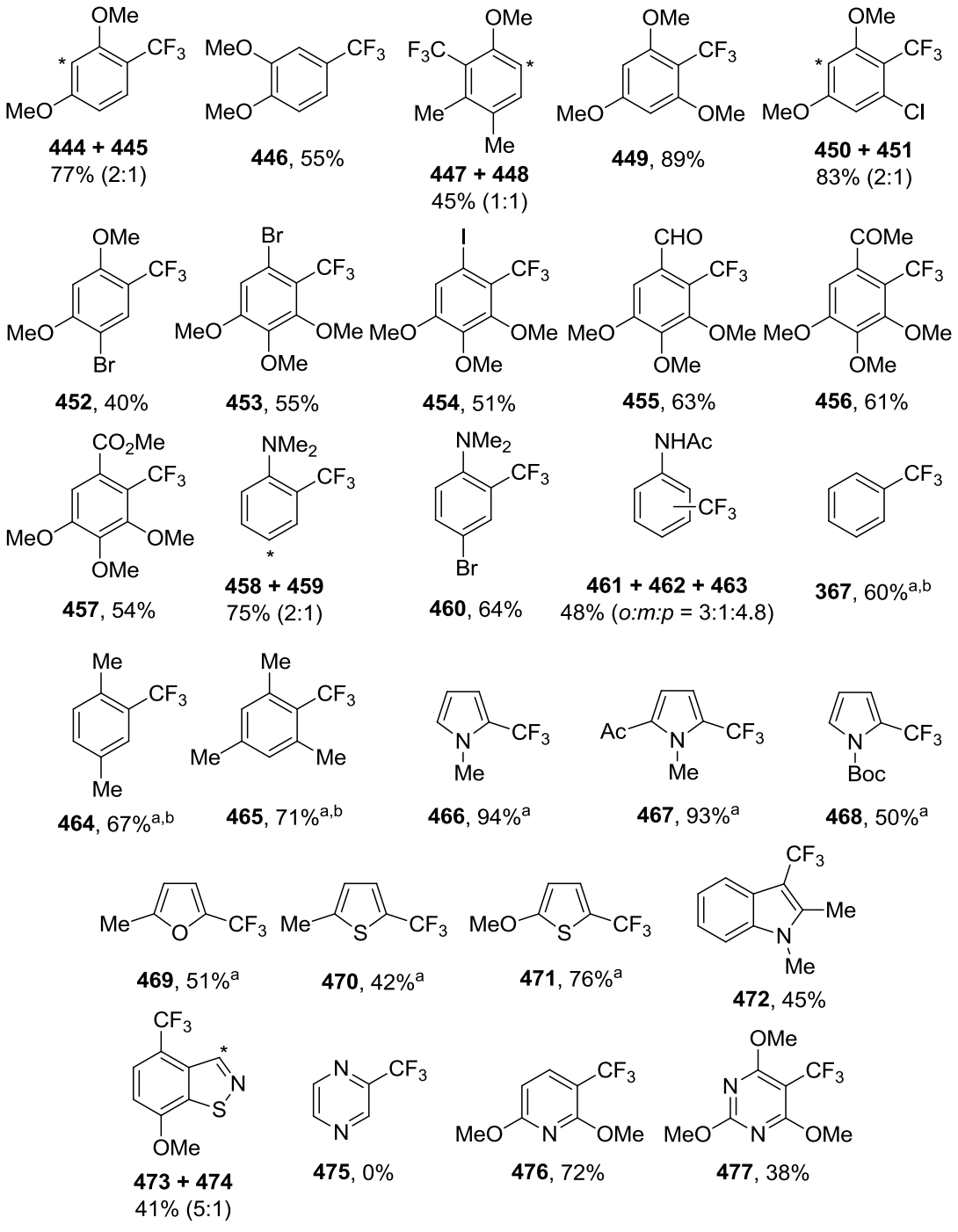
Substrate scope was then investigated under these optimised conditions. Although the best result was obtained through the use of $TESCF_3$ as the trifluoromethylating reagent, it was decided to continue with the cheaper $TMSCF_3$ reagent since the difference in yields was only marginal. The investigation of the reaction scope established that the procedure was effective for a variety of electron-rich arenes and heteroarenes with broad functional group tolerance (Table 18). Isomeric mixtures were generally observed for unsymmetrical substrates, with the electron-donating substituents generally *ortho*- and *para*-directing unless affected by steric hindrance. For example, trifluoromethylation of 1,3-dimethoxybenzene takes place at the 2- and 4-positions to afford a mixture of **445** and **444** respectively, leaving only the 5-position (*meta*-position) unreacted.

Methoxy and methyl groups were well-tolerated (**444**-**451**). More importantly, the reaction was compatible with halogen groups, illustrating an orthogonal reactivity to conventional C–X trifluoromethylations. The useful building blocks **450**, **451**, **452**, **453** and **454** were prepared in this fashion. Other functional groups such as aldehydes (**455**), ketones (**456**) and esters (**457**) were likewise tolerated. Dialkylanilines could also be trifluoromethylated under the silver-catalysed conditions. A slight preference for *ortho* over *para* selectivity was observed for simple dimethylaniline (**458**-**459**). The two positions are probably equally reactive, but the greater number of *ortho* positions gives a better chance for the substitution to take place at these sites. The bromo substituent at the 4-position was also tolerated, giving the *ortho*-trifluoromethylated isomer as a single product (**460**). The reaction of anilide resulted in a more complex mixture, producing all the possible regioisomers (**461**-**463**). The amide functionality is only moderately directing the *ortho*- and *para*-positions, thus allowing the *meta*-substituted product **462** to be formed to some extent. The steric effect of this functional group also influences product distributions, giving the *para*-substituted isomer **463** as the major product. The reaction was less effective for less electron-rich arenes such as benzene (**367**), *p*-xylene (**464**) and mesitylene (**465**), requiring an excess of the arene coupling partner and the raised reaction temperature (70 °C) for efficient reactions.

Table 18 Substrate scope investigation of silver-catalysed C–H trifluoromethylation.



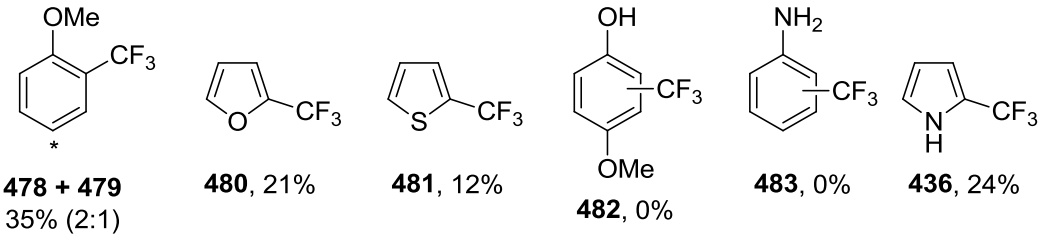
Ar—H or Het—H (**135**, **82**) → Ar—CF$_3$ or Het—CF$_3$ (**433**, **428**)



Reaction conditions: Performed on a 0.3 mmol scale in DMSO (1 ml); Isolated yields; For isomer mixtures, the minor regioisomeric positions are labeled with *. [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] Reaction conducted at 70 °C with 5-10 equiv. of arene.

The reaction could also be extended to electron-rich heteroarenes. *N*-Methyl pyrroles are particularly good substrates, affording exclusively the 2-trifluoromethylated products in excellent yields (**466**-**467**). The electron-withdrawing Boc group had a slightly negative effect on the reaction, resulting in a reduced yield of the desired product (**468**). Furans (**469**), thiophenes (**470**-**471**) and indoles (**472**) were all productive, indicating that the method is viable for the major classes of electron-rich heteroarenes. The regioselectivity of these substrates is governed by the electronics of the heteroarenes, with the most nucleophilic C2-positions generally undergoing preferential substitutions. The preferred selectivity can be altered with the introduction of electron-donating substituents. The trifluoromethylation of 7-methoxy-1,2-benzoisothiazole was favoured at the C4-position over C3 (**473**-**474**). Electron-deficient heteroarenes were not generally effective in this reaction (**475**), but could be efficiently captured by masking the azine nucleus with electron-donating groups (**476**-**477**).

Although a range of functional groups were well-tolerated, the reaction was found to be greatly influenced by electronic effects, requiring electron-donating substituents for efficient reactions. Removing methyl or methoxy substituents from otherwise effective substrates largely affected their reactivities and resulted in inefficient trifluoromethylation (Scheme 113). Anisole (**478**-**479**), furan (**480**) and thiophene (**481**) all gave much poorer results compared to their analogues bearing an additional electron-donating substituent. In addition, arenes substrates with protic functional groups (**482**-**483)** failed to undergo the trifluoromethylation, possibly because such functional groups accelerate the decomposition of $TMSCF_3$. Likewise, the reaction of *N*-H pyrrole (**436**) was found to be much less efficient than *N*-Me analogues.



478 + 479
35% (2:1)

480, 21%

481, 12%

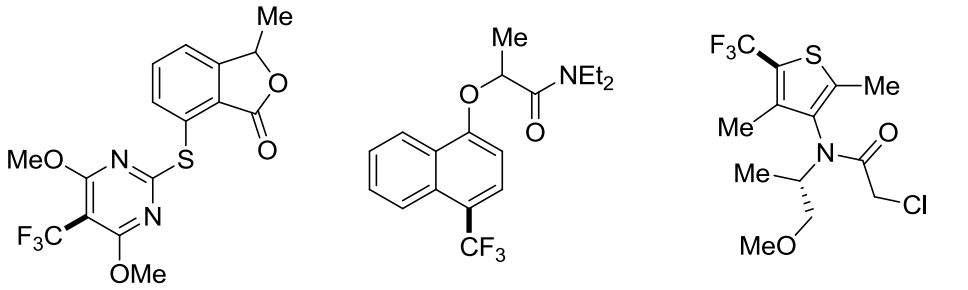
482, 0%

483, 0%

436, 24%

Scheme 113 Substrates that resulted in no or poor trifluoromethylation.

We next turned our attention to the trifluoromethylation of more complex biologically active molecules. Introduction of the CF_3 group at unactivated C–H positions represent a very versatile approach to fluorine incorporation for modulation of biological activity, demanding mild reaction conditions that are tolerant of functional groups and reasonable stoichiometries with respect to the C–H substrates. Accordingly, we extended the reaction to some complex molecules in the agrochemical field, an area where the CF_3 group is particularly prevalent. A number of agrochemicals provided by Syngenta were subjected to our silver-catalysed protocol, and it was found that selective trifluoromethylation could be achieved for the three commercial herbicides pyriftalid, napropamide and (S)-dimethenamid (Scheme 114). The CF_3 group was not incorporated into the isobenzofuranone ring in pyriftalid, indicating that the electron-donating effects of the methoxy groups wins to give the selective trifluoromethylation at the pyrimidine ring (**484**). The α-hydroxyamide functionality in napropamide was expected to be both *ortho*- and *para*-directing, but only the *para*-trifluoromethylated product **485** was obtained as a single isomer under our reaction conditions. This is probably due to the steric effect of the bulky substituent hindering the *ortho*-position. The electron-rich thiophene ring in (*S*)-dimethenamid was very reactive, affording the corresponding trifluoromethylated product **486** in 86% yield. Notably, the α-chloro-amide functionality, which is labile toward nucleophilic reagents under forcing conditions, was well-tolerated, illustrating the mildness of our reaction conditions.



484, 42%
CF_3-Pyriftalid

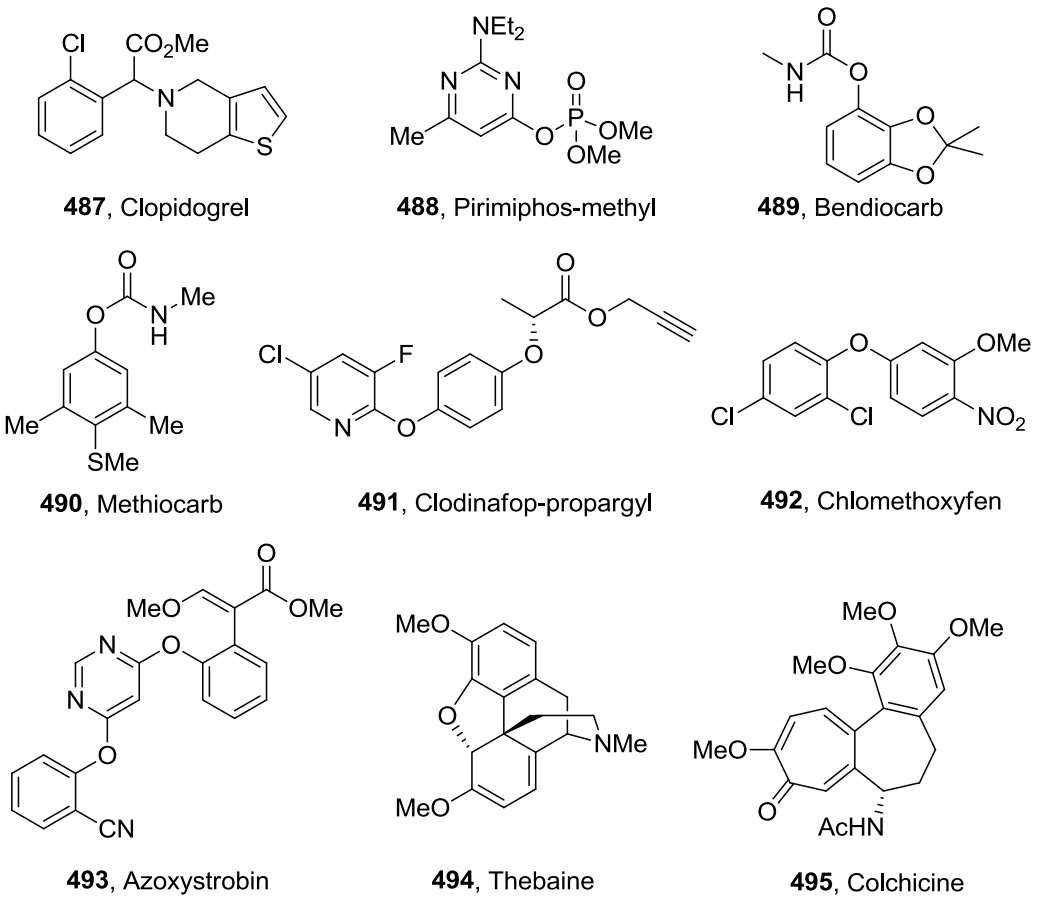
485, 51%
CF_3-Napropamide

486, 86%
CF_3-*(S)*-Dimethenamid

Scheme 114 Silver-catalysed trifluoromethylation of complex agrochemicals.

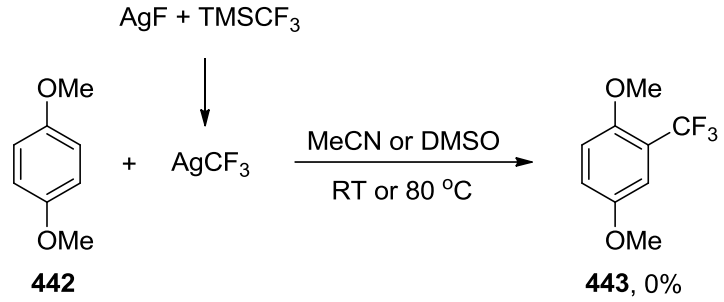
The reaction works at room temperature under air, does not require excessive stoichiometries of substrate or reagent, and is operationally simple to carry out. Therefore, this is an attractive protocol for the late-stage installation of the CF_3 group,

and the reaction with advanced intermediates should accelerate the discovery of new drugs. However, there are still some improvements to be made in terms of substrate scope if this method is to be used more generally for trifluoromethylation of large aromatic molecules. In addition to the above examples, a range of pharmaceuticals, agrochemicals and natural products were investigated (Scheme 115). Unfortunately, the reactions with these substrates failed to give the corresponding trifluoromethylated products, showing its limitations with certain functional groups and less electron-rich aromatic systems. α-Amino ester (**487**), phosphorothioate (**488**), protic amides (**489**,**490** and **495**) were incompatible under our reaction conditions. As seen in the examples of small molecules, those substrates with mildly electron-rich aromatic rings also resulted in no product formation (**491**-**494)**. Further optimisation would be required for an alternative system that could improve these limitations.



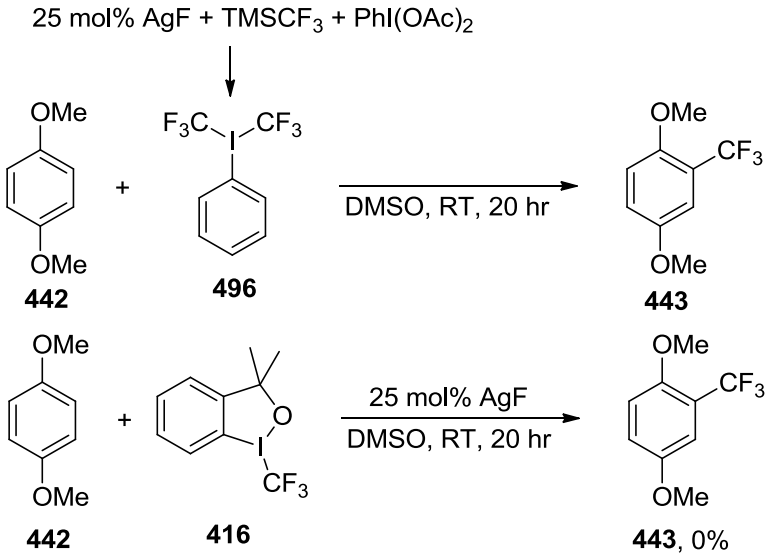
Scheme 115 Selected examples of complex substrates that resulted in no product formation.

Finally, the mechanism of the reaction was investigated, with four possible pathways being considered. First, although less likely, the possibility of C–H activation with $AgCF_3$ could not be excluded.[229] 1,4-Dimethoxybenzene **442** was treated with $AgCF_3$, which was prepared *in situ* according to literature,[228] but no reaction could be observed in both acetonitrile and DMSO as solvents even under thermal conditions (Scheme 116). This suggested that organometallic $AgCF_3$ intermediates are not participating under our reaction conditions.



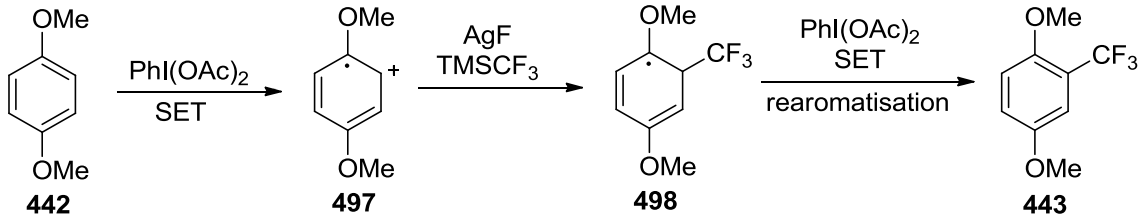
Scheme 116 Investigation of the trifluoromethylation *via* $AgCF_3$ intermediates.

Second, a simple electrophilic aromatic substitution pathway was studied (Scheme 117). It was thought that a Togni's reagent-like CF_3^+ intermediate **496** could be formed by substitution of the acetoxy group of $PhI(OAc)_2$ with CF_3^-, which could then participate in S_EAr of electron-rich arenes. However, the control experiment with Togni's reagent in both the presence and absence of AgF gave no reaction, ruling out the S_EAr pathway.



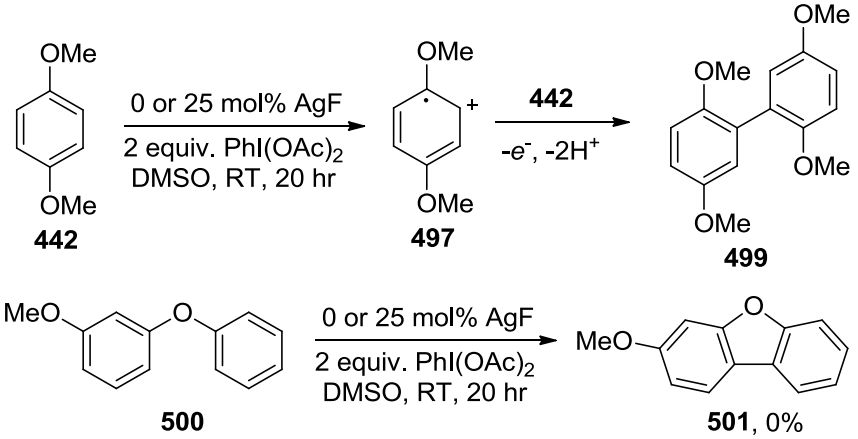
Scheme 117 Investigation of the trifluoromethylation *via* S_EAr.

Third, we considered the possibility of initial arene oxidation by $PhI(OAc)_2$, followed by CF_3^- addition to the cationic arene intermediate **497** (Scheme 118). Extensive work by Kita has demonstrated the C–H functionalisation of electron-rich arenes using $PhI(TFA)_2$ in the presence of stoichiometric $BF_3.OEt_2$ and nucleophiles, where the arene oxidation mechanism has been proposed.[232]



Scheme 118 Proposed mechanism for trifluoromethylation *via* initial arene oxidation followed by nucleophilic addition.

If this mechanism is in operation in our reaction, the electron-rich arene itself should react with the cationic arene intermediate to give homocoupling products. However, the control experiment in the absence of $TMSCF_3$ gave no reaction for both **442** and the tethered phenoxy substrate **500**, indicating that the present conditions using silver(I) fluoride and $PhI(OAc)_2$ are not sufficiently oxidising to enable the arene oxidation pathway (Scheme 119).

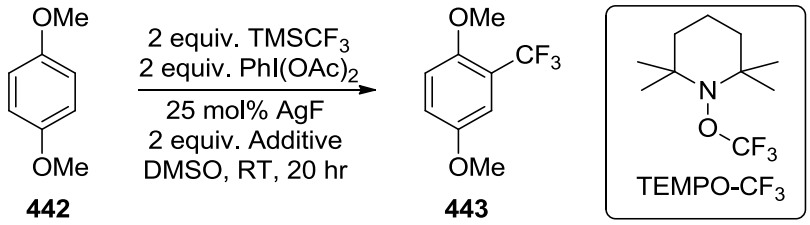


Scheme 119 Investigation of oxidative reactions in the absence of $TMSCF_3$.

Lastly, a marked preference of the reaction for electron-rich substrates indicated the likelihood of a radical pathway.[233,223] The CF_3 radical has an electrophilic nature due to the inductive effect of the electron-withdrawing fluorines. Consequently, it reacts better with electron-rich substrates and shows a similar selectivity pattern to S_EAr when

reacted with arenes. These are consistent with our results, where we showed that electron-donating substituents activate the *ortho*- and *para*-positions under the silver-catalysed conditions. The radical mechanism was further investigated by control experiments using TEMPO and galvinoxyl. The reaction shuts down using either radical scavenger (Table 19, Entries 1-2), and the TEMPO–CF_3 adduct was clearly observed in the crude ^{19}F NMR when TEMPO was used. This supports the intermediacy of the CF_3 radical, although the formation of TEMPO–CF_3 *via* oxidation of TEMPO[234] followed by nucleophilic addition of the CF_3 anion cannot be ruled out.

Table 19 Radical quenching of silver-catalysed trifluoromethylation of 1,4-methoxybenzene



442 **443**

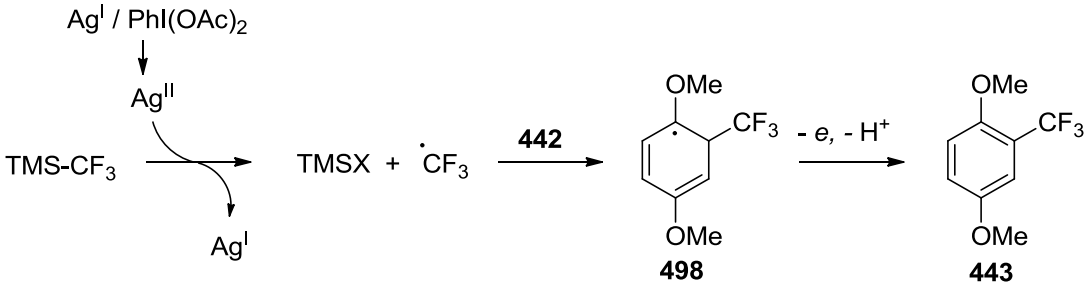
Entry	Additive	Product (%)[a]	TEMPO–CF_3 (%)[a]
1	TEMPO	<1	89
2	galvinoxyl	<1	-
3[b,c]	TEMPO	<1	<1
4[b,d]	TEMPO	<1	44
5[b]	AgF (0.25)	<1	91

Reaction conditions: Performed on a 0.3 mmol scale in DMSO (1 ml); [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] No addition of 1,4-dimethoxybenzene. [c] Stoichiometric AgF and no addition of $PhI(OAc)_2$. [d] No addition of AgF.

The role of the silver catalyst was then investigated in the absence of the arene coupling partner **442**. The mixture of silver(I) fluoride (1 equiv.), $TMSCF_3$ (1 equiv.) and TEMPO (1 equiv.) in DMSO at room temperature gave only trace quantities of TEMPO–CF_3 (Entry 3), indicating that Ag^I alone is insufficiently oxidising to generate the CF_3 radical. The hypervalent iodine oxidant alone was moderately effective, affording 44% of TEMPO–CF_3 (Entry 4). The combination of catalytic silver(I) fluoride

(25 mol%) and stoichiometric $PhI(OAc)_2$ (1 equiv.) was highly effective, giving 91% of TEMPO–CF_3 (Entry 5).

These results indicated that Ag^{II} may be involved in oxidation of $TMSCF_3$. The combination of Ag^{I} and $PhI(OAc)_2$ generates Ag^{II} *in situ*,[167] which may interact better with $TMSCF_3$ than $PhI(OAc)_2$ does on its own for the CF_3 radical generation. A possible radical mechanism is proposed accordingly, whereby $TMSCF_3$ is oxidised by Ag^{II} to the CF_3 radical, followed by $S_{Ar}H$ addition to **498**, then a second one electron oxidation and rearomatisation to give the product **443** (Scheme 120).



Scheme 120 A proposed mechanism for silver-catalysed radical trifluoromethylation.

While this trifluoromethylation work was under review for publication, Qing reported the hydrotrifluoromethylation of unactivated alkenes using similar silver-catalysed conditions (Ag^{I}/$PhI(OAc)_2$).[235] The author also proposed a mechanism that involves the CF_3 radical intermediate in this work, which is in accordance with our work.

4.1.3 Conclusions

In conclusion, a new silver-catalysed protocol has been developed which allows the C–H trifluoromethylation of a wide range of electron-rich arenes and heteroarenes under mild reaction conditions using relatively inexpensive $TMSCF_3$ as the CF_3 radical source. It has been found that the reaction is tolerant of many functional groups including halogens, showing an orthogonal reactivity to conventional C–X trifluoromethylations. Electronic effects play an important role, with additional substitution of electron-donating groups onto aromatic systems leading to dramatically improved results.

The reaction works at room temperature and is operationally simple to carry out. The value of this transformation has been further demonstrated by its successful reaction with complex agrochemical molecules, indicating that the protocol can be useful for late stage discovery approach. However, less electron-rich substrates and site selective direct trifluoromethylation remain challenging and merit further investigation.

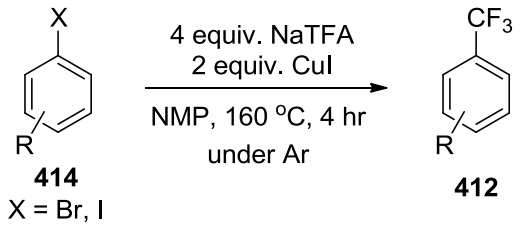
4.2 Copper-catalysed decarboxylative C–H trifluoromethylation of simple arenes using NaTFA as a trifluoromethylating reagent

4.2.1 Introduction and aims

As discussed in earlier sections, recent progress in transition metal-catalysed trifluoromethylation has allowed efficient, mild and simple methods for Ar–CF_3 bond formation using various CF_3 sources. A recurring problem is that most of those CF_3 sources are expensive for industrial applications. For example, $TMSCF_3$, the reagent employed in the previous chapter on silver-catalysed radical trifluoromethylation, is inexpensive compared to other CF_3^+ reagents and stable in air, making it one of the most widely used CF_3 reagents in normal laboratory reactions. This reagent, however, is not suitable for large scale reactions as it is still too expensive, generates undesired organosilyl waste, and requires ozone depleting chemicals in its preparation. The development of new protocols that use cheap and simple reagents is therefore desired for wider applications.

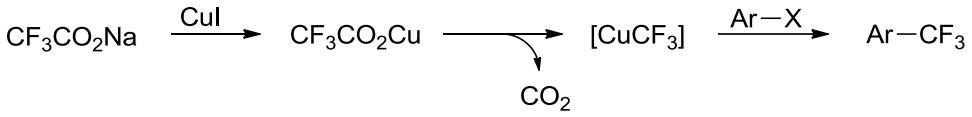
Fluoroform (CF_3H), a cheap and readily available reagent as a side product of Teflon manufacturing, is clearly the best feedstock in terms of atom economy. Grushin developed a novel method for the direct cupration of fluoroform, by treating it with copper (I) chloride and potassium *tert*-butoxide in DMF.[236] The resulting $CuCF_3$ solution can be stabilised with $[NEt_3][HF]_3$, and has since been utilised in numerous trifluoromethylation reactions of both aryl halides[236,237] and arylboronic acids.[238] Although a major step forward, the use of gaseous fluoroform is inconvenient for some applications.

A number of methods have been developed using cheap and easy to handle trifluoroacetate salts, or related derivatives, as alternative CF_3 reagents.[239] The CF_3 source from these reagents can be accessed by copper-mediated decarboxylative activation and the subsequent formation of a $CuCF_3$ species as the key intermediate. In 1981, Matsui *et al* reported the first copper-mediated decarboxylative trifluoromethylation of aryl halides **414** using sodium trifluoroacetate (NaTFA) (Scheme 121).[240] The mixture of the reagents in NMP was heated at 160 °C under an argon atmosphere to afford the trifluoromethylated products **412** in good yields. This reaction was carried out under moisture-free conditions in order to avoid the protodehalogenation of the starting halides **414** to the corresponding arene by-products. In this pioneering work, only a few examples were included with a limited number of functional groups.



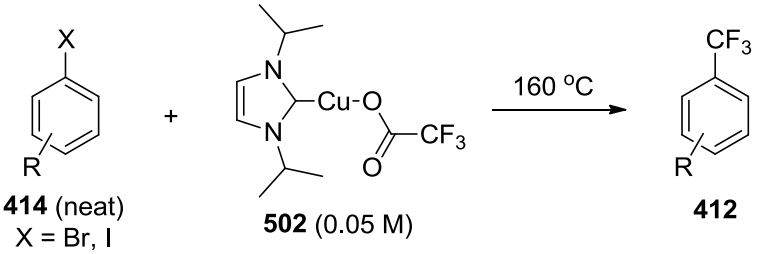
Scheme 121 The first example of Cu-mediated decarboxylative Ar–CF_3 bond formation using NaTFA as the CF_3 source.

In 1982, Suzuki applied the same conditions to the trifluoromethylation of polymethyliodobenzene using HMPA as solvent, but in rather poor yields.[241] A few years later, Chambers showed that a wider range of substrates including some heterocyclic halides could be trifluoromethylated using the original method.[242] The latter group also carried out mechanistic studies to propose that the reaction proceeds *via* S_NAr of *in situ* generated $CuCF_3$ on aryl halides (Scheme 122). Addition of coordinating ligands inhibited decarboxylation of sodium trifluoroacetate, indicating that initial formation of a copper carboxylate complex is crucial. Silver(I) iodide was found to promote the decarboxylation of trifluoroacetate as well, but the subsequent reaction with aryl halides does not take place.



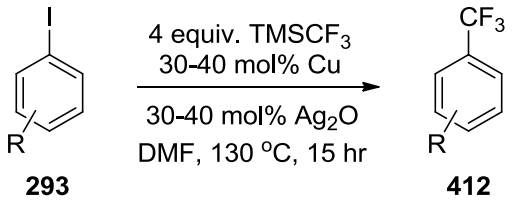
Scheme 122 Proposed mechanism for the Cu-mediated decarboxylative trifluoromethylation of aryl halides using NaTFA as the CF_3 source.

In 2010, Vicic reported the effect of *N*-heterocyclic carbene (NHC) ligands on decarboxylative trifluoromethylation.[243] A number of well-defined NHC-copper-trifluoroacetate complexes were reacted with neat excess aryl halides **414** to produce **412**, with [(Sl*i*Pr)Cu(TFA)] **502** giving the most efficient reaction among those tested (Scheme 123). The use of copper (I) iodide and sodium trifluoroacetate instead under these conditions resulted in no product formation, indicating that the [(NHC)Cu(TFA)] complexes outperform the ligandless copper system. However, this is only the case when the reaction is performed under solvent-free conditions. As found in previous studies, the ligandless CuI/NaTFA system in Lewis basic solvents lead to efficient trifluoromethylation, and the replacement with ligated complexes did not afford any improvement. The ligand systems could be useful where the use of polar solvents need to be avoided.



Scheme 123 The decarboxylative Ar–CF_3 bond formation using well-defined [(NHC)Cu(TFA)] complexes.

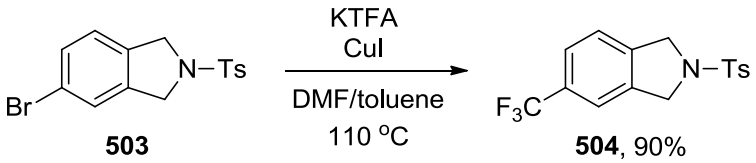
In 2011, Li and Duan reported a catalytic protocol for the decarboxylative trifluoromethylation of aryl iodides **293** (Scheme 124).[244] Using a bimetallic catalytic system of copper powder (30-40 mol%) and silver(I) oxide (30-40%), a wide range of aryl iodides **293** were trifluoromethylated to benzotrifluorides **412** at lower temperatures than previously reported.[240] Silver in this reaction may act not only as an oxidant for copper but also to facilitate the decarboxylation of trifluoroacetate,[107] allowing milder reaction conditions.



293 **412**

Scheme 124 Ag/Cu-catalysed Ar–CF_3 bond formation using NaTFA as the CF_3 source.

The copper-mediated decarboxylative trifluoromethylation has also found some applications in the synthesis of CF_3-containing intermediates for potential drug molecules.[239] The combination of sodium trifluoroacetate and copper(I) iodide has been utilised in most of these syntheses, including a large scale reaction of 1-iodo-2,5-dimethoxy-4-methylbenzene that afforded a 67% yield of the corresponding trifluoromethylated product.[245] This example shows that cheap trifluoroacetate reagents can be efficiently applied in large scale reactions. Potassium and ammonium trifluoroacetate salts have also been utilised as alternatives to the sodium salt, with some of these reactions taking place under milder conditions. Branch reported the interesting synthesis of novel 2,3-dihydro-1*H*-isoindoles as selective dopamine D_3 receptor compounds.[246] In this work, the author applied the copper-assisted decarboxylative trifluoromethylation method to obtain 5-trifluoromethyl derivative **504** from the bromide **503**, using potassium trifluoroacetate as the CF_3 source (Scheme 125). An excellent yield of **504** was achieved by heating the reaction mixture at only 110 ℃.

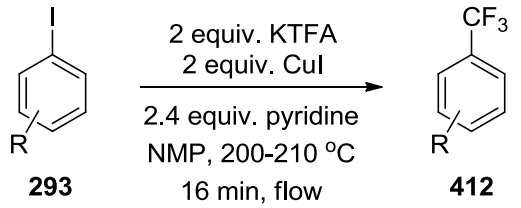


503 **504**, 90%

Scheme 125 The synthesis of 5-trifluoromethyl-2,3-dihydro-1*H*-isoindoles using KTFA as the CF_3 source.

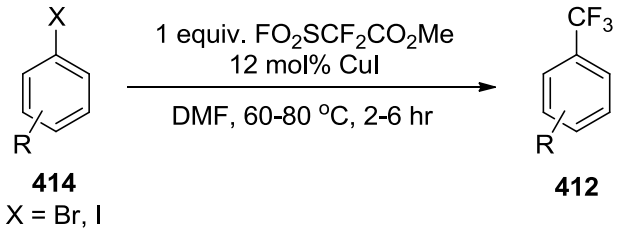
Very recently, Buchwald developed a simple and efficient technique to allow the decarboxylative trifluoromethylation in flow (Scheme 126).[247] Aryl iodides **293** were applied to the mixture of copper(I) iodide, pyridine and potassium trifluoroacetate in a flow reactor at 200-210 ℃ to afford **412** in excellent yields. This method tolerates a variety of functional groups, and requires very short reaction times to achieve full

conversion of **293**. Another advantage of flow chemistry involves the ease of scale up, and the robustness of this system was further demonstrated by its successful application in a large scale reaction (10 mmol).



Scheme 126 Cu-mediated decarboxylative Ar–CF_3 bond formation in flow.

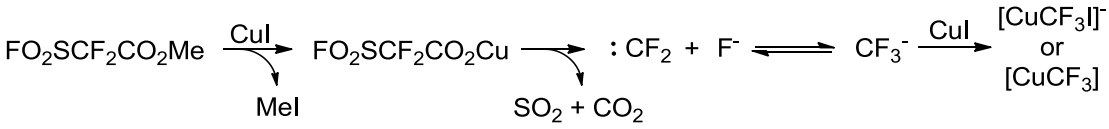
Besides trifluoroacetate salts, difluoromethyl- and trifluoromethyl-substituted carboxylic esters have also been found to generate $CuCF_3$ species under thermal conditions in the presence of copper, which could then be harnessed in trifluoromethylation reactions. In 1989, Chen reported a copper-mediated trifluoromethylation of aryl halides **414** using methyl fluorosulfonyldifluoroacetate (MFSDA) (Scheme 127).[248] Notably, this reaction requires only catalytic amounts of copper(I) iodide (12 mol%) and low reaction temperatures (60-80 °C) to obtain good yields of the trifluoromethylated products **412**. MFSDA is an air- and moisture-stable commercially available reagent that is easy to handle and also inexpensive, making this method attractive for some applications.



Scheme 127 Cu-catalysed Ar–CF_3 bond formation using methyl fluorosulfonyldifluoroacetate as the CF_3 source.

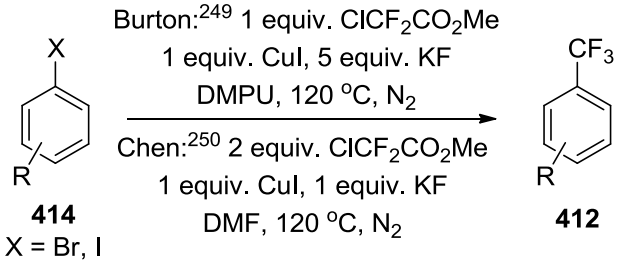
The formation of a difluorocarbene intermediate was proposed in this work (Scheme 128).[248] The Krapcho demethylation of MFSDA with copper(I) iodide and subsequent elimination of SO_2 and CO_2 would produce difluorocarbene and a fluoride ion, which are in equilibrium with the trifluoromethyl anion (CF_3^-). $CuCF_3$ complexes are readily

formed in the presence of CuI, thus shifting the equilibrium in the forward direction. The S_NAr of $CuCF_3$ on aryl halides **414** provides benzotrifluorides **412**.



Scheme 128 The formation of $CuCF_3$ from MFSDA.

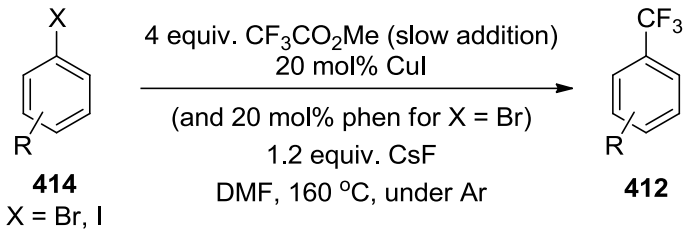
In 1991, the groups of Burton[249] and Chen[250] independently and simultaneously reported similar methods using cheaper methyl chlorodifluoroacetate (Scheme 129). These reactions were conducted on large scales (10-20 mmol) using reasonable stoichiometries of reagents, but required higher loadings of copper(I) iodide and higher reaction temperatures than that with MFSDA. Both groups also proposed mechanisms that involve *in situ* generation of $CuCF_3$ *via* a difluorocarbene intermediate. An external fluoride reagent was needed in these reactions to trap the carbene intermediate and form the trifluoromethyl anion source. Later in 1993, Chen extended the reaction to methyl bromo- and methyl iododifluoroacetates, showing that these reagents can also be used under similar conditions but at lower reaction temperatures (80-90 °C).[251]



Scheme 129 Cu-mediated Ar–CF_3 bond formation using methyl chlorodifluoroacetate as the CF_3 source.

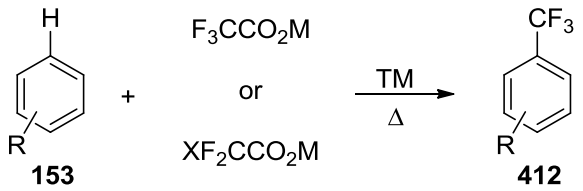
Recently in 2010, Langlois reported the first use of methyl trifluoroacetate (MTFA) as the CF_3 reagent for trifluoromethylation of aryl halides.[252] A number of benzotrifluorides were synthesised using MTFA (5 equiv.), copper(I) iodide (1 equiv.) and cesium fluoride (2.5 equiv.) either in DMF at 180 °C or in sulfolane at lower temperatures (140-180 °C), but only a few substrates were included in this work. A more practical catalytic method was reported by Beller in 2012 (Scheme 130).[253] A

variety of aryl halides **414** were successfully reacted with MTFA in the presence of catalytic copper(I) iodide (20 mol%) and stoichiometric cesium fluoride (1.2). A slow addition of MTFA was found to be critical for achieving a catalytic reaction. This controls the ratio of MTFA to catalytic copper in the reaction mixture, therefore not requiring a stoichiometric amount of copper to stabilise the *in situ* generated CF_3^-. Addition of cesium fluoride was required to initiate the reaction by demethylation, and 1,10-phenanthroline as a ligand for less reactive aryl bromides. This protocol could be practically useful because it uses a cheap trifluoromethylating reagent, shows a good functional group tolerance, and is applicable on large scale.



Scheme 130 Cu-catalysed Ar–CF_3 bond formation using methyl chlorodifluoroacetate as the CF_3 source.

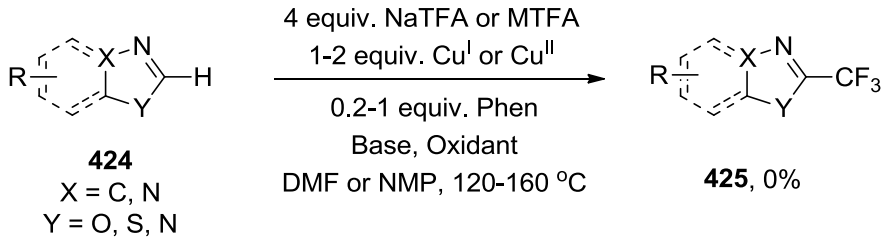
Despite the above developments, milder, more efficient, and more atom economical reactions would still be desirable. Trifluoroacetate salts and the related derivatives had been employed only in the reactions with aryl halides, and we were thus interested in investigating these CF_3 reagents in decarboxylative C–H trifluoromethylation reactions. The aim was to use the decarboxylative activation to form CF_3^- species *in situ* and design an optimal condition to react it selectively with aromatic C–H bonds (Scheme 131). This approach would benefit from the use of two cheap and readily available reactants.



Scheme 131 Ar–CF_3 bond formation *via* decarboxylative/C–H activations.

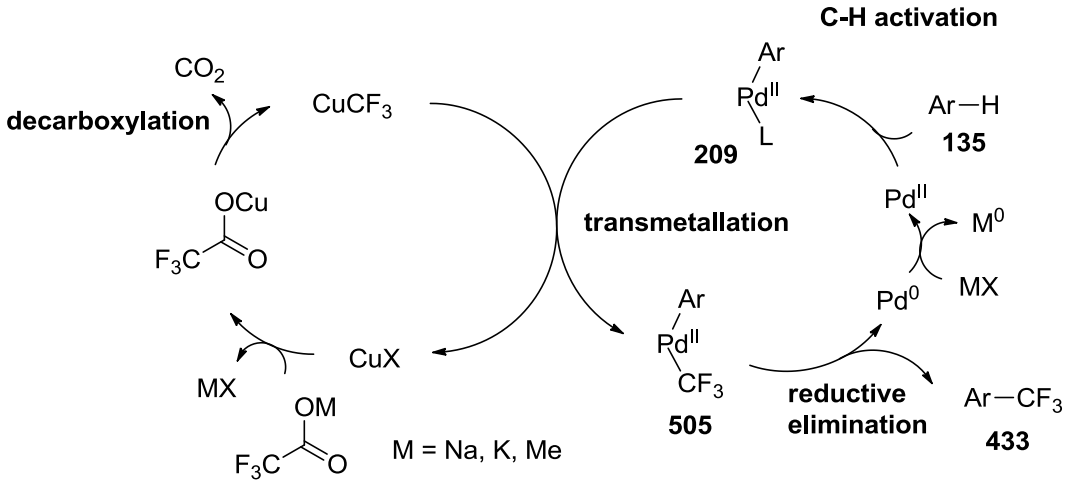
4.2.2 Results and discussion

The search for suitable conditions for decarboxylative C–H trifluoromethylation began with attempting to modify Qing's copper-catalysed conditions, which were reported to trifluoromethylate a variety of simple heteroarenes using $TMSCF_3$ as the CF_3 source (Scheme 106).[222] The key intermediate involved in this reaction is $CuCF_3$, which participates in a Cu^I/Cu^{III} catalytic cycle for the Ar–CF_3 formation. Since the formation of $CuCF_3$ from trifluoroacetate salts is also well-known from the above discussed reactions (Scheme 121-130), it was believed that $TMSCF_3$ in the copper-catalysed trifluoromethylation could be replaced with trifluoroacetate reagents and a suitable decarboxylation event. Using sodium or methyl trifluoroacetate, Qing's and a series of modified conditions were investigated on a number of heteroarenes **424** (Scheme 132). The decarboxylation of trifluoroacetates takes place at high temperatures (>110 °C), so more forcing conditions were applied. Common solvents for the decarboxylative trifluoromethylation (DMF and NMP) were employed and the copper catalyst, base, oxidant and temperature were varied.



Scheme 132 Attempts toward Cu-mediated decarboxylative C–H trifluoromethylation of simple heteroarenes.

Unfortunately, none of the investigated conditions gave the trifluoromethylated products **425**. The formation of fluoroform and consumption of trifluoroacetate were observed by crude ^{19}F NMR, indicating that the decarboxylation of trifluoroacetates does take place to some extent under the reaction conditions, although not as efficiently as expected. The subsequent C–CF_3 bond formation, however, does not occur nor homocoupling of **424**, suggesting that the coordination of copper to trifluoroacetates may reduce its activity towards the heteroaryl C–H bonds. This prompted us to consider an alternative strategy using bimetallic catalytic systems (Scheme 133).

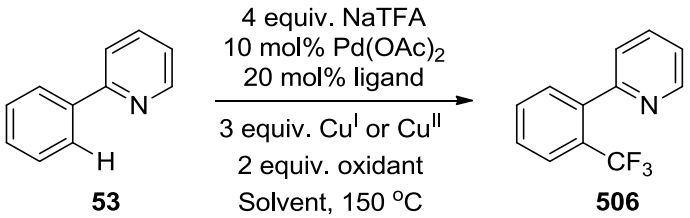


Scheme 133 Cu/Pd-Catalysed decarboxylative C–H trifluoromethylation.

Bimetallic systems have been widely utilised in decarboxylative/C–H activation reactions between aromatic carboxylic acids and simple arenes (section 1.3). In these reactions, the first metal mediates the decarboxylation step while the second metal is used as a catalyst for the C–H activation and C–C bond formation. It was thought that the decarboxylative C–H trifluoromethylation should also be achievable under similar conditions using copper for the activation of trifluoroacetates and palladium for the direct activation of aromatic C–H bonds and subsequent cross-coupling process. Using 2-phenylpyridine **53** as the substrate and sodium trifluoroacetate as the CF_3 source, a number of copper salts, ligands and oxidants were initially screened for the investigation of directing group assisted C–H trifluoromethylation (Table 20). Sodium trifluoroacetate was oven-dried at 100 °C prior to use since this led to much better decarboxylation. The reaction temperature was kept at 150 °C as lower temperatures gave poorer decarboxylation while higher temperatures did not lead to any improvement.

The conditions using copper(II) acetate were disappointing, with the variations of ligands (Entries 1-3) and oxidants (Entries 4-7) not affecting the reaction and giving no product formation. However, a very small amount of Ar–CF_3 species could be detected by ^{19}F NMR when copper(I) iodide was employed instead (Entry 8). The same NMR peak was also observed when performed in the absence of any oxidants (Entry 9). DMF proved slightly more effective, affording an improved NMR yield of the observed species (Entry 10). These results were encouraging, although the yields were negligible so that the product could not be isolated for identification.

Table 20 Initial optimisation studies of Cu/Pd-catalysed decarboxylative aromatic C–H trifluoromethylation using NaTFA as the CF_3 source



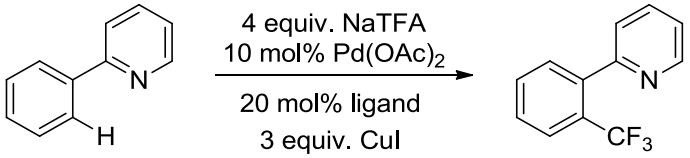
Entry	Cu	Ligand	Oxidant	Solvent	Yield (%)[a]
1	$Cu(OAc)_2$	Phen	$PhI(OAc)_2$	NMP	0
2	$Cu(OAc)_2$	PPh_3	$PhI(OAc)_2$	NMP	0
3	$Cu(OAc)_2$	dppe	$PhI(OAc)_2$	NMP	0
4	$Cu(OAc)_2$	dppe	$PhI(TFA)_2$	NMP	0
5	$Cu(OAc)_2$	dppe	selectfluor	NMP	0
6	$Cu(OAc)_2$	dppe	$Ce(SO_4)_2$	NMP	0
7	$Cu(OAc)_2$	dppe	$K_2S_2O_8$	NMP	0
8	CuI	dppe	$PhI(OAc)_2$	NMP	<1
9	CuI	dppe	-	NMP	<1
10	CuI	dppe	-	DMF	5

Reaction conditions: Performed on a 0.3 mmol scale in 2.5 ml of a chosen solvent; [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard.

We next conducted a further ligand screen using combinations of palladium (II) acetate (10 mol%) and copper(I) iodide (3 equiv.) (Table 21). A series of phosphine ligands were investigated since these have been successfully used in various palladium-catalysed trifluoromethylation reactions. It has been shown that these ligands are able to promote the unfavourable Ar–CF_3 bond forming reductive elimination step from the Pd^{II} centre.[254,216] However, poor yields were still obtained using these ligands despite the efficient decarboxylation of trifluoroacetate. Simple monodentate ligands were ineffective (Entries 1-2), as were chelating biphosphine ligands (Entries 3-5). Slightly better yields were obtained with some dialkylbiaryl phosphine ligands (Entries 6-11), but still less than when dppe ligand was used. Surprisingly, the reaction was more

efficient when performed in the absence of ligands (Entry 12), and even more so under palladium-free conditions (Entry 13). With the latter condition, the product was isolated and confirmed to be the *ortho*-trifluoromethylated arene **506**.

Table 21 Ligand screening of Cu/Pd-catalysed decarboxylative aromatic C–H trifluoromethylation using NaTFA as the CF_3 source

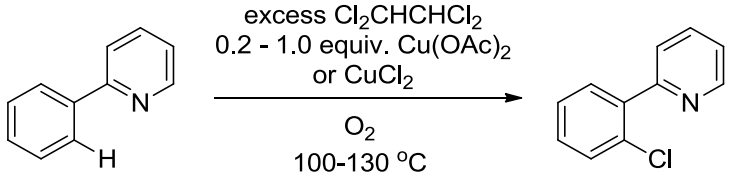


53 **506**

Entry	Pd	Ligand[a]	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	2
2	$Pd(OAc)_2$	PCy_3	<1
3	$Pd(OAc)_2$	dcpe	2
4	$Pd(OAc)_2$	dppf	0
5	$Pd(OAc)_2$	XantPhos	2
6	$Pd(OAc)_2$	*t*Bu-XPhos	4
7	$Pd(OAc)_2$	XPhos	4
8	$Pd(OAc)_2$	SPhos	3
9	$Pd(OAc)_2$	DavePhos	4
10	$Pd(OAc)_2$	BrettPhos	1
11	$Pd(OAc)_2$	Me_4-*t*Bu-XPhos	2
12	$Pd(OAc)_2$	-	7
13	-	-	11 (6[c])

Reaction conditions: Performed on a 0.3 mmol scale in DMF (2.5 ml). [a] See ligand list for the structures. [b] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [c] Isolated yield; the lower yield is due to the product loss during the purification, which arose from poor separation between the starting material and product on column chromatography.

In 2006, Yu reported the copper-mediated C–H functionalisation of 2-phenylpyridines with diverse nucleophiles (Scheme 134).[255] The *ortho*-selective functionalisation was achieved using only a copper catalyst and molecular oxygen as the oxidant in varying solvents. In this work, the author proposed that the reaction proceeds *via* a single electron transfer from the aryl ring to the coordinated copper species, which is followed by nucleophilic attack on the resulting radical cation. A similar mechanism may be in operation in our reaction, giving a better conversion in the absence of both palladium and ligands.

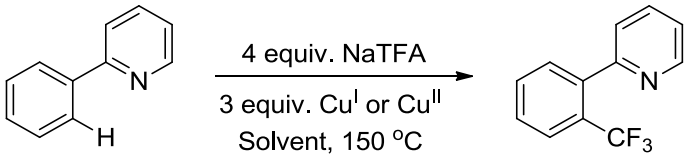


53 **507**

Scheme 134 Cu-catalysed C–H functionalisation with nucleophiles.

Although an additional transition metal catalyst and certain ligands may enhance the reaction through different pathways, it was decided to study copper-only systems for further optimisation (Table 22). A solvent screen was first conducted. The poor solubility of sodium trifluoroacetate in toluene, anisole, diglyme and dioxane was problematic, resulting in inefficient decarboxylation in such solvents (Entries 1-4). A mixture with an otherwise efficient DMF did not improve the reaction (Entry 5). Some common polar solvents produced the desired product **506**, but in lower yields (Entries 6-7) except in sulfolane (Entry 8) which gave the same result as in DMF. Further investigation was performed using DMF as the solvent since no better yields were obtained in any other solvents.

Table 22 Solvent screening of Cu-mediated decarboxylative aromatic C–H trifluoromethylation using NaTFA as the CF_3 source



53 **506**

Entry	Pd	Solvent	Yield (%)[a]
1	CuI	Toluene	0
2	CuI	Anisole	0
3	CuI	Diglyme	0
4	CuI	Dioxane	0
5	CuI	Dioxane/DMF (1:1)	0
6	CuI	DMSO	4
7	CuI	DMA	6
8	CuI	Sulfolane	11
9	CuCl	DMF	4
10	CuSCN	DMF	2
11	Cu_2O	DMF	0
12	CuF_2	DMF	0
13	$CuCl_2$	DMF	<1
14	$CuBr_2$	DMF	<1
15	$CuCO_3$	DMF	0
16	$Cu(OAc)_2$	DMF	<1
17	$Cu(OTf)_2$	DMF	0
18[b]	Cu/Ag_2O (1:1)	DMF	1

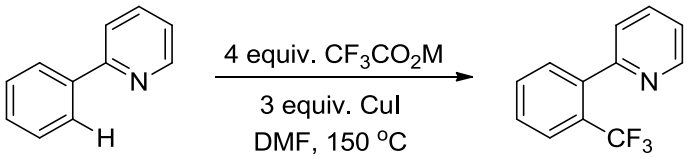
Reaction conditions: Performed on a 0.3 mmol scale in 2.5 ml of a chosen solvent; [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] Addition of 50 mol% each of Cu and Ag_2O.

The effects of copper(I) and copper(II) salts were next investigated. Unfortunately, the reaction proved almost specific to copper (I) iodide, with none of the other tested copper salts giving productive results. Efficient decarboxylation was achieved, but the subsequent coupling between $CuCF_3$ and the *ortho* C–H bond appeared to be poor. Copper(I) salts (Entries 9-11) generally afforded better yields of **506** than copper(II) salts (Entries 12-17). A combination of copper and silver was also investigated (Entry 18). This condition has been used in Duan's decarboxylative trifluoromethylation of aryl iodides (Scheme 124), where silver is believed to enhance the activity of the copper catalyst. However, this was not the case in our C–H activation reactions, with the use of copper bronze and silver (I) oxide still giving a poor yield of **506**.

Disappointing results in the solvent and copper screenings left us to consider the variation of trifluoroacetate source and the reaction concentration (Table 23). As discussed earlier, a number of other trifluoroacetate sources have also been employed in decarboxylative trifluoromethylation reactions. Besides those already reported in literature (Entries 1 and 6), other non-reported trifluoroacetate salts (Entries 2-5) were also investigated. However, the reaction proved specific to the sodium salt under the optimised conditions. Among those investigated, the potassium salt was the only one that underwent decarboxylation, but no trifluoromethylation with 2-phenylpyridine **53** took place (Entry 1). It was surprising to find that decarboxylation was not observed even with methyl trifluoroacetate (Entry 6).

The reaction concentration was found to affect the reaction significantly. A more dilute mixture in 3.5 ml of DMF decreased the yield of **506** to 7% (Entry 7) while this was dramatically increased to 23% in 1.0 ml DMF (Entry 8). A more concentrated mixture in 0.5 ml of DMF, however, gave a much poorer yield (Entry 9). This indicated that a concentrated mixture may be desirable for better reaction of $CuCF_3$ with the C–H bond, but not too concentrated due to the poor solubility of copper(I) iodide in DMF.

Table 23 Investigation of the trifluoroacetate source and the reaction concentration



53 **506**

Entry	TFA	DMF	Yield (%)[a]
1	KTFA	2.5 ml	0
2	CsTFA	2.5 ml	0
3[b]	$Cu(TFA)_2$	2.5 ml	0
4	$Zn(TFA)_2$	2.5 ml	0
5	$Pd(TFA)_2$	2.5 ml	0
6[c]	MTFA	2.5 ml	0
7	NaTFA	3.5 ml	7
8	NaTFA	1.0 ml	23
9	NaTFA	0.5 ml	5

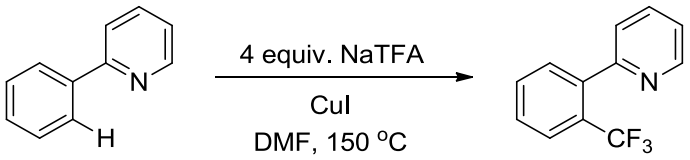
Reaction conditions: Performed on a 0.3 mmol scale; [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] No addition of CuI. [c] Addition of 1.2 equiv. of CsF.

Finally, the effects of the stoichiometry of copper(I) iodide and reaction atmospheres were investigated (Table 24). 2 equiv. of copper (I) iodide was found to be as efficient, giving 24% of the trifluoromethylated product **506** (Entry 1), but lowering the loading to 1 equiv. resulted in decrease in yields (Entry 2). An inert nitrogen atmosphere dramatically decreased the yield (Entry 3), and the use of 4Å molecular sieves completely shuts down the reaction (Entry 4). In addition, the control reaction using a non-dried DMF that contained a small amount of water still gave a similar result to when using an anhydrous solvent (Entry 5).

In the copper-mediated decarboxylative trifluoromethylation of aryl iodides previously reported by others (Schemes 121-130),[239] the reactions are performed under moisture-free inert atmospheres in order to avoid the protodehalogenation of the starting halides substrates. This is not the case for the decarboxylative trifluoromethylation of aromatic

C–H bonds, and it was thought that this oxidative transformation should be facilitated under oxidising conditions. However, the reaction under an oxygen atmosphere was not effective either (Entry 6). In the investigation of the copper source (Table 22), we found that Cu^{II} is much less efficient than Cu^{I} for this reaction. It may be that Cu^{I} is oxidised to Cu^{II} under an oxygen atmosphere, thus leading to a poor reaction. These results indicate that only certain levels of either oxygen or water, or both, are required for efficient reactions. Further investigations would be required to rationalise these observations.

Table 24 Investigation of the effects of the stoichiometry of CuI and the reaction under varying atmospheres



53 **506**

Entry	CuI (equiv.)	atm	Additives	Yield (%)[a]
1	2	air	-	24
2	1	air	-	15
3	2	N_2	-	11
4	2	N_2	M.S.	0
5[b]	2	N_2	-	20
6	2	O_2	-	5

Reaction conditions: Performed on a 0.3 mmol scale. [a] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [b] Use of non-dried DMF.

The decarboxylative C–H trifluoromethylation is an attractive approach towards the synthesis of benzotrifluorides. This chemistry offers many advantages in using cheap trifluoromethylating reagents and cheap aromatic compounds for $Ar–CF_3$ bond formation, and therefore, would be worth further development.

4.2.3 Conclusions

The decarboxylative C–H trifluoromethylation of simple arenes has been investigated using trifluoroacetate derivatives as the CF_3 source. A range of copper/palladium bimetallic and copper-only systems have been applied to aromatic substrates, and it has been found that 2-phenylpyridine can be trifluoromethylated selectively at the *ortho*-position. The current optimised conditions using copper(I) iodide and sodium trifluoroacetate in DMF lead to 24% of the desired trifluoromethylated product. Much work remains to be done to improve this reaction. Future work should involve the investigations of other C–H components and trifluoromethylating reagents using varied reaction conditions. A new protocol that allows the decarboxylation of trifluoroacetate derivatives under milder conditions should also be sought. Further development of this reaction should find an efficient method for the synthesis of benzotrifluorides.

5 Experimental

5.1 General Experimental

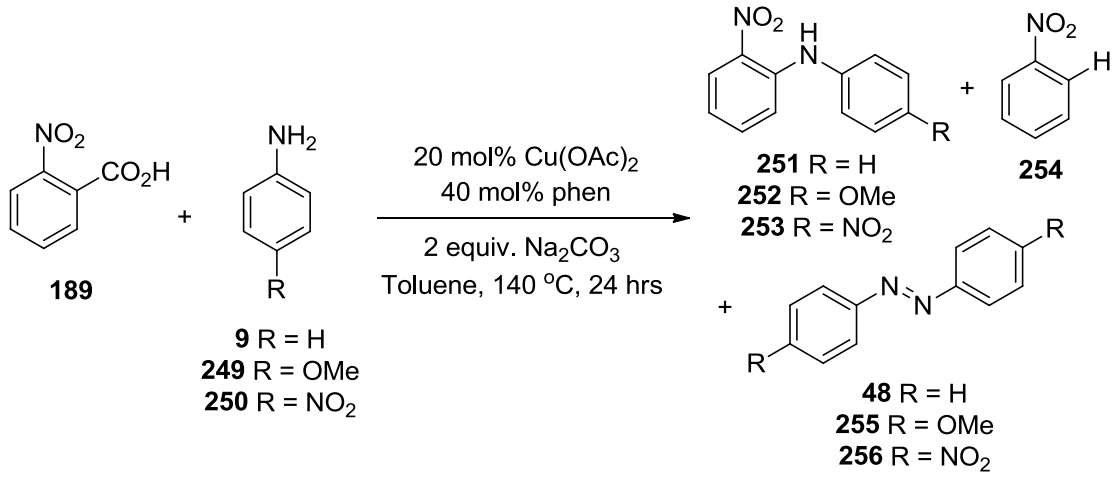
Melting points are uncorrected. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Brüker Ava400 (400 MHz) and Brüker Ava500 (500 MHz) instruments, with chemical shift values reported in ppm relative to residual solvent peaks: proton ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm) and carbon ($CDCl_3$: 77.0 ppm, DMSO-d_6: 39.5 ppm). Data for ^{1}H and ^{19}F NMR are presented as follows: chemical shift (in ppm on the δ scale), multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), the coupling constant (J, in Hertz) and integration. ^{13}C data are reported as the ppm on the δ scale followed by the interpretation and multiplicity where appropriate.

Microwave experiments were performed in a Biotage microwave initiator using sealed pressure-proof vials. Gas chromatography-mass spectrometry (GC/MS) was performed using Agilent 5975C Triple Axis GCMS (EI/CI). Electrospray and electron impact high resolution mass spectrometry was performed using Thermo Finnigan MAT95XP mass spectrometer. The data is recorded as the method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light and potassium permanganate stains. The compounds were purified by flash chromatography using Merck Kieselgel 60 (particle size 40-63 μm) silica under a positive pressure. The eluent is quoted as a percentage.

Anhydrous solvents and deuterated solvents were bought from Sigma-Aldrich and used as received. All other chemicals were purchased from a chemical supplier and used as received, unless otherwise stated.

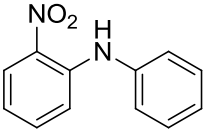
5.2 Experimental procedures for the decarboxylative C–N bond formation

General procedure for copper-catalysed intermolecular decarboxylative amination



An oven-dried reaction vial (5 mL) was charged with 2-nitrobenzoic acid **189** (75.2 mg, 0.45 mmol), anilines (0.3 mmol), copper(II) acetate (10.9 mg, 0.06 mmol), 1,10-phenanthroline, (21.6 mg, 0.12 mmol), sodium carbonate (63.6 mg, 0.6 mmol) and anhydrous toluene (3 mL). The mixture was heated at 140 ℃ for 24 hours, then allowed to cool down, diluted with EtOAc (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2) to yield the C–N bond forming product, and protodecarboxylation and diazo by-products.

2-Nitro-*N*-phenylaniline 251[256]

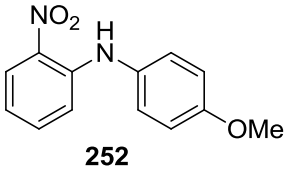


251

Prepared following the general procedure using aniline **9** (27.3 μl, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% DCM in hexane to afford **251** as an orange solid (Yield = 4%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (bs, NH), 8.21 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.29–

7.21 (m, 4H), 6.77 (t, J = 7.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8 (C), 138.4 (C), 135.6 (CH), 132.1 (C), 129.6 (CH), 126.4 (CH), 125.4 (CH), 124.2 (CH), 117.4 (CH), 116.0 (CH).

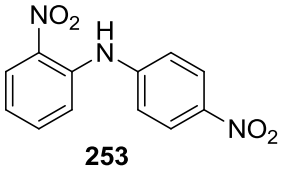
_N_-(4-Methoxyphenyl)-2-nitroaniline 252[257]



252

Prepared following the general procedure A using 4-methoxyaniline **249** (36.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% EtOAc in hexane to afford **252** as an orange solid (Yield = 9%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (bs, NH), 8.19 (dd, J = 8.6, 1.6 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.71 (ddd, J = 8.6, 7.0, 1.3 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 (C), 144.5 (C), 135.7 (CH), 132.4 (C), 131.2 (C), 127.0 (CH), 126.6 (CH), 116.8 (CH), 115.6 (CH), 114.9 (CH), 55.5 (CH_3).

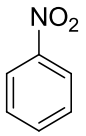
2-Nitro-_N_-(4-nitrophenyl)aniline 253



253

Prepared following the general procedure A using 4-nitroaniline **250** (41.4 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 50% DCM in hexane to afford **253** as an orange solid (Yield = 3%); Mp = 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (bs, NH), 8.27–8.23 (m, 1H), 8.26 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 3.7 Hz, 2H), 7.34 (d, J = 9.1 Hz, 2H), 7.06–7.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8 (C), 143.1 (C), 138.8 (C), 136.1 (C), 135.7 (CH), 126.9 (CH), 125.8 (CH), 120.8 (CH), 119.9 (CH), 117.9 (CH); IR (neat): 3325, 1614, 1589, 1574, 1498, 1433, 1355, 1247, 1160 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{12}H_{10}O_4N_3$: 260.0666, found: 260.0662.

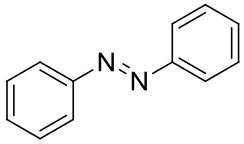
Nitrobenzene 254[118]



254

Isolated as the major by-products following the general procedure A using anilines (0.3 mmol). The reaction mixture was purified by flash chromatography to afford **254** as a yellow oil (Yield = 16-19%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25–8.23 (m, 2H), 7.73–7.68 (m, 1H), 7.58–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0 (C), 134.4 (CH), 129.2 (CH), 123.3 (CH).

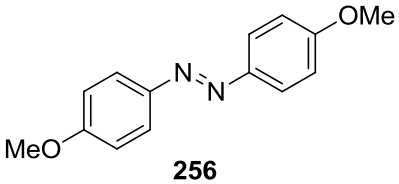
1,2-Diphenyldiazene 255[162]



255

Isolated as a by-product following the general procedure A using aniline **9** (27.3 µl, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% DCM in hexane to afford **255** as a yellow oil (Yield = 2%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.88 (m, 4H), 7.51–7.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 130.9 (CH), 129.1 (CH), 122.8 (CH).

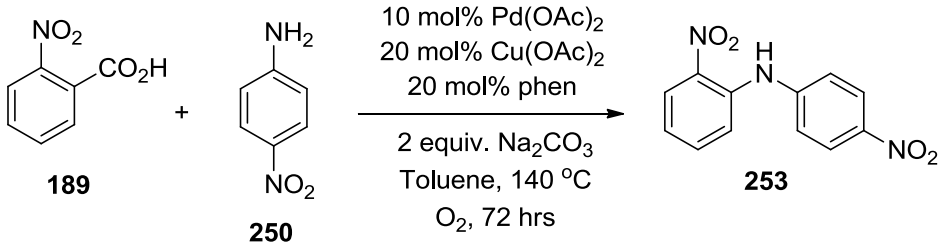
1,2-Bis(4-methoxyphenyl)diazene 256[162]



256

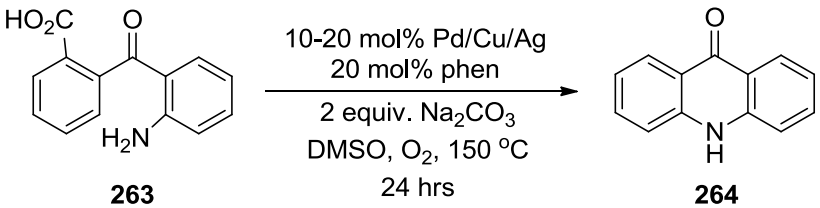
Isolated as a by-product following the general procedure A using 4-methoxyaniline **249** (36.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% EtOAc in hexane to afford **256** as an orange solid (Yield = 9%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 9.0 Hz, 4H), 7.00 (d, J = 9.0 Hz, 4H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6 (C), 147.1 (C), 124.3 (CH), 114.2 (CH), 55.6 (CH_3).

General procedure for copper/palladium-catalysed intermolecular decarboxylative amination



An oven-dried reaction vial (5 mL) was charged with 2-nitrobenzoic acid **189** (75.2 mg, 0.45 mmol), 4-nitroaniline **250** (41.4 mg, 0.3 mmol), palladium(II) acetate (6.7 mg, 0.03 mmol), copper(II) acetate (10.9 mg, 0.06 mmol), 1,10-phenanthroline, (10.8 mg, 0.06 mmol), sodium carbonate (63.6 mg, 0.6 mmol). The reaction vial was sealed and purged with 3 cycles of oxygen gas, and was then left under oxygen atmosphere (balloon). Anhydrous toluene (3 mL) was added and the mixture was heated at 140 ℃ for 72 hours, then allowed to cool down, diluted with EtOAc (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography using 50% DCM in hexane to afford **253** as an orange solid (Yield = 30%). The NMR data were consistent with the above result.

General procedure for copper/silver/palladium-catalysed intramolecular decarboxylative amination



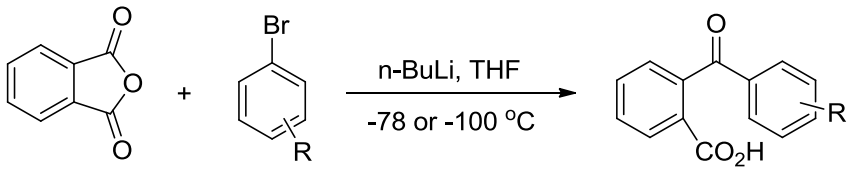
An oven-dried reaction vial (5 mL) was charged with 2-(2'-aminobenzoyl)benzoic acid **263** (72.3 mg, 0.3 mmol), palladium(II) acetate (6.7 mg, 0.03 mmol), copper(II) acetate (10.9 mg, 0.06 mmol), silver(I) carbonate (16.5 mg, 0.06 mmol) 1,10-phenanthroline,

(10.8 mg, 0.06 mmol), sodium carbonate (63.6 mg, 0.6 mmol). The reaction vial was sealed and purged with 3 cycles of oxygen gas, and was then left under oxygen atmosphere (balloon). Anhydrous DMSO (3 mL) was added and the mixture was heated at 150 °C for 24 hours, then allowed to cool down, diluted with EtOAc (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography using 20% EtOAc in hexane to afford **264** as a yellow solid (Yield = 83%);[258] ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.74 (bs, NH), 8.24 (dd, J = 8.1, 1.3 Hz, 2H), 7.76–7.72 (m, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.29–7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3 (CO), 141.3, 134.0, 126.5, 121.4, 121.0, 117.8.

5.3 Experimental procedures for the decarboxylative radical arylation

5.3.1 Decarboxylative Pschorr reaction

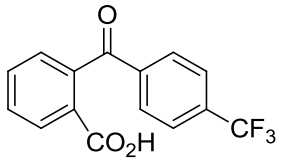
General procedure for the preparation of starting materials:



322 **323** **311**

Benzoic acids **314**, **327**, **329**, **333**, **346,** and **350** were purchased from commercial suppliers. All other starting materials were prepared according to the literature procedure of Parham and Piccirilli.[197] Aryllithium derivatives were prepared at -78 °C, or at -100 °C for those substrates containing nitro substituents (**352** and **354**).

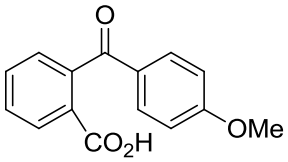
2-(4-Trifluoromethylbenzoyl)benzoic acid 331



331

White Solid (Recrystallised from $CHCl_3$); Yield = 46%; Mp = 186–188 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.63 (br s, 1 CO_2H), 8.03 (d, J = 7.4 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.78 (td, J = 7.6, 1.2 Hz, 1H), 7.71 (td, J = 7.6, 1.2 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.6 (CO), 166.8 (CO_2H), 140.8 (C), 140.2 (C), 132.8 (CH), 132.3 (q, J_{C-F} = 26.8 Hz, C), 130.2 (CH), 129.9 (CH), 129.7 (C), 129.4 (2CH), 127.5 (CH), 125.7 (q, J_{C-F} = 3.6 Hz, 2CH), 123.8 (q, J_{C-F} = 272.4 Hz, CF_3); IR (neat): 2838, 2556, 1674, 1595, 1427, 1319, 1308, 1159, 1122 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{15}H_{10}O_3F_3$: 295.0577, found: 295.0577.

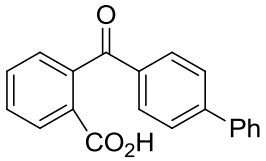
2-(4-Methoxybenzoyl)benzoic acid 335



335

White Solid (Recrystallised from MeCN); Yield = 52%; Mp = 148–150 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.12 (br s, 1 CO_2H), 7.98 (dd, J = 7.8, 0.9 Hz, 1H), 7.70 (td, J = 7.5, 1.3 Hz, 1H), 7.63 (td, J=7.6, 1.3 Hz, 1H), 7.59 (d, J=8.8 Hz, 2H), 7.37 (dd, J=7.5, 0.9 Hz, 1H), 7.02 (d, J=8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.0 (CO), 166.9 (CO_2H), 163.1 (C), 141.7 (C), 132.3 (CH), 131.3 (2CH), 129.9 (C), 129.8 (C), 129.7 (CH), 129.5 (CH), 127.3 (CH), 113.9 (2CH), 55.5 (CH_3); IR (neat): 2980, 1683, 1662, 1596, 1454, 1281, 1253, 1168, 1147 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{15}H_{13}O_4$: 257.0809, found: 257.0800.

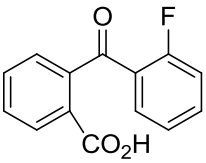
2-([1,1'-Biphenyl]-4-carbonyl)benzoic acid 337



337

White Solid (Recrystallised from $CHCl_3$); Yield = 57%; Mp = 230–231 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.27 (br s, 1 CO_2H), 8.03 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 8.3, 1.2 Hz, 2H), 7.76 – 7.66 (m, 6H), 7.49 (t, J = 7.5 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.0 (CO), 166.9 (CO_2H), 144.5 (C), 141.4 (C), 138.9 (C), 135.7 (C), 132.5 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.1 (CH), 128.4 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH); IR (neat): 2834, 1689, 1670, 1597, 1312, 1282, 1258, 1165, 1148 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{20}H_{15}O_3$: 303.1016, found: 303.1019.

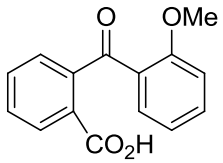
2-(2-Fluorobenzoyl)benzoic acid 339



339

White Solid (Recrystallised from $CHCl_3$); Yield = 51%; Mp = 136–138 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.27 (br s, 1 CO_2H), 7.94 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.66 – 7.62 (m, 3H), 7.43 (dd, J = 7.6, 0.9 Hz, 1H), 7.32 (td, J = 7.6, 0.9 Hz, 1H), 7.26 (t, J = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.2 (CO), 167.1 (CO_2H), 160.9 (d, J_{C-F} = 256.2 Hz, C-F), 143.0 (C), 135.1 (d, J_{C-F} = 7.9 Hz, CH), 132.4 (CH), 131.0 (CH), 129.9 (CH), 129.6 (CH), 129.4 (C), 126.9 (CH), 125.4 (d, J_{C-F} = 8.6 Hz, C), 124.5 (d, J_{C-F} = 3.2 Hz, CH), 116.7 (d, J_{C-F} = 22.1 Hz, CH); IR (neat): 2838, 1694, 1668, 1608, 1482, 1455, 1321, 1296, 1214, 1159, 1152 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{14}H_{10}O_3F$: 245.0609, found: 245.0601.

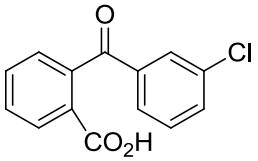
2-(2-Methoxybenzoyl)benzoic acid 341



341

White Solid (Recrystallised from MeCN); Yield = 65%; Mp = 146–147 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.00 (br s, 1 CO_2H), 7.85 (dd, J = 7.6, 1.0 Hz, 1H), 7.63 – 7.54 (m, 4H), 7.28 (dd, J = 7.6, 1.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.0 (CO), 167.6 (CO_2H), 158.8 (C), 144.1 (C), 134.3 (CH), 131.6 (CH), 130.9 (CH), 130.0 (C), 129.2 (CH), 129.0 (CH), 126.8 (CH), 126.5 (C), 120.3 (CH), 112.9 (CH), 55.6 (CH_3); IR (neat): 3333, 1729, 1603, 1466, 1286, 1253, 1225, 1200, 1124 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{15}H_{13}O_4$: 257.0809, found: 257.0798.

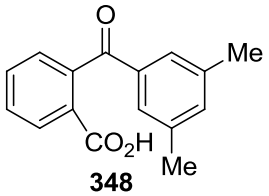
2-(3-Chlorobenzoyl)benzoic acid 343



343

White Solid (Recrystallised from MeCN); Yield = 55%; Mp = 166–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.33 (br s, 1 CO_2H), 8.01 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.6, 1.2 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.68 (td, J = 7.6, 1.2 Hz, 1H), 7.61 (s, 1H), 7.54 – 7.46 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.2 (CO), 166.8 (CO_2H), 140.6 (C), 138.8 (C), 133.5 (C), 132.8 (CH), 132.7 (CH), 130.8 (CH), 130.1 (CH), 129.8 (CH), 129.7 (C), 127.8 (CH), 127.6 (CH), 127.4 (CH); IR (neat): 2838, 1672, 1593, 1571, 1287, 1247, 1164, 1148 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{14}H_{10}O_3Cl$: 261.0313, found: 261.0313.

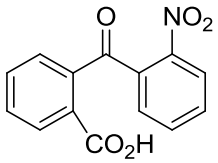
2-(3,5-Dimethylbenzoyl)benzoic acid 348



348

White Solid (Recrystallised from $CHCl_3$); Yield = 60%; Mp = 178–180 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.16 (br s, 1 CO_2H), 7.98 (d, J = 7.5 Hz, 1H), 7.71 (td, J = 7.2, 1.2 Hz, 1H), 7.64 (td, J = 7.5, 1.3 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.25 (s, 1H), 7.24 (s, 2H), 2.27 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.5 (CO), 166.9 (CO_2H), 141.6 (C), 137.8 (C), 137.0 (C), 134.5 (CH), 132.3 (CH), 129.9 (C), 129.7 (CH), 129.6 (CH), 127.4 (CH), 126.6 (CH), 20.7 (CH_3); IR (neat): 3509, 3419, 2919, 1682, 1657, 1595, 1312, 1263, 1232, 1166, 1148 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{16}H_{15}O_3$: 255.1016, found: 255.1018.

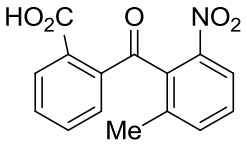
2-(2-Nitrobenzoyl)benzoic acid 352



352

White Solid (Recrystallised from $CHCl_3$); Yield = 37%; Mp = 174–176 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.33 (br s, 1 CO_2H), 8.07 (d, J = 7.8 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.78 (td, J = 7.4, 0.9 Hz, 1H), 7.71 (td, J = 7.5, 1.3 Hz, 1H), 7.67 (td, J = 7.4, 0.9 Hz, 1H), 7.51 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.2 (CO), 168.1 (CO_2H), 148.1 (C), 137.5 (C), 133.0 (CH), 132.9 (CH), 132.5 (C), 132.1 (C), 131.8 (CH), 131.4 (CH), 130.7 (CH), 129.3 (CH), 129.1 (CH), 124.3 (CH); IR (neat): 2863, 1695, 1680, 1532, 1520, 1346, 1297, 1273, 1159, 1143 cm^{-1}; HRMS (ES$^+$) cald. for $(M+H)^+$ $C_{14}H_{10}NO_5$: 272.0554, found: 272.0553.

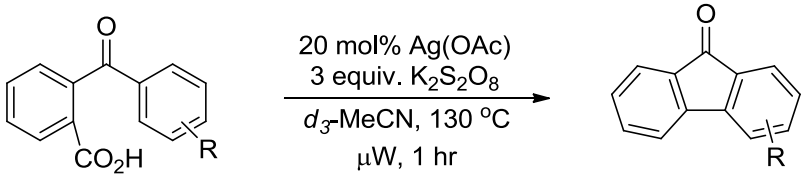
2-(2-Methyl-6-nitrobenzoyl)benzoic acid 354



354

White Solid (Recrystallised from $CHCl_3$); Yield = 33%; Mp = 218–220 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.23 (br s, 1 CO_2H), 8.12 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.71 (td, J = 7.4, 1.3 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.62 (dd, J = 7.6, 1.0 Hz, 1H), 7.54 (td, J = 7.5, 1.2 Hz, 1H), 7.49 (dd, J = 7.8, 1.0 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.3 (CO), 170.1 (CO_2H), 146.7 (C), 137.4 (C), 136.9 (CH), 135.2 (C), 134.0 (C), 133.6 (C), 133.5 (CH), 130.6 (CH), 130.0 (CH), 128.1 (CH), 122.4 (CH), 18.7 (CH_3); IR (neat): 2870, 1708, 1680, 1596, 1532, 1383, 1350, 1299, 1264, 1248 cm^{-1}; HRMS (ES^+) cald. for $(M+H)^+$ $C_{15}H_{12}NO_5$: 286.0710, found: 286.0711.

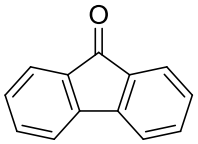
General procedure for decarboxylative Pschorr reaction:



311 **312**

A septum-sealed microwave tube (5 mL) charged with compound **311** (0.3 mmol), silver(I) acetate (10.0 mg, 0.06 mmol) and potassium peroxydisulfate (243.3 mg, 0.9 mmol) in deuterated-acetonitrile (2 mL) was irradiated in a microwave reactor at 130 °C for 1 hour. The reaction mixture was allowed to cool down, diluted with Et_2O (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2, Et_2O/Hexane: 5–40 %) to yield the product **312** as a yellow or pale yellow solid.

Fluoren-9-one 63[259]

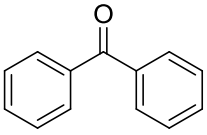


63

Prepared following the general procedure using 2-benzoylbenzoic acid **314** (67.8 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% Et_2O in hexane to afford **63** as a yellow solid (Yield = 76%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 7.4 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.30 (td, J = 7.2, 1.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9 (CO), 144.3 (C), 134.6 (CH), 134.0 (C), 129.0 (CH), 124.2 (CH), 120.2 (CH).

63 was also prepared as a result of decarboxylation/denitration C–C coupling, using 2-(2-nitrobenzyl)benzoic acid **352** (Yield = 25%). The NMR data were consistent with the above.

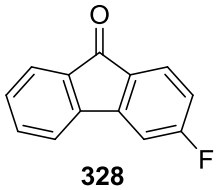
Benzophenone 318[260]



318

Isolated as a by-product during the optimisation studies using 2-benzoylbenzoic acid **314** (67.8 mg, 0.3 mmol) and acetonitrile as the solvent. The reaction mixture was purified by flash chromatography using 20% Et_2O in hexane to afford **318** as a white solid (Yield = 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.79 (m, 4H), 7.62–7.57 (m, 2H), 7.51–7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7 (CO), 137.5 (C), 132.4 (CH), 130.0 (CH), 128.2 (CH).

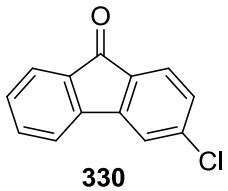
3-Fluorofluoren-9-one 328[259]



328

Prepared following the general procedure using 2-(4-fluorobenzoyl)benzoic acid **327** (73.3 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **328** as a pale yellow solid (Yield = 70%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67–7.65 (m, 2H), 7.53–7.49 (m, 2H), 7.34 (td, J = 6.9, 1.9 Hz, 1H), 7.20 (dd, J = 8.3, 2.2 Hz, 1H), 6.95 (td, J = 8.6, 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1 (CO), 167.3 (d, J_{C-F} = 255.6 Hz, C-F), 147.5 (d, J_{C-F} = 9.9 Hz, C), 142.8 (d, J_{C-F} = 2.3 Hz, C), 134.7 (CH), 134.6 (C), 130.2 (d, J_{C-F} = 2.7 Hz, C), 129.8 (CH), 126.5 (d, J_{C-F} = 10.1 Hz, CH), 124.3 (CH), 120.6 (CH), 115.5 (d, J_{C-F} = 23.2 Hz, CH), 108.4 (d, J_{C-F} = 24.4 Hz, CH).

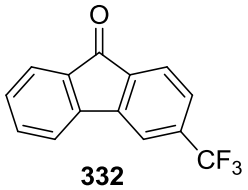
3-Chlorofluoren-9-one 330[259]



330

Prepared following the general procedure using 2-(4-chlorobenzoyl)benzoic acid **329** (78.2 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in hexane to afford **330** as a yellow solid (Yield = 84%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.52–7.50 (m, 3H), 7.37–7.32 (m, 1H), 7.27 (dd, J = 7.9, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5 (CO), 146.1 (C), 143.1 (C), 141.0 (C), 134.9 (CH), 134.4 (C), 132.4 (C), 129.8 (CH), 129.0 (CH), 125.4 (CH), 124.6 (CH), 121.0 (CH), 120.6 (CH).

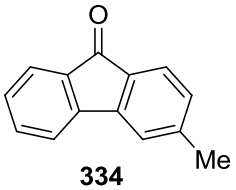
3-(Trifluoromethyl)fluoren-9-one 332[261]



332

Prepared following the general procedure using 2-((4-trifluoromethyl)benzoyl)benzoic acid **331** (88.3 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **332** as a pale yellow solid (Yield = 77%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.60–7.54 (m, 3H), 7.37 (td, J = 7.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5 (CO), 144.9 (C), 143.2 (C), 136.6 (C), 136.1 (q, J_{C-F} = 32.1 Hz, C), 135.3 (CH), 133.9 (C), 130.0 (CH), 126.3 (q, J_{C-F} = 4.0 Hz, CH), 124.8 (CH), 124.4 (CH), 123.5 (q, J_{C-F} = 272.9 Hz, C), 120.8 (CH), 117.2 (q, J_{C-F} = 3.7 Hz, CH).

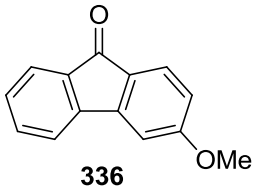
3-Methylfluoren-9-one 334[259]



334

Prepared following the general procedure using 2-(4-methylbenzoyl)benzoic acid **333** (72.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **334** as a yellow solid (Yield = 46%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.49–7.44 (m, 2H), 7..32 (s, 1H), 7.27 (td, J = 7.1, 1.6 Hz, 1H), 7.08 (d, J = 7.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (CO), 145.8 (C), 144.8 (C), 144.3 (C), 134.7 (C), 134.4 (CH), 131.8 (C), 129.6 (CH), 128.9 (CH), 124.3 (CH), 124.1 (CH), 121.2 (CH), 120.0 (CH), 22.2 (CH_3).

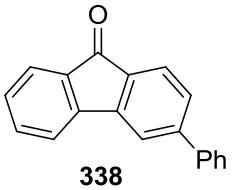
3-Methoxyfluoren-9-one 336[261]



336

Prepared following the general procedure using 2-(4-methoxybenzoyl)benzoic acid **335** (76.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% Et_2O in hexane to afford **336** as a yellow solid (Yield = 58%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.30 (td, J = 7.3, 1.8 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.74 (dd, J = 8.2, 2.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5 (CO), 165.4 (C), 147.0 (C), 143.3 (C), 135.4 (C), 134.1 (CH), 129.3 (CH), 127.2(C), 126.3 (CH), 123.9 (CH), 120.1 (CH), 113.0(CH), 107.1 (CH), 55.8 (CH_3).

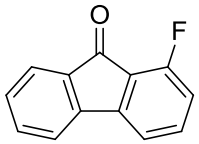
3-Phenylfluoren-9-one 338[259]



338

Prepared following the general procedure using 2-([1,1'-biphenyl]-4-carbonyl)benzoic acid **337** (90.7 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **338** as a yellow solid (Yield = 65%); Mp = 230 – 231 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72–7.71 (m, 2H), 7.68–7.64 (m, 3H), 7.57 (d, J = 7.4 Hz, 1H), 7.52–7.48 (m, 4H), 7.44–7.41 (m, 1H), 7.32 (td, J = 7.4, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5 (CO),147.8 (C), 145.1 (C), 144.1 (C), 140.2 (C), 134.7 (C), 134.6 (CH), 132.9 (C), 129.2 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 124.7 (CH), 124.2 (CH), 120.3 (CH), 119.2 (CH); HRMS (ES^+) cald. for $(M+H)^+$ $C_{19}H_{13}O$: 257.0961, found: 257.0952.

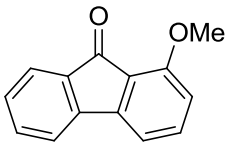
1-Fluorofluoren-9-one 340[259]



340

Prepared following the general procedure using 2-(2-fluorobenzoyl)benzoic acid **339** (73.3 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **340** as a pale yellow solid (Yield = 69%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 7.3 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.51 (td, J = 7.3, 1.0 Hz, 1H), 7.50–7.46 (m, 1H), 7.35–7.32 (m, 2H), 6.95 (t, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.2 (CO), 159.3 (d, J_{C-F} = 264.1 Hz, C-F), 146.3 (d, J_{C-F} = 3.6 Hz, C), 143.4 (d, J_{C-F} = 3.5 Hz, C), 137.0 (d, J_{C-F} = 8.3 Hz, CH), 134.6 (CH), 133.9 (C), 129.7 (CH), 124.5 (CH), 120.6 (CH), 120.0 (d, J_{C-F} = 12.9 Hz, C), 117.5 (d, J_{C-F} = 20.9 Hz, CH), 116.4 (d, J_{C-F} = 2.9 Hz, CH).

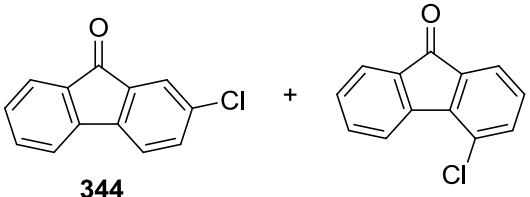
1-Methoxyfluoren-9-one 342[262]



342

Prepared following the general procedure using 2-(2-methoxybenzoyl)benzoic acid **341** (76.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 30% Et_2O in hexane to afford **342** as a yellow solid (Yield = 51%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9 (CO), 158.4 (C), 146.5 (C), 143.2 (C), 136.8 (CH), 134.5 (C), 133.9 (CH), 129.2 (CH), 123.9 (CH), 120.2 (CH), 120.1 (C), 113.0 (CH), 112.9 (CH), 55.9 (CH_3).

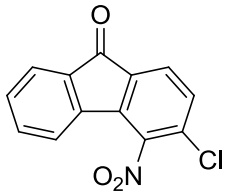
2-Chlorofluoren-9-one 344 and 4-Chlorofluoren-9-one 345[263]



344 **345**

Prepared following the general procedure using 2-(3-chlorobenzoyl)benzoic acid **343** (78.2 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in hexane to afford **344** and **345** as an inseparable mixture (**344**:**345** = 1:1.4) and as a pale yellow solid (Yield = 70%); 2-Chlorofluoren-9-one **344**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 7.4 Hz, 1H), 7.61 (s, 1H), 7.50 (d, J = 3.9 Hz, 2H), 7.45–7.44 (m, 2H), 7.33–7.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.4 (CO), 143.6 (C), 142.5 (C), 135.6 (C), 135.0 (CH), 134.9 (CH), 134.0 (C), 133.9 (C), 129.3 (CH), 124.6 (CH), 124.5 (CH), 121.3 (CH), 120.4 (CH); 4-Chlorofluoren-9-one **345**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5 (CO), 143.1 (C), 140.6 (C), 136.3 (C), 136.1 (CH), 135.0 (C), 134.1 (CH), 130.0 (CH), 129.5 (C), 129.4 (CH), 124.4 (CH), 124.1 (CH), 122.5 (CH).

3-Chloro-4-nitrofluoren-9-one 347

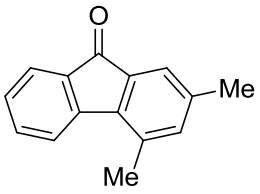


347

Prepared following the general procedure using 2-(4-chloro-3-nitrobenzoyl)benzoic acid **346** (91.7 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% Et_2O in hexane to afford the major isomer **347** as a pale yellow solid; (Yield = 56%); The other isomer was detected in low yields by ^{1}H NMR, but could not be isolated on column chromatography; Mp = 198 – 200 °C; **^{1}**H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.55 (td, J = 7.6, 1.2 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.45 (td, J = 7.6 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7 (CO), 138.6 (C), 136.3 (C), 135.6 (CH), 134.0 (C), 133.9 (C),

131.3 (CH), 131.0 (C), 130.9 (CH), 126.1 (CH), 125.2 (CH), 122.5 (CH); IR (neat): 2919, 2851, 1713, 1588, 1566, 1525, 1370, 1357, 1195, 1178, 1157 cm^{-1}; HRMS (ES^+) cald. for $(M+H)^+$ $C_{13}H_7NO_3Cl$: 260.0109, found: 260.0108.

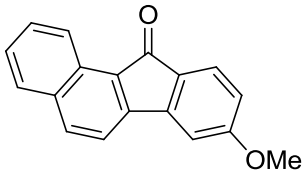
2,4-Dimethylfluoren-9-one 349[261]



349

Prepared following the general procedure using 2-(3,5-dimethylbenzoyl)benzoic acid **348** (76.3 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% Et_2O in hexane to afford **349** as a yellow solid (Yield = 45%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.45 (td, J = 7.5, 1.2 Hz, 1H), 7.33 (s, 1H), 7.24 (td, J = 7.2, 0.7 Hz, 1H), 7.05 (s, 1H), 2.53 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.5 (CO), 145.5 (C), 139.5 (C), 138.9 (C), 137.9 (CH), 134.8 (C), 134.6 (CH), 134.5 (C), 133.3 (C), 127.9 (CH), 124.1 (CH), 122.9 (CH), 122.6 (CH), 21.1 (CH_3), 20.0 (CH_3).

8-Methoxybenzo[a]fluoren-11-one 351[264]

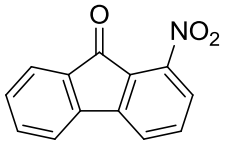


351

Prepared as with general procedure using 1-(4-methylbenzoyl)-2-naphthoic acid **350** but an additional equivalent of silver (I) acetate (10.0 mg, 0.06 mmol) and potassium peroxydisulfate (243.3 mg, 0.9 mmol) were added and further heated for 1 hr under microwave irradiation. The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford **351** as a yellow solid (Yield = 31%); ^1H NMR (500 MHz, $CDCl_3$): δ 8.96 (dd, J = 8.5, 0.7 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.58–7.55 (m, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.43 (m, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.68 (dd, J = 8.1, 2.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2 (CO), 165.0 (C), 146.3 (C), 144.6 (C), 135.2 (CH), 134.5

(C), 130.0 (C), 129.2 (CH), 128.4 (CH), 128.1 (C), 127.4 (C), 126.4 (CH), 125.7 (CH), 124.3 (CH), 117.9 (CH), 111.9 (CH), 107.7 (CH), 55.7 (CH_3).

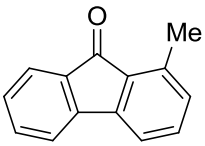
2-Nitrofluoren-9-one 353[265]



353

Prepared following the general procedure using 2-(2-nitrobenzoyl)benzoic acid **352** (81.4 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% Et_2O in hexane to afford **353** as a yellow solid (Yield = 12%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (dd, J = 7.5, 0.7 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.61–7.55 (m, 3H), 7.40 (td, J = 7.3, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.5 (CO), 146.6 (C), 146.3 (C), 142.1 (C), 135.5 (CH), 135.3 (CH), 133.3 (C), 130.5 (CH), 125.3 (CH), 125.0 (C), 123.6 (CH), 123.1 (CH), 120.7 (CH).

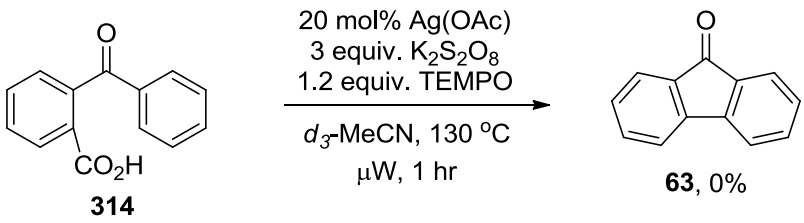
1-Methylfluoren-9-one 355[261]



355

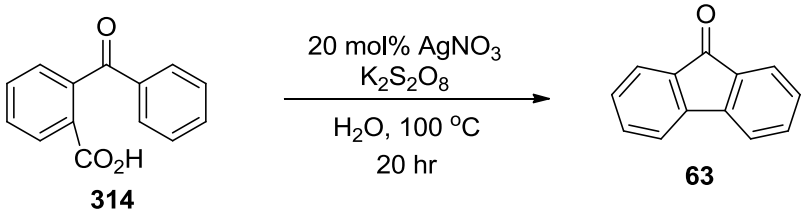
Prepared following the general procedure using 2-(2-methyl-6-nitrobenzoyl)benzoic acid **354** (85.6 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in hexane to afford the decarboxylation/denitration product **355** as a yellow solid (Yield = 27%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 7.3 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.46 (td, J = 7.3, 1.1 Hz, 1H), 7.36–7.32 (m, 2H), 7.28 (td, J = 7.3, 1.2 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1 (CO), 144.8 (C), 143.8 (C), 139.5 (C), 134.3 (CH), 134.0 (CH), 131.8 (CH), 130.9 (C), 128.9 (CH), 123.8 (CH), 120.0 (CH), 117.8 (CH), 17.8 (CH_3).

Procedure for radical quenching experiment



A septum-sealed microwave tube (5 mL) charged with 2-benzoylbenzoic acid **314** (67.8 mg, 0.3 mmol), silver(I) acetate (10.0 mg, 0.06 mmol) and potassium peroxydisulfate (243.3 mg, 0.9 mmol), (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (56.3 mg, 0.36 mmol) in deuterated-acetonitrile (2 mL) was irradiated in a microwave reactor at 130 °C for 1 hour. The reaction mixture was allowed to cool down, diluted with Et_2O (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. LC/MS analysis suggested no product formation, and purification by column chromatography (SiO_2, Et_2O/Hexane: 20%) did not yield the fluorenone product **63**.

Procedure for slow addition experiments under aqueous conditions

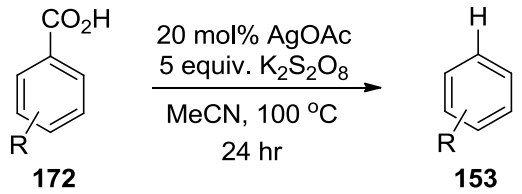


A septum-sealed microwave tube (5 mL) charged with 2-benzoylbenzoic acid **314** (67.8 mg, 0.3 mmol) and silver(I) acetate (10.0 mg, 0.06 mmol) in water (2 mL) was heated up to 100 °C. To this mixture was slowly added 3 ml of saturated aqueous solution of potassium peroxydisulfate (~1.95 equiv.) over 10 hrs using a syringe pump. The reaction mixture was allowed to cool down and Et_2O (10 mL) was added. The resulting mixture was extracted repeatedly with 10 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The

crude was purified by flash chromatography using 20% Et_2O in hexane to afford **63** as a yellow solid (Yield = 19%). The NMR data were consistent with the above results.

5.3.2 Protodecarboxylation of benzoic acids

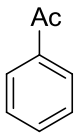
General procedure for silver-catalysed protodecarboxylation of benzoic acids



172 **153**

A septum-sealed microwave tube (5 mL) charged with benzoic acid **172** (0.3 mmol), silver(I) acetate (10.0 mg, 0.06 mmol) and potassium peroxydisulfate (405.5 mg, 1.5 mmol) in acetonitrile (3 mL) was heated at 100 ℃ for 24 hours. The reaction mixture was allowed to cool down, diluted with Et_2O (10 mL) and poured into saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with Et_2O (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was loaded onto a short column of silica and eluted with Et_2O/Pentane 0–10 %. The product-containing fractions were combined and concentrated under reduced pressure to the yield product **153**. For volatile compounds, nitromethane (1 equiv., 0.3 mmol) was added as an internal standard to the crude, and yields were determined by ^1H NMR spectroscopy in $CDCl_3$ ($MeNO_2$; δ_H = 4.33 ppm). The identity of the product was further confirmed by ^1H NMR of the crude mixture.

Acetophenone 359[266]



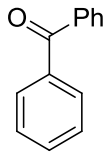
359

Prepared following the general procedure using 4-acetylbenzoic acid **358** (49.2 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **359** as a colourless oil (Yield = 78%); ^1H NMR (400 MHz, $CDCl_3$): δ

7.97–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2 (CO), 137.1 (C), 133.1 (CH), 128.5 (2CH), 128.3 (2CH), 26.6 (CH_3).

Compound **359** was also prepared following the same procedure using 3-acetylbenzoic acid **360** (49.2 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **359** as a colourless oil (Yield = 63%). The NMR data were consistent with the above.

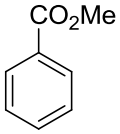
Benzophenone 318[260]



318

Prepared following the general procedure using 4-benzoylbenzoic acid **361** (54.7 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **318** as a colourless oil (Yield = 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.79 (m, 4H), 7.62–7.57 (m, 2H), 7.51–7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7 (CO), 137.5 (C), 132.4 (CH), 130.0 (CH), 128.2 (CH).

Methyl benzoate 363[267]

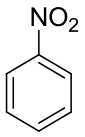


363

Prepared following the general procedure with 4-(methoxycarbonyl)benzoic acid **362** (54.0 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **363** as a colourless oil (Yield = 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.03 (m, 2H), 7.57–7.53 (m, 1H), 7.45–7.41 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (CO), 132.8 (CH), 130.1 (C), 129.5 (CH), 128.3 (CH), 52.0 (CH_3).

Compound **363** was also prepared following the same procedure using 3-(methoxycarbonyl)benzoic acid **364** (54.0 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **363** as a colourless oil (Yield = 81%). The NMR data were consistent with the above.

Nitrobenzene 254[118]



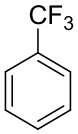
254

Prepared from 4-nitrobenzoic acid **190** (50.1 mg, 0.3 mmol), following the modified procedure using silver (I) acetate (20.0 mg, 0.12 mmol) and potassium peroxydisulfate (405.5 mg, 1.5 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **254** as a yellow oil (Yield = 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22–8.19 (m, 2H), 7.71–7.67 (m, 1H), 7.56–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1 (C), 134.5 (CH), 129.2 (CH), 123.4 (CH).

Compound **254** was also prepared following the same procedure using 3-nitrobenzoic acid **365** (50.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **254** as a yellow oil (Yield = 54%). The NMR data were consistent with the above.

2-Nitrobenzoic acid **189** (50.1 mg, 0.3 mmol) was protodecarboxylated to compound **254** following the general procedure. The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **254** as a yellow oil (Yield = 84%). The NMR data were consistent with the above.

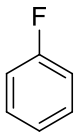
(Trifluoromethyl)benzene 367[227]



367

Prepared following the general procedure using 3-(trifluoromethyl)benzoic acid **366** (36.6 mg, 0.3 mmol). The yield of compound **367** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 68%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 7.7 Hz, 2H), 7.44 (d, J = 7.1 Hz, 1H), 7.38 (t, J = 7.7 Hz, 2H).

Fluorobenzene 369

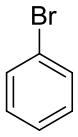


369

Prepared following the general procedure using 4-fluorobenzoic acid **368** (42.0 mg, 0.3 mmol). The yield of compound **369** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 64%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.17 (m, 2H), 6.99 (t, J = 7.4 Hz, 1H), 6.92–6.87 (m, 2H).

Compound **369** was also prepared following the same procedure using 3-fluorobenzoic acid **370** (42.0 mg, 0.3 mmol). The yield of compound **369** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 57%). The ^{1}H NMR data was consistent with the above.

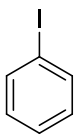
Bromobenzene 11



11

Prepared following the general procedure using 4-bromobenzoic acid **371** (60.3 mg, 0.3 mmol). The yield of compound **11** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 67%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.17–7.13 (m, 1H), 6.92–6.87 (m, 2H).

Iodobenzene 17

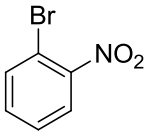


17

Prepared following the general procedure using 4-iodobenzoic acid **372** (74.4 mg, 0.3 mmol). The yield of compound **17** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 40%), and the identity of the product was further

confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.7 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 7.8 Hz, 2H).

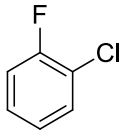
1-Bromo-2-nitrobenzene 6[268]



6

Prepared following the general procedure using 3-bromo-4-nitrobenzoic acid **373** (73.8 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in pentane to afford **6** as a yellow oil (Yield = 43%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.82 (m, 1H), 7.77–7.72 (m, 1H), 7.49–7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1 (CH), 133.2 (CH), 128.2 (CH), 125.6 (CH), 114.4 (C).

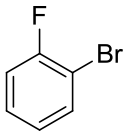
1-Chloro-2-fluorobenzene 375[269]



375

Prepared following the general procedure using 3-chloro-4-fluorobenzoic acid **374** (52.4 mg, 0.3 mmol). The yield of compound **375** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 74%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (td, J = 7.7, 1.7 Hz, 1H), 7.19–7.11 (m, 1H), 7.06–6.97 (m, 2H).

1-Bromo-2-fluorobenzene 377

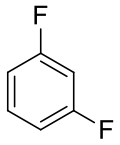


377

Prepared following the general procedure using 3-bromo-4-fluorobenzoic acid **376** (65.7 mg, 0.3 mmol). The yield of compound **377** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 75%), and the identity of the product was

further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.41 (m, 1H), 7.20–7.16 (m, 1H), 7.01 (td, J = 8.6, 1.5 Hz, 1H), 6.95–6.91 (m, 1H).

1,3-Difluorobenzene 379



379

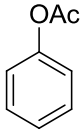
Prepared following the general procedure using 3,5-difluorobenzoic acid **378** (47.4 mg, 0.3 mmol). The yield of compound **379** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 39%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.14 (m, 1H), 6.91 (tt, J = 8.7, 2.4 Hz, 1H), 6.76–6.72 (m, 1H), 6.70–6.63 (m, 1H).

Benzene 291

291

Prepared following the general procedure using benzoic acid **380** (36.6 mg, 0.3 mmol). The yield of compound **291** was determined by ^{1}H NMR using nitromethane as the internal standard (Yield = 52%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 6H).

Phenyl acetate 382[270]



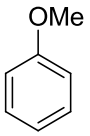
382

Prepared following the general procedure using 4-acetoxybenzoic acid **381** (54.0 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in pentane to afford **382** as a colourless oil (Yield = 25%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 2H), 7.25–7.21 (m, 1H), 7.10–7.07 (m, 2H), 2.31 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 169.5 (CO), 150.6 (C), 129.4 (CH), 125.8 (CH), 121.6 (CH), 21.1 (CH_3).

Compound **382** was also prepared following the same procedure using 2-acetoxybenzoic acid **383** (54.0 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in pentane to afford **382** as a colourless oil (Yield = 31%). The NMR data were consistent with the above.

Anisole 384

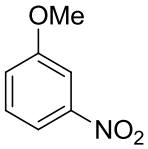


384

Prepared following the general procedure using 4-methoxybenzoic acid **191** (45.6 mg, 0.3 mmol). The yield of compound **384** was determined by ^1H NMR using nitromethane as the internal standard (Yield = 34%), and the identity of the product was further confirmed by ^1H NMR of the crude mixture; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.13 (m, 2H), 6.82–6.76 (m, 3H), 3.67 (s, 3H).

Compound **384** was also prepared following the same procedure using 3-methoxybenzoic acid **385** (45.6 mg, 0.3 mmol). The yield of compound **384** was determined by ^1H NMR using nitromethane as the internal standard (Yield = 45%). The ^1H NMR data was consistent with the above.

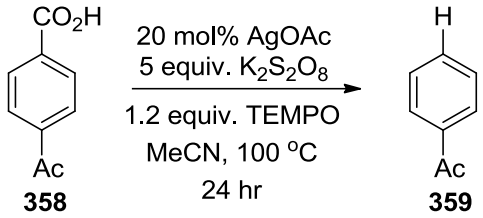
1-Methoxy-3-nitrobenzene 387[119]



387

Prepared following the general procedure using 2-nitro-4-methoxybenzoic acid **386** (59.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in pentane to afford **387** as a colourless oil (Yield = 58%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.84–7.81 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 7.73–7.72 (t, J = 2.3 Hz, 1H), 7.45–7.41 (t, J = 8.2 Hz, 1H), 7.24–7.21 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C), 149.2 (C), 129.9 (CH), 121.3 (CH), 115.7 (CH), 108.1 (CH), 55.8 (CH_3).

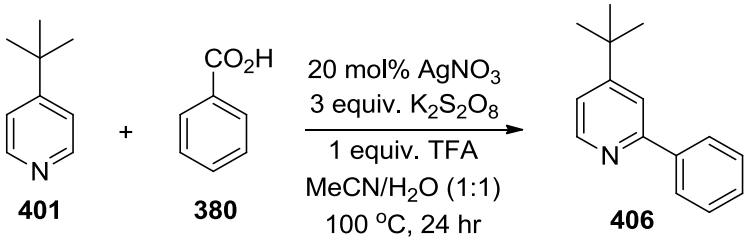
Procedure for radical quenching experiment



A septum-sealed microwave tube (5 mL) charged with 4-acetylbenzoic acid **358** (49.2 mg, 0.3 mmol), silver(I) acetate (10.0 mg, 0.06 mmol), potassium peroxydisulfate (405.5 mg, 1.5 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (56.3 mg, 0.36 mmol in acetonitrile (3 mL) was heated at 100 ℃ for 24 hours. The reaction mixture was allowed to cool down, diluted with Et_2O (10 mL) and poured into H_2O (5 mL). The resulting mixture was extracted repeatedly with 10 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. LC/MS analysis suggested no product formation, and purification by column chromatography (SiO_2, Et_2O/pentane: 10%) did not yield the prtodecarboxylation product **359**. Only the starting material **358** was recovered in a 93% yield.

5.3.3 Intermolecular decarboxylative arylation

A current optimised procedure for silver-catalysed decarboxylative arylation of pyridine



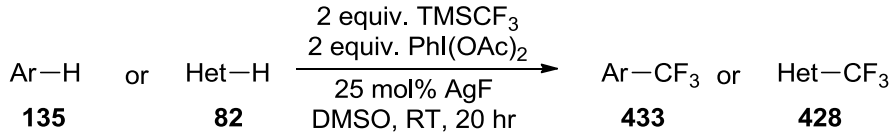
To a solution of 4-(*tert*-butyl)pyridine **401** (44.3 μl, 0.3 mmol) in acetonitrile (1.5 mL) was added trifluoroacetic acid (23.0 μl, 0.3 mmol) followed by benzoic acid (73.2 mg, 0.6 mmol). Water (1.0 mL) was then added, followed by silver(I) nitrate (10.2 mg, 0.06 mmol) in water (0.5 mL). Potassium peroxydisulfate (243.3 mg, 0.9 mmol) was then

added and the solution was stirred vigorously at 100 °C. After 10 hours, silver (I) nitrate (10.2 mg, 0.06 mmol) and potassium peroxydisulfate (243.3 mg, 0.9 mmol) were added and further heated for 14 hours. The mixture was cooled, diluted with EtOAc (5 mL) and washed with 5% $NaHCO_3$ aqueous solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated and dried *in vacuo*. The residue was purified by flash chromatography using 20% EtOAC in hexane to afford 4-(*tert*-butyl)-2-phenylpyridine **406** as a brown oil (Yield = 58%);[190] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J=5.3 Hz, 1H), 7.98–7.96 (m, 2H), 7.71 (d, J=1.8 Hz, 1H), 7.48–7.46 (m, 2H), 7.24 (dd, J=5.3, 1.8 Hz, 1H), 1.37 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (C), 157.5 (C), 149.5 (CH), 140.0 (C), 128.7 (CH), 128.6 (CH), 127.0 (CH), 119.3 (CH), 117.8 (CH), 34.9 (C), 30.6 (CH_3).

5.4 Experimental procedures for the direct trifluoromethylation of simple arenes and heteroarenes

5.4.1 Silver-catalysed radical trifluoromethylation using $TMSCF_3$

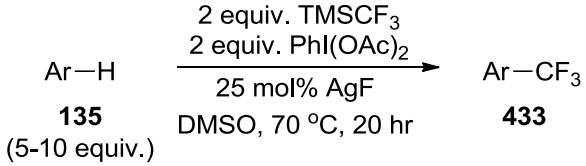
General procedure A: Trifluoromethylation of electron-rich (hetero)arenes



An oven-dried reaction vial (5 mL) was charged with (hetero)arene **135** or **82** (0.3 mmol), (diacetoxyiodo)benzene (193.3 mg, 0.6 mmol), trimethyl(trifluoromethyl)silane (88.7 μL, 0.6 mmol) and anhydrous DMSO (1 mL). The mixture was stirred at room temperature for 1 min and silver(I) fluoride (9.5 mg, 0.075 mmol) was slowly added to the stirring mixture. The vial was sealed with a septum cap and the reaction was kept stirring at the same temperature for 20 hours. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material

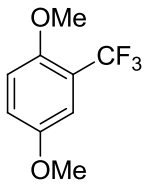
was purified by column chromatography (SiO_2, using the noted solvent mixture) to yield the desired trifluoromethylated product **433** or **428**. For volatile compounds, 4-fluoroanisole (3 equiv., 0.9 mmol) was added as an internal standard to the crude, and yields were determined by ^{19}F NMR spectroscopy in $CDCl_3$ (δ_F = -124.8 ppm). The identity of the products was further confirmed by ^1H NMR of the crude mixture (and GC/MS analysis for unknown compounds).

General procedure B: Trifluoromethylation of unactivated arenes (**367**, **464**, **465**)



An oven-dried reaction vial (5 mL) was charged with trimethyl(trifluoromethyl)silane (73.9 μL, 0.5 mmol), arene **135** (2.5 mmol or 5.0 mmol), (diacetoxyiodo)benzene (322.1 mg, 1.0 mmol), silver (I) fluoride (15.9 mg, 0.125 mmol) and anhydrous DMSO (0.5 mL). The vial was sealed with a septum cap and the reaction was heated at 70 °C for 20 h. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. 4-Fluoroanisole (3 equiv.) was added as an internal standard to the crude, and the reaction was analysed by ^{19}F NMR spectroscopy in $CDCl_3$. The identity of the products was further confirmed by ^1H NMR of the crude mixture.

1,4-Dimethoxy-2-(trifluoromethyl)benzene 443[271]

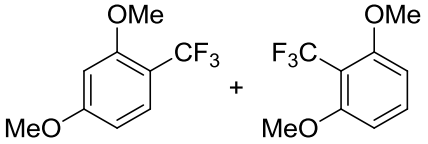


443

Prepared following general procedure A using 1,4-dimethoxybenzene **442** (41.4 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% DCM in pentane to afford **443** as a colourless oil (Yield = 58%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 3.1 Hz, 1H), 7.02 (dd, J = 9.0, 3.1 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 3.86 (s,

3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (C), 151.5 (C), 123.4 (q, J_{C-F} = 272.4 Hz, CF_3), 119.4 (q, J_{C-F} = 31.1 Hz, C), 118.1 (CH), 113.5 (CH), 112.8 (q, J_{C-F} = 5.5 Hz, CH), 56.5 (CH_3), 55.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4 (s, CF_3).

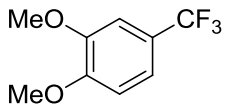
1,3-Dimethoxy-4-(trifluoromethyl)benzene 444[271] **and 1,3-dimethoxy-2-(trifluoromethyl)benzene 445**[271]



444 **445**

Prepared following general procedure A using 1,3-dimethoxybenzene (41.4 mg (39.3 μL), 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% DCM in pentane to afford **444** and **445** as a mixture of isomers as a colourless oil (Yield = 77%, **444**:**445** = 2:1). 1,3-Dimethoxy-4-(trifluoromethyl)benzene **444**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.6 Hz, 1H), 6.52 (s, 1H), 6.48 (d, J = 8.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 158.8 (C), 128.2 (q, J_{C-F} = 5.4 Hz, CH), 124.0 (q, J_{C-F} = 271.2 Hz, CF_3), 111.6 (q, J_{C-F} = 31.3 Hz, C), 103.7 (CH), 99.3 (CH), 55.8 (CH_3), 55.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.3 (s, CF_3); 1,3-Dimethoxy-2-(trifluoromethyl)benzene **445**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 2H), 3.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C), 133.0 (CH), 124.1 (q, J_{C-F} = 274.5 Hz, CF_3), 107.1 (q, J_{C-F} = 29.5 Hz, C), 104.8 (CH), 56.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -54.9 (s, CF_3).

1,2-dimethoxy-4-(trifluoromethyl)benzene 446[271]

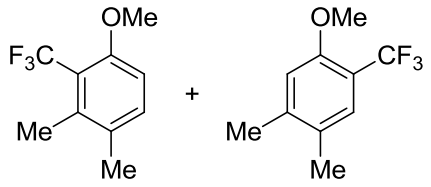


446

Prepared following general procedure A using 1,2-dimethoxybenzene (41.4 mg (38.2 μL), 0.3 mmol). The reaction mixture was purified by flash chromatography using 30% DCM in pentane to afford **446** as a colourless oil (Yield = 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (ddd, J = 8.4, 2.0, 0.8 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (C), 149.0 (C), 124.3 (q, J_{C-F} = 271.3 Hz, CF_3), 122.9 (q, J_{C-F} = 32.7 Hz, C), 118.3 (q, J_{C-F} = 4.2 Hz,

CH), 110.6 (CH), 108.0 (q, J_{C-F} = 3.4 Hz, CH), 56.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.5 (s, CF_3).

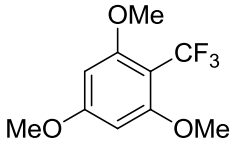
3,4-Dimethyl-2-(trifluoromethyl)anisole 447 and 3,4-dimethyl-6-(trifluoromethyl)anisole 448



447 **448**

Prepared following general procedure A using 3,4-dimethylanisole (40.9 mg (41.9 μL), 0.3 mmol). The reaction mixture was purified by flash chromatography using 100% pentane to afford **447** and **448** as colourless oils (Yield = 45%, **447**:**448** = 1:1). 3,4-Dimethyl-2-(trifluoromethyl)anisole **447**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.5, Hz, 1H), 3.84 (s, 3H), 2.36 (q, J_{H-F} = 2.9 Hz, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8 (C), 137.3 (q, J_{C-F} = 1.5 Hz, C), 133.5 (CH), 130.0 (C), 125.2 (q, J_{C-F} = 275.9 Hz, CF_3), 117.7 (q, J_{C-F} = 28.1 Hz, C), 110.0 (CH), 56.3 (CH_3), 20.3 (CH_3), 16.7 (q, J_{C-F} = 4.6 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -53.5 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{10}H_{12}O_1F_3$: 205.0835, found: 205.0835; 3,4-Dimethyl-6-(trifluoromethyl)anisole **448**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 6.79 (s, 1H), 3.87 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 142.1 (C), 128.0 (C), 127.8 (q, J_{C-F} = 5.1 Hz, CH), 123.9 (q, J_{C-F} = 271.8 Hz, CF_3), 115.9 (q, J_{C-F} = 30.5 Hz, C), 113.6 (CH), 56.0 (CH_3), 20.3 (CH_3), 18.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.7 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{10}H_{12}O_1F_3$: 205.0835, found: 205.0835.

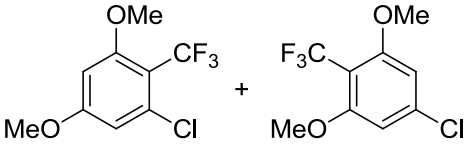
1,3,5-Trimethoxy-4-(trifluoromethyl)benzene 449



449

Prepared following general procedure A using 1,3,5-trimethoxybenzene (50.5 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% Et_2O in pentane to afford **449** as a white solid (Yield = 89%). Mp = 52 – 54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 2H), 3.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (C), 160.4 (C), 124.3 (q, J_{C-F} = 273.4 Hz, CF_3), 100.3 (q, J_{C-F} = 30.0 Hz, C), 91.2 (CH), 56.2 (CH_3), 55.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -54.1 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{10}H_{12}O_3F_3$: 237.0733, found: 237.0736.

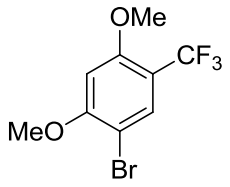
1-Chloro-3,5-dimethoxy-2-(trifluoromethyl)benzene 450 and 1-chloro-3,5-dimethoxy-4-(trifluoromethyl)benzene 451



450 **451**

Prepared following general procedure A using 1-chloro-3,5-dimethoxybenzene (51.8 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% DCM in pentane to afford **450** as a colourless oil and **451** as a white solid (Yield = 83%, **450**:**451** = 2:1). 1-Chloro-3,5-dimethoxy-2-(trifluoromethyl)benzene **450**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, J = 2.4 Hz, 1H), 6.41 (d, J = 2.4, Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C), 160.5 (C), 134.8 (q, J_{C-F} = 1.8 Hz, C), 123.5 (q, J_{C-F} = 273.9 Hz, CF_3), 109.8 (q, J_{C-F} = 30.5 Hz, C), 108.2 (CH), 98.4 (CH), 56.4 (CH_3), 55.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -54.5 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_9O_2Cl_1F_3$: 241.0238, found: 241.0242; 1-Chloro-3,5-dimethoxy-4-(trifluoromethyl)benzene **451**: Mp = 70 – 72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 2H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (C), 139.1 (C), 123.7 (q, J_{C-F} = 274.7 Hz, CF_3), 105.8 (q, J_{C-F} = 30.0 Hz, C), 105.6 (CH), 56.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.1 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_9O_2Cl_1F_3$: 241.0238, found: 241.0242.

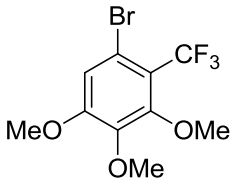
1-Bromo-2,4-dimethoxy-5-(trifluoromethyl)benzene 452



452

Prepared following general procedure A using 1-bromo-2,4-dimethoxybenzene (65.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 50% Et_2O in iso-hexane to afford **452** as a white solid (Yield = 40%). Mp = 130 – 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 6.51 (s, 1H), 3.94 (s, 3H), 3.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 158.3 (q, J_{C-F} = 2.3 Hz, C), 131.3 (q, J_{C-F} = 5.4 Hz, CH), 123.0 (q, J_{C-F} = 271.5 Hz, CF_3), 112.2 (q, J_{C-F} = 32.0 Hz, C), 101.1 (C), 96.7 (CH), 56.4 (CH_3), 56.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.5 (s, CF_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_9O_2Br_1F_3$: 284.9733, found: 284.9741.

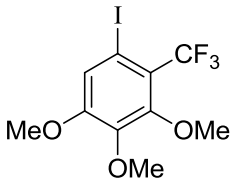
1-Bromo-3,4,5-trimethoxy-2-(trifluoromethyl)benzene 453



453

Prepared following general procedure A using 1-bromo-3,4,5-trimethoxybenzene (74.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% DCM in pentane to afford **453** as a yellow oil (Yield = 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 154.3 (C), 142.6 (C), 122.9 (q, J_{C-F} = 274.6 Hz, CF_3), 116.9 (q, J_{C-F} = 29.8 Hz, C), 114.2 (CH), 114.1 (q, J_{C-F} = 2.1 Hz, C), 62.1 (CH_3), 60.8 (CH_3), 56.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.5 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{10}H_{11}O_3Br_1F_3$: 314.9838, found: 314.9837.

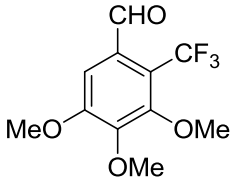
1-Iodo-3,4,5-trimethoxy-2-(trifluoromethyl)benzene 454



454

Prepared following general procedure A using 1-iodo-3,4,5-trimethoxybenzene (88.2 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% DCM in pentane to afford **454** (as a mixture with a small amount of an inseparable impurity) as a yellow oil (Yield = 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 154.2 (C), 143.5 (C), 122.1 (q, J_{C-F} = 275.0 Hz, CF_3), 121.5 (CH), 120.3 (q, J_{C-F} = 29.8 Hz, C), 82.7 (q, J_{C-F} = 2.5 Hz, C), 62.1 (CH_3), 60.8 (CH_3), 56.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.7 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{10}H_{11}O_3F_3I_1$: 362.9699, found: 362.9698.

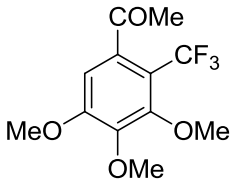
2-(Trifluoromethyl)-3,4,5-trimethoxybenzaldehyde 455



455

Prepared following general procedure A using 3,4,5-trimethoxybenzaldehyde (58.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 40% DCM in pentane to afford **455** as a yellow oil (Yield = 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (q, J_{H-F} = 2.4 Hz, 1H), 7.34 (s, 1H), 3.95 (s, 6H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (q, J_{C-F} = 6.0 Hz, CO), 155.8 (C), 152.8 (q, J_{C-F} = 2.5 Hz, C), 147.3 (C), 130.8 (C), 124.1 (q, J_{C-F} = 275.1 Hz, CF_3), 117.9 (q, J_{C-F} = 31.2 Hz, C), 107.2 (CH), 62.0 (CH_3), 61.0 (CH_3), 56.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -51.1 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{11}H_{12}O_4F_3$: 265.0682, found: 265.0682.

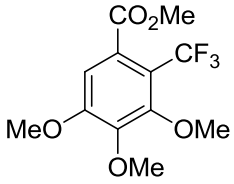
2'-(Trifluoromethyl)-3',4',5'-trimethoxyacetophenone 456



456

Prepared following general procedure A using 3',4',5'-trimethoxyacetophenone (63.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 100% DCM to afford **456** as a yellow oil (Yield = 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.45 (q, J_{H-F} = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4 (CO), 156.2 (C), 152.7 (q, J_{C-F} = 1.9 Hz, C), 143.4 (C), 137.6 (q, J_{C-F} = 2.6 Hz, C), 123.4 (q, J_{C-F} = 273.1 Hz, CF_3), 112.8 (q, J_{C-F} = 31.0 Hz, C), 104.4 (CH), 61.7 (CH_3), 60.8 (CH_3), 56.2 (CH_3), 31.3 (q, J_{C-F} = 3.1 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.0 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_{12}H_{14}O_4F_3$: 279.0839, found: 279.0839.

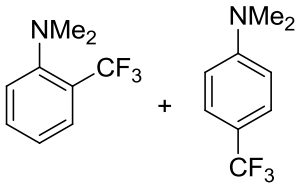
Methyl 2-(trifluoromethyl)-3,4,5-trimethoxybenzoate 457



457

Prepared following general procedure A using methyl 3,4,5-trimethoxybenzoate (67.9 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 100% DCM to afford **457** as a yellow oil (Yield = 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (CO), 155.9 (C), 152.9 (q, J_{C-F} = 1.7 Hz, C), 144.1 (C), 128.4 (q, J_{C-F} = 2.9 Hz, C), 123.0 (q, J_{C-F} = 273.0 Hz, CF_3), 114.5 (q, J_{C-F} = 30.9 Hz, C), 106.8 (CH), 61.8 (CH_3), 60.8 (CH_3), 56.2 (CH_3), 52.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.9 (s, CF_3); HRMS (ES^+) cald. for (M) $C_{12}H_{13}O_5F_3$: 294.0710, found: 294.0709.

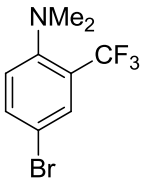
***N*,*N*-Dimethyl-2-(trifluoromethyl)aniline 458 and *N*,*N*-Dimethyl-4-(trifluoromethyl)aniline 459**[272]



458 **459**

Prepared following general procedure A using *N*,*N*-dimethylaniline (53.2 mg (58.4 μL), 0.3 mmol). The reaction mixture was purified by flash chromatography using 100% pentane to afford a mixture of **458** and **459** as a colourless oil (Yield = 75%, **458**:**459** = 2:1). *N*,*N*-Dimethyl-2-(trifluoromethyl)aniline **458**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, J = 7.9, 1.5 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 2.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (C), 132.6 (CH), 127.3 (q, J_{C-F} = 5.5 Hz, CH), 125.6 (q, J_{C-F} = 28.9 Hz, C), 123.6 (CH), 124.2 (q, J_{C-F} = 273.0 Hz, CF_3), 122.7 (CH), 45.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -60.1 (s, CF_3); *N*,*N*-Dimethyl-4-(trifluoromethyl)aniline **459**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3 (C), 126.3 (q, J_{C-F} = 3.8 Hz, CH), 125.2 (q, J_{C-F} = 270.2 Hz, CF_3), 117.4 (q, J_{C-F} = 32.8 Hz, C), 111.1 (CH), 40.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -60.8 (s, CF_3).

4-Bromo-*N*,*N*-dimethyl-2-(trifluoromethyl)aniline 460

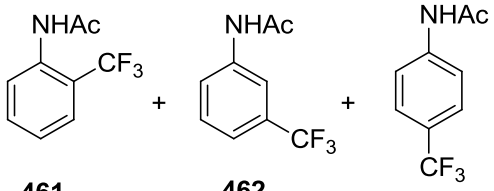


460

Prepared following general procedure A using 4-bromo-*N*,*N*-dimethylaniline (60.0 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 100% pentane to afford **460** (as a mixture with a small amount of an inseparable impurity) as a yellow oil (Yield = 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 2.4 Hz, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 2.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 135.5 (CH), 130.5 (q, J_{C-F} = 5.8 Hz, CH), 127.1 (q, J_{C-F} = 29.7 Hz, C), 124.4 (CH), 123.2 (q, J_{C-F} = 273.6 Hz, CF_3), 116.0 (C), 45.5 (CH_3); ^{19}F

NMR (376 MHz, $CDCl_3$): δ -60.3 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_{10}N_1Br_1F_3$: 267.9943, found: 267.9942.

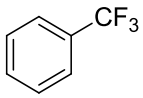
2-(Trifluoromethyl)acetanilide 461, 3-(trifluoromethyl)acetanilide 462[273] and 4-(trifluoromethyl)acetanilide 463[274]



461 **462** **463**

Prepared following general procedure A using acetanilide (40.6 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 10% Et_2O in pentane to afford **461** and an inseparable mixture of **462** and **463**, each as off-white solids (Yield = 48%, **461**:**462**:**463** = 3:1:4.3). 2-(Trifluoromethyl)acetanilide **461**: Mp = 72 – 74 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.42 (bs, NH), 7.23 (t, J = 7.5 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (CO), 135.2 (C), 132.8 (CH), 126.0 (q, J_{C-F} = 3.5 Hz, CH), 124.7 (CH), 124.5 (CH), 24.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -60.6 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_9O_1N_1F_3$: 204.0631, found: 204.0632. 3-(Trifluoromethyl)acetanilide **462**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.63 (bs, NH), 7.42 (t, J = 7.9, 1H), 7.35 (t, J = 7.7 Hz, 1H), 2.20 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -62.8 (s, CF_3). 4-(Trifluoromethyl)acetanilide **463**: ^1H NMR (400 MHz, $CDCl_3$): 7.63 (d, J = 8.6 Hz, 2H), 7.63 (bs, NH), 7.55 (d, J = 8.6 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (CO), 140.9 (C), 126.2 (q, J_{C-F} = 3.7 Hz, CH), 125.9 (C), 124.1 (q, J_{C-F} = 271.4 Hz, CF_3), 119.3 (CH), 24.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.1 (s, CF_3).

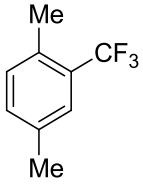
1,1,1-Trifluorotoluene 367[227]



367

Prepared following general procedure B using benzene (390.6 mg (447 μL), 5.0 mmol). The yield of compound **367** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 60%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.7 Hz, 2H), 7.62 (t, J = 7.1 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8 (s, CF_3).

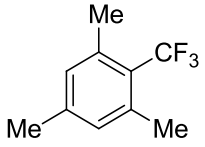
1,4-Dimethyl-2-(trifluoromethyl)benzene 464[227]



464

Prepared following general procedure B using p-xylene (530.9 mg (617 μL), 5.0 mmol). The yield of compound **464** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 67%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.32 (d, J = 7.5 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.8 (s, CF_3).

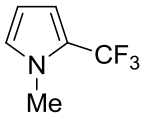
1,3,5-Trimethyl-2-(trifluoromethyl)benzene 465[227]



465

Prepared following general procedure B using mesitylene (300.5 mg (348 μL), 2.5 mmol). The yield of compound **463** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 71%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 2.35–2.33 (m, 6H), 2.20 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -53.8 (s, CF_3).

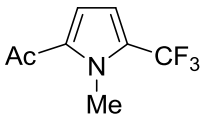
***N*-Methyl-2-(trifluoromethyl)pyrrole 466**[227]



466

Prepared following general procedure A using *N*-methylpyrrole (24.3 mg (26.6 μL), 0.3 mmol). The yield of compound **466** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 94%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (t, J = 2.1 Hz, 1H), 6.56–6.54 (m, 1H), 6.10 (t, J = 3.2 Hz, 1H), 3.72 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.8 (s, CF_3).

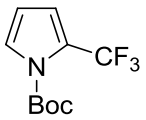
2-Acetyl-*N*-methyl-5-(trifluoromethyl)pyrrole 467[275]



467

Prepared following general procedure A using *N*-methyl-2-acetylpyrrole (36.9 mg (35.5 μL), 0.3 mmol). The yield of compound **467** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 93%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 4.3 Hz, 1H), 6.54 (d, J = 4.3 Hz, 1H), 4.00 (s, 3H), 2.47 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -59.8 (s, CF_3).

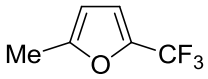
***N*-Boc-2-(trifluoromethyl)pyrrole 468**[227]



468

Prepared following general procedure A using *N*-Boc-pyrrole (50.2 mg (50.2 μL), 0.3 mmol). The yield of compound **468** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 50%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, J = 3.3, 1.9 Hz, 1H), 6.74 – 6.72 (m, 1H), 6.19 (t, J = 3.3 Hz, 1H), 1.61 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3 (s, CF_3).

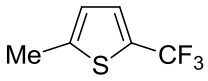
2-Methyl-5-(trifluoromethyl)furan 469[227]



469

Prepared following general procedure A using 2-methylfuran (24.6 mg (27.1 μL), 0.3 mmol). The yield of compound **469** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 51%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, J = 1.8 Hz, 1H), 6.03 (d, J = 3.3 Hz, 1H), 2.32 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (s, CF_3).

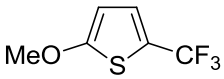
2-Methyl-5-(trifluoromethyl)thiophene 470[227]



470

Prepared following general procedure A using 2-methylthiophene (29.5 mg (29.0 μL), 0.3 mmol). The yield of compound **470** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 42%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J = 3.6, 1.1 Hz, 1H), 6.68 (m, 1H), 2.48 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.1 (s, CF_3).

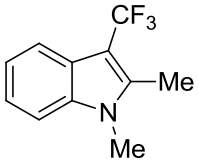
2-Methoxy-5-(trifluoromethyl)thiophene 471



471

Prepared following general procedure A using 2-methoxythiophene (34.3 mg (30.2 μL), 0.3 mmol). The yield of compound **471** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 76%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 – 7.04 (m, 1H), 6.11 (dd, J = 4.1, 0.7 Hz, 1H), 3.87 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.3 (s, CF_3); GC/MS: M($C_6H_5OSF_3$) = 182.0, found = 182.0.

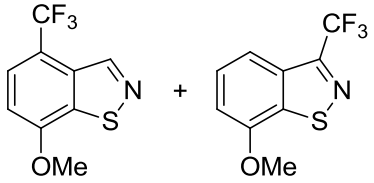
1,2-Dimethyl-3-(trifluoromethyl)indole 472[221]



472

Prepared following general procedure A using 1,2-dimethylindole (43.6 mg, 0.3 mmol). The yield of compound **472** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 45%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.27 – 7.16 (m, 3H), 3.62 (s, 3H), 2.50 (q, J_{H-F} = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3 (C), 136.1 (C), 125.5 (q, J_{C-F} = 266.7 Hz, CF_3), 124.4 (q, J_{C-F} = 1.6 Hz, C), 121.9 (CH), 121.0 (CH), 119.0 (CH), 109.2 (CH), 102.5 (q, J_{C-F} = 35.1 Hz, C), 29.4 (CH_3), 10.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -53.6 (s, CF_3).

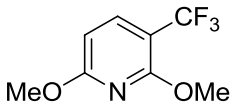
7-Methoxy-4-(trifluoromethyl)-1,2-benzisothiazole 473 and 7-methoxy-3-(trifluoromethyl)-1,2-benzisothiazole 474



473 **474**

Prepared following general procedure A using 7-methoxy-1,2-benzisothiazole (49.5 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% DCM in iso-hexane to afford a mixture of **473** and **474** as a white solid (Yield = 41%, **473**:**474** = 5:1). 7-Methoxy-4-(trifluoromethyl)-1,2-benzisothiazole **473**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (q, J_{H-F} = 1.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 152.9 (q, J_{C-F} = 2.1 Hz, CH), 144.0 (C), 133.6 (q, J_{C-F} = 1.3 Hz, C), 125.5 (q, J_{C-F} = 5.1 Hz, CH), 124.1 (q, J_{C-F} = 271.5 Hz, CF_3), 118.0 (q, J_{C-F} = 34.1 Hz, C), 105.0 (CH), 56.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -59.9 (s, CF_3); 7-Methoxy-3-(trifluoromethyl)-1,2-benzisothiazole **474**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 4.02 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.6 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_9H_7O_1N_1F_3S_1$: 234.0195, found: 234.0194.

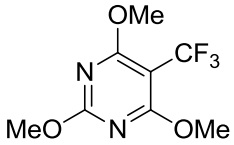
2,6-dimethoxy-3-(trifluoromethyl)pyridine 476



476

Prepared following general procedure A using 2,6-dimethoxypyridine (41.7 mg (39.6 μL), 0.3 mmol). The reaction mixture was purified by flash chromatography using pentane to afford **476** as a white solid (Yield = 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C), 160.4 (C), 138.8 (q, J_{C-F} = 4.5 Hz, CH), 123.7 (q, J_{C-F} = 270.1 Hz, CF_3), 104.3 (q, J_{C-F} = 33.5 Hz, C), 100.8 (CH), 53.9 (CH_3), 53.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.9 (s, CF_3); HRMS (ES^+) cald. for $(M+H)^+$ $C_8H_9O_2N_1F_3$: 208.0580, found: 208.0582.

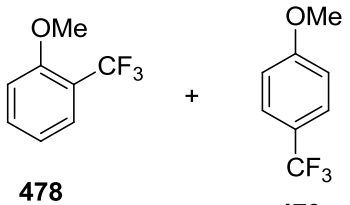
2,4,6-trimethoxy-5-(trifluoromethyl)pyrimidine 477[227]



477

Prepared following general procedure A using 2,4,6-trimethoxypyrimidine (51.1 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 30% DCM in pentane to afford **477** as a white solid (Yield = 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 6H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (C), 164.9 (C), 123.4 (q, J_{C-F} = 271.2 Hz, CF_3), 89.2 (q, J_{C-F} = 34.2 Hz, C), 55.1 (CH_3), 54.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.9 (s, CF_3).

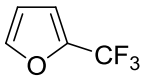
1-Methoxy-2-(trifluoromethyl)benzene 478 and 1-methoxy-4-(trifluoromethyl)benzene 479[227]



478 **479**

Prepared following general procedure A using anisole (32.4 mg (32.6 μL), 0.3 mmol). The yields of compounds **478** and **479** were determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 35%, **278**:**279** = 2:1), and the identity of the products was further confirmed by ^{1}H NMR of the crude mixture; 1-Methoxy-2-(trifluoromethyl)benzene **478**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7, Hz, 1H), 7.00–6.96 (m, 2H), 3.86 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 (s, CF_3); 1-Methoxy-4-(trifluoromethyl)benzene **479**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -61.5 (s, CF_3).

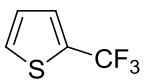
2-(Trifluoromethyl)furan 480[276]



480

Prepared following general procedure A using furan (20.4 mg (21.8 μL), 0.3 mmol). The yield of compound **480** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 21%); ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.4 (s, CF_3).

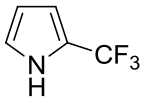
2-(Trifluoromethyl)thiophene 481[272]



481

Prepared following general procedure A using thiophene (25.2 mg (24.0 μL), 0.3 mmol). The yield of compound **481** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 12%); ^{19}F NMR (376 MHz, $CDCl_3$): δ -54.9 (s, CF_3).

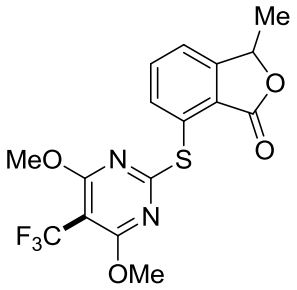
2-(Trifluoromethyl)pyrrole 436[227]



436

Prepared following general procedure A using pyrrole (20.1 mg (20.8 μL), 0.3 mmol). The yield of compound **436** was determined by ^{19}F NMR using 4-fluoroanisole as the internal standard (Yield = 21%), and the identity of the product was further confirmed by ^{1}H NMR of the crude mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (bs, NH), 6.98 (s, 1H), 6.57 (s, 1H), 6.17 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -60.1 (s, CF_3).

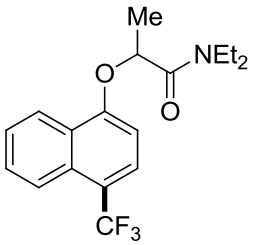
Pyriftalid-CF_3 483



483

Prepared following general procedure A using (±)-pyriftalid (95.5 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 70% DCM in iso-hexane to afford 48**3** as a white solid (Yield = 42%). Mp = 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 5.53 (q, J = 6.7 Hz, 1H), 3.76 (s, 6H), 1.64 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C), 167.9 (C), 167.3 (C), 152.7 (C), 136.3 (CH), 133.9 (CH), 129.5 (C), 127.2 (C), 123.1 (q, J_{C-F} = 272.4 Hz, CF_3), 122.6 (CH), 91.6 (q, J_{C-F} = 34.3 Hz, C), 76.2 (CH), 54.8 (CH_3), 20.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -56.3 (s, CF_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_{16}H_{14}O_4N_2F_3S_1$: 387.0621, found: 387.0620.

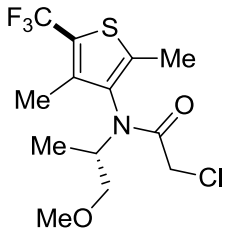
Napropamide-CF_3 484



484

Prepared following general procedure A using (±)-napropamide (81.4 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 20% EtOAc in iso-hexane to afford **484** as a white solid (Yield = 51%). Mp = 77–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.63 (ddd, J = 9.0, 6.8, 1.5 Hz, 1H), 7.56 (ddd, J = 8.7, 6.9, 1.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.17 (q, J = 6.7 Hz, 1H), 3.59–3.34 (m, 4H), 1.76 (d, J = 6.7 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (CO), 156.2 (C), 130.2 (C), 128.1 (CH), 126.0 (CH), 125.9 (C), 125.5 (q, J_{C-F} = 6.1 Hz, CH), 124.9 (q, J_{C-F} = 272.3 Hz, CF_3), 124.0 (q, J_{C-F} = 2.4 Hz, CH), 122.7 (CH), 118.9 (q, J_{C-F} = 30.3 Hz, C), 103.3 (CH), 74.3 (CH), 41.1 (CH_2), 40.4 (CH_2), 17.9 (CH_3), 14.1 (CH_3), 12.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -59.1 (s, CF_3). HRMS (ES^+) cald. for $(M+H)^+$ $C_{18}H_{21}O_2N_1F_3$: 340.1519, found: 340.1518.

(S)-Dimethenamid-CF_3 485

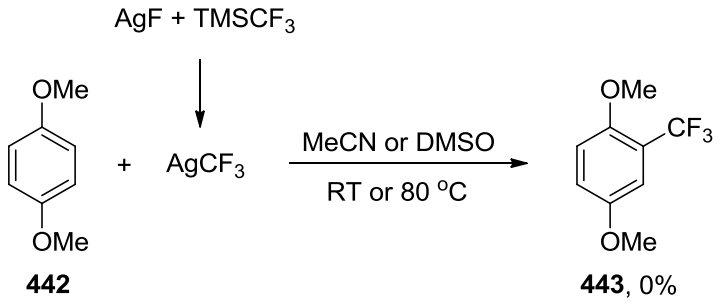


485

Prepared following general procedure A using (*S*)-dimethenamid (82.7 mg, 0.3 mmol). The reaction mixture was purified by flash chromatography using 5% Et_2O in DCM to afford **5** as a yellow oil (Yield = 86%). Mixture of rotamers (1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57–4.49 (m, $1H_{(rot\ maj)}$), 4.47–4.39 (m, $1H_{(rot\ min)}$), 3.62 (s, $2H_{(rot\ maj)}$), 3.62 (s, $2H_{(rot\ min)}$), 3.51–3.45 (m, $2H_{(rot\ min)}$), 3.40–3.31 (m, $2H_{(rot\ maj)}$), 3.27 (s, $3H_{(rot\ maj)}$), 3.21 (s, $3H_{(rot\ min)}$), 2.40 (s, $3H_{(rot\ maj)}$), 2.39 (s, $3H_{(rot\ min)}$), 2.18 (q, J_{H-F} = 1.8 Hz, $3H_{(rot\ min)}$), 2.17 (q, J_{H-F} = 1.9 Hz, $3H_{(rot\ min)}$), 1.21 (d, J = 7.0 Hz, $3H_{(rot\ min)}$), 1.12 (d, J = 7.0 Hz,

$3H_{(rot\ maj)}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 ($CO_{(rot\ maj)}$), 167.0 ($CO_{(rot\ min)}$), 139.8 (q, J_{C-F} = 1.9 Hz, $C_{(rot\ maj)}$), 139.4 (q, J_{C-F} = 1.9 Hz, $C_{(rot\ min)}$), 138.1 (q, J_{C-F} = 3.0 Hz, $C_{(rot\ min)}$), 137.9 (q, J_{C-F} = 3.0 Hz, $C_{(rot\ maj)}$), 135.4 ($C_{(rot\ min)}$), 134.9 ($C_{(rot\ maj)}$), 122.5 (q, J_{C-F} = 269.3 Hz, $CF_{3(rot\ maj)}$), 122.5 (q, J_{C-F} = 269.4 Hz, $CF_{3(rot\ min)}$), 122.1 (q, J_{C-F} = 8.5 Hz, $C_{(rot\ maj)}$), 121.7 (q, J_{C-F} = 8.3 Hz, $C_{(rot\ min)}$), 74.1 ($CH_{2(rot\ maj)}$), 73.9 ($CH_{2(rot\ min)}$), 58.5 ($CH_{3(rot\ maj)}$), 58.4 ($CH_{3(rot\ min)}$), 55.2 ($CH_{2(rot\ min)}$), 54.4 ($CH_{2(rot\ maj)}$), 42.4 (CH), 15.6 ($CH_{3(rot\ min)}$), 14.9 ($CH_{3(rot\ maj)}$), 13.8 ($CH_{3(rot\ min)}$), 13.2 ($CH_{3(rot\ maj)}$), 12.8 ($CH_{3(rot\ maj)}$), 12.4 ($CH_{3(rot\ min)}$); ^{19}F NMR (376 MHz, $CDCl_3$): δ -55.4 (s, $CF_{3(rot\ min)}$), -55.5 (s, $CF_{3(rot\ maj)}$). $[\alpha]_D$ = +0.4° (*c* = 0.9, MeOH). HRMS (ES^+) cald. for $(M+H)^+$ $C_{13}H_{18}O_2N_1S_1Cl_1F_3$: 344.0693, found: 344.0693.

Procedure for the investigation of $AgCF_3$ C –H activation mechanism



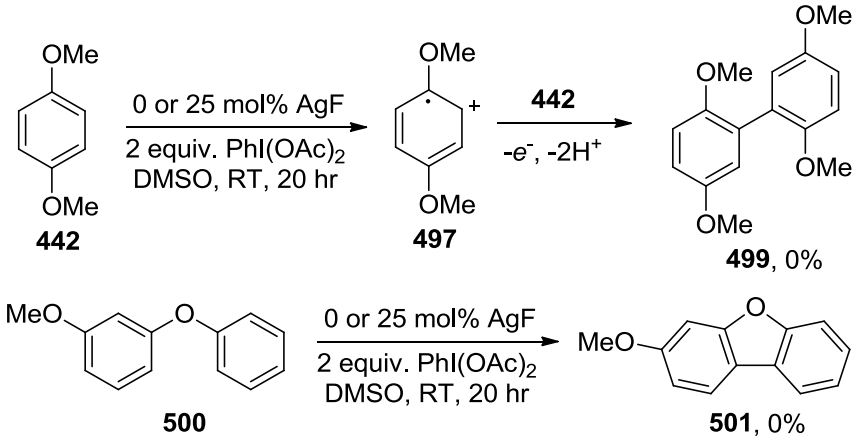
442 **443**, 0%

Silver(I) fluoride (38.1 mg, 0.3 mmol) was weighed in an oven-dried reaction vial (5 ml) and dissolved in solvent (DMSO or MeCN, 1 ml). Trimethyl(trifluoromethyl)silane (44.4 μL, 0.3 mmol) was added, and the reaction mixture was stirred at room temperature for 15 minutes. 1,4-Dimethoxybenzene **442** (41.4 mg, 0.3 mmol) was then added to the reaction mixture. The vial was sealed with a septum cap and the reaction was stirred either at room temperature or at 80 °C for 20 hours. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was analysed by ^{19}F NMR spectroscopy (4-fluoroanisole as the internal standard) in $CDCl_3$ to reveal no product was formed. Purification by column chromatography (SiO_2, DCM/pentane: 20%) gave only the starting material **442**.

Procedure for the investigation of electrophilic trifluoromethylation mechanism

An oven-dried reaction vial (5 mL) was charged with 1,4-dimethoxybenzene **442** (41.4 mg, 0.3 mmol), 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole **416** (148.5 mg, 0.45 mmol) and anhydrous DMSO (1 mL). The mixture was stirred at room temperature for 1 min and silver(I) fluoride (9.5 mg, 0.075 mmol) was slowly added to the stirring mixture. The vial was sealed with a septum cap and the reaction was kept stirring at the same temperature for 20 hours. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was analysed by ^{19}F NMR spectroscopy (4-fluoroanisole as the internal standard) in $CDCl_3$ to reveal no product was formed. Purification by column chromatography (SiO_2, DCM/pentane: 20%) gave only the starting material **442**.

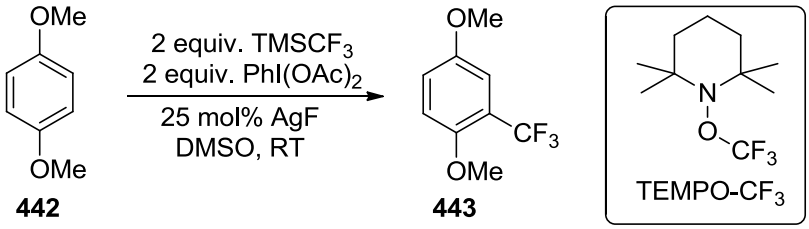
Procedure for the investigation of arene oxidation mechanism



An oven-dried reaction vial (5 mL) was charged with arene (**442** or **500**) (0.3 mmol) and (diacetoxyiodo)benzene (193.3 mg, 0.6 mmol) in anhydrous DMSO (1 mL). The mixture was stirred at room temperature for 1 min and silver(I) fluoride (9.5 mg, 0.075

mmol) was added slowly. The vial was sealed with a septum cap and the reaction was kept stirring at the same temperature for 20 hours. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (SiO_2, DCM/pentane: 20%) only to recover the starting material. Neither homocoupling product nor cyclisation product was observed by LC/MS or GC/MS analysis.

Procedure for radical quenching experiment:

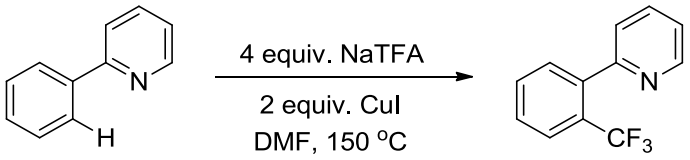


Additive	Yield (%)
TEMPO	<1
Galvinoxyl	<1

To an oven-dried reaction vial (5 mL) charged with 1,4-dimethoxybenzene **442** (41.4 mg, 0.3 mmol), (diacetoxyiodo)benzene (193.3 mg, 0.6 mmol), a radical scavenger (0.6 mmol) and trimethyl(trifluoromethyl)silane (88.7 μL, 0.6 mmol) in anhydrous DMSO (1 mL) was slowly added silver(I) fluoride (9.5 mg, 0.075 mmol). The vial was sealed with a septum cap and the reaction was stirred at room temperature for 20 h. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was analysed by ^{19}F NMR spectroscopy (4-fluoroanisole as the internal standard) in $CDCl_3$. No trifluoromethylation product was formed with either TEMPO or galvinoxyl. With TEMPO, a characteristic oxygen-CF_3 ^{19}F NMR peak was obtained, indicating the formation of TEMPO-CF_3; ^{19}F NMR: δ -55.6 (89% NMR yield); This species has been reported in similar control experiments by a number of other groups.[277,278,279]

5.4.2 Copper-mediated C–H trifluoromethylation using NaTFA

A current optimised procedure for trifluoromethylation of 2-phenylpyridine



53 **506**

An oven-dried reaction vial (5 mL) was charged with 2-phenylpyridine **53** (42.9 µl, 0.3 mmol), copper (I) iodide (114.3 mg, 0.6 mmol), sodium trifluoroacetate (163.2 mg, 1.2 mmol) and anhydrous DMF (1 mL). The vial was sealed with a septum cap, and the mixture was heated up to 150 ℃ and stirred at that temperature for 24 hours. The resulting mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using 30% Et_2O in hexane to afford 2-(2-(trifluoromethyl)phenyl)pyridine **506** as a colourless oil (Yield = 23%);[218] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 4.3 Hz, 1H), 7.74 (d, J = 10.1 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.54–7.48 (m, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.29–7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7 (C), 149.1 (CH), 140.0 (C), 135.8 (CH), 131.5 (CH), 131.4 (CH), 128.2 (CH), 128.1 (q, J_{C-F} = 31.1 Hz, C), 126.3 (q, J_{C-F} = 5.4 Hz, CH), 124.0 (q, J_{C-F} = 272.8 Hz, CF_3), 123.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.1 (s, CF_3).

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