QUEEN MARY UNIVERSITY OF LONDON

Controlling Regioseletivity and Enantioselectivity in C–H activation

Submitted in partial fulfillment of the requirements of the Degree of Doctor of Philosophy

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2015

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Abstract

The direct functionalisation of C–H bonds has emerged in recent years as an efficient and atom-economic alternative to the traditional cross coupling reaction. One of the challenges towards this goal is the selective transformation of a particular C–H bond amongst many other C–H bonds. This thesis describes studies on the use of CO_2 as a traceless promoter for controlling *meta*-regioselective arylation of phenols and a separate investigation into an enantioselective arylation of pre-chiral η^6-arene tricarbonyl chromium complexes.

The introduction provides a general review of recent advances in the use of coordinating moieties as directing groups for selective activation of aromatic C–H bonds. The challenge of *meta*-selective C–H activation and the direct functionalisation of phenols is assessed and discussed. To overcome the scarce methods for accessing *meta*-arylated phenols, our objective was to develop an efficient methodology for the *meta*-arylation of phenols. Our strategy includes an *ortho*-carboxylation of the phenol followed by *ortho*-arylation of the salicylic acids and the subsequent protodecarboxylation to afford *meta*-arylphenols is proposed.

A step-wise approach towards our aim is applied. First, a convenient and efficient method for the carboxylation of phenols is presented in Chapter 2. Then, a tandem arylation/decarboxylation reaction of salicylic acids is described in Chapter 3. Last, an efficient methodology for the *meta*-arylation of phenols *via* carboxylation/arylation/decarboxylation processes in one-pot is presented in the following section in Chapter 3. To demonstrate the utility of this powerful methodology, an efficient synthesis of ϒ-secretase inhibitor and the further transformation of the *meta*-arylphenols are shown. Furthermore, an alternative method is described for the synthesis of *meta*-arylphenols *via* a tandem oxidation/arylation/decarboxylation reaction of salicylaldehydes.

In Chapter 4, an approach towards the development of enantioselective C–H arylation leading to planar chirality is stated. Preliminary results are presented for this ongoing project.

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List of abbreviations

- ^{t}AmylOH = 2-Methyl-2-butanol
- Boc-Ile-OH = *N*-(*tert*-Butoxycarbonyl)-L-isoleucine
- Boc-Val-OH = *N*-(*tert*-Butoxycarbonyl)-L-valine
- Boc-Phe-OH = *N*-(*tert*-Butoxycarbonyl)-L-phenylalanine
- Bz-Leu-OH (L-MPAA) = *N*-Benzoyl-L-leucine
- COD = 1,5-Cyclooctadiene
- COE = Cyclooctene
- cm-Phos = 2-[2-(Dicyclohexylphosphino)phenyl]-1-methyl-1H-indole
- CMD = Concerted-metalation-deprotonation
- DABCO = 1,4-Diazabicyclo[2.2.2]octane
- DCE = 1,2-Dichloroethane
- DCM = Dichloromethane
- DMF = Dimethylformamide
- DMSO = Dimethylsulfoxide
- DGs = Directing groups
- dppb = 1,4-Bis(diphenylphosphino)butane
- dppp = 1,3-Bis(diphenylphosphino)propane
- dppe = 1,2-Bis(diphenylphosphino)ethane
- dba = Dibenzylideneacetone
- EDGs = Electron-donating groups
- EWGs = Electron-withdrawing groups
- *ee* = Enantiomeric excess
- ES = Electrospray
- FePc = Iron-phthalocyanine
- GC-MS = Gas Chromatography-Mass Spectrometry
- HDL = High-density lipoprotein cholesterol
- HPLC = High-performance liquid chromatography
- HRMS = High Resolution Mass Spectrometry
- IR = Infrared

- Ind = Indenyl
- LDL = Low-density lipoprotein cholesterol
- NMR = Nuclear magnetic resonance
- NMP = *N*-methyl-2-pyrrolidone
- PEPPSI-IPr = [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
- PEPPSI-IPent = [1,3-Bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
- PG = Protecting group
- RDGs = Removable directing groups
- (*R*)-MOP = (*R*)-(+)-2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
- S_EAr = Electrophilic aromatic substitution
- sox = Sulfoxide-oxazoline
- (*S*)-BINAP = (S)-(−)-(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
- (*S*)-BIANP(O) = (*S*)-(−)-(2'-(diphenylphosphanyl)-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide
- (*S*)-*H₈*-BINAP = (*S*)-(−)-2,2′-Bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl
- (*S*)-*H₈*-BINAP(O) = (*S*)-(−)-(2'-(diphenylphosphanyl)-4'a,5,5',6,6',7,7',8,8',8'a-decahydro-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide
- (*S*)-MeO-BIPHEP = (*S*)-(−)-2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
- (*S*)-SEGPHOS = (*S*)-(−)-5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
- (*S*)-BINOL = (*S*)-(−)-1,1′-Binaphthalene-2,2′-diol
- TFA = Trifluoroacetic acid
- TEMPO = 2,2,6,6-Tetramethyl-1-piperidinyloxy
- $TMSCHN_2$ = Trimethylsilyldiazomethane
- THF = Tetrahydrofuran
- Ts = Tosyl
- TBAI = Tetrabutylammonium iodide
- TMP = 2,2,6,6-tetramethylpiperidine
- TLC = Thin Layer Chromatography
- UV = Ultraviolet radiation

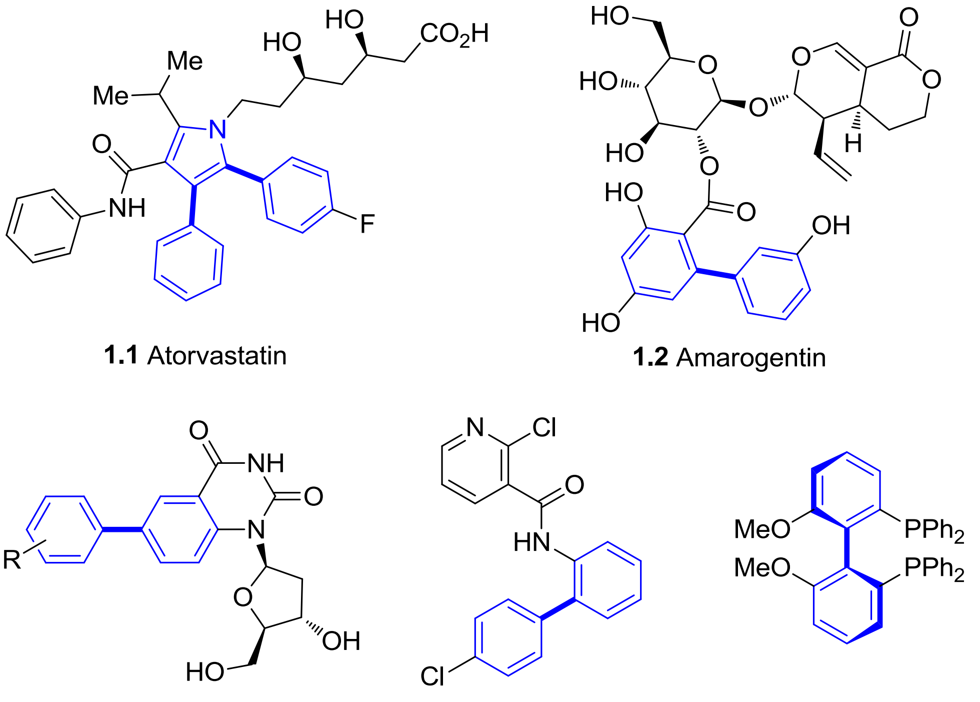
Chapter 1

Chapter 1 Background and Objectives

1.1 *Meta*-selective C–H activation

1.1.1 Introduction

Aryl–aryl bond formation is of great interest in organic synthesis as the biaryl motif is widely found in a variety of natural products as well as pharmaceuticals, agrochemicals and advanced materials. Aromatic rings are also relevant constituents of many ligands, being particularly interesting the axial chiral biaryls used in enantioselective catalysis. Examples of these are shown in **Scheme 1.1**.



1.1 Atorvastatin

1.2 Amarogentin

1.3 Fluorescent pyrimidine analogs

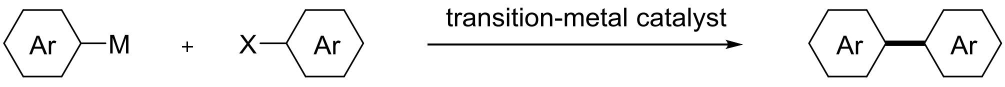
1.4 Boscalid

1.5 (*S*)-MeO-BIPHEP

Scheme 1.1 Molecules that contain biaryl substructure

The calcium salt of atorvastatin (**1.1**), sold under the trade name LIPITOR®, is one of the most popular drugs containing the biaryl substructure. As a prescription medicine it is used for not only lowering "bad" cholesterol (LDL), but also raising "good" cholesterol (HDL) in blood. It was the most worldwide sold drug in 2009, which generated $16,537 million in revenue as reported by Pfizer.[1] Amarogentin (**1.2**) is one of the most bitter natural compounds known, it is found in the gentian root which is used for the treatment of digestive disorders.[2] Fluorescent materials **1.3**, frequently based on the biaryl core are increasingly important in sensing applications. Boscalid (**1.4**) is a fungicide widely used to control a range of plant pathogens in broadacre and horticultural crops. Chiral ligands are vital components in enantioselective transformations and many of them contain the biaryl motif, for example the MeO-BIPHEP ligand (**1.5**). Its applications include Rh(I)-catalysed asymmetric isomerizations of allylamines to enamines[3] and Pd(0)-mediated cyclizations of hydroxy allylic carbonates.[4] All of these examples demonstrate that the construction of aryl–aryl bond constitutes an important tool in organic synthetic chemistry.

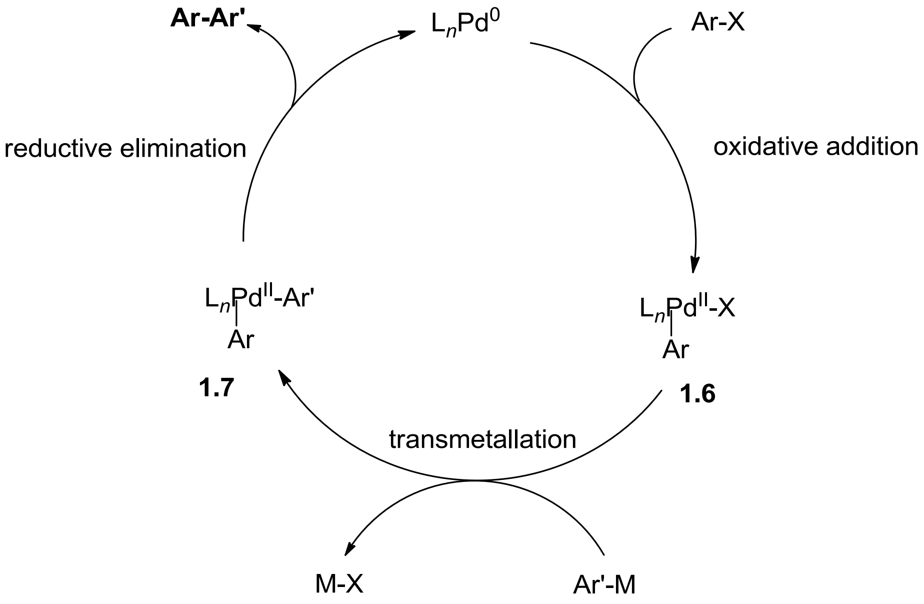
In order to stitch the carbon atoms together, chemists historically had to kick-start the reaction between two carbon atoms using reactive reagents. Such methods do work when building up simple molecules, but it encounters problems when creating more complex molecules due to the undesired by-products. However, particularly in the case of biaryl synthesis, palladium catalysed cross couplings has provided a precise and efficient method to construct C–C bond. The importance and high impact of this transformation was recognized in 2010, when Richard F. Heck, Ei-ichi Negishi and Akira Suzuki received the Nobel Prize in Chemistry for their contributions on "*Palladium-catalysed cross-couplings in organic synthesis*".[5] Some specific reactions, named after the chemist who developed each particular cross-coupling, are shown in **Scheme 1.2**.



M=$B(OR)_2$, Suzuki Coupling
M=ZnR, Negishi Coupling
M=SiR_3, Hiyama Coupling
M=MgX, Kumada Coupling
M=SnR_3, Stille Coupling

Scheme 1.2 Traditional cross-coupling transformations

The mechanisms of these traditional transformations usually involve the oxidative addition of the haloarene to Pd(0) to form the Pd(II) species **1.6**, followed by transmetallation from the organometallic reagent into species **1.6**, forming the diaryl-Pd(II) species **1.7**. The biaryl product is formed after reductive elimination from species **1.7**, simultaneously regenerating Pd(0) (**Scheme 1.3**).



Scheme 1.3 Mechanism of the traditional Pd-catalysed cross coupling

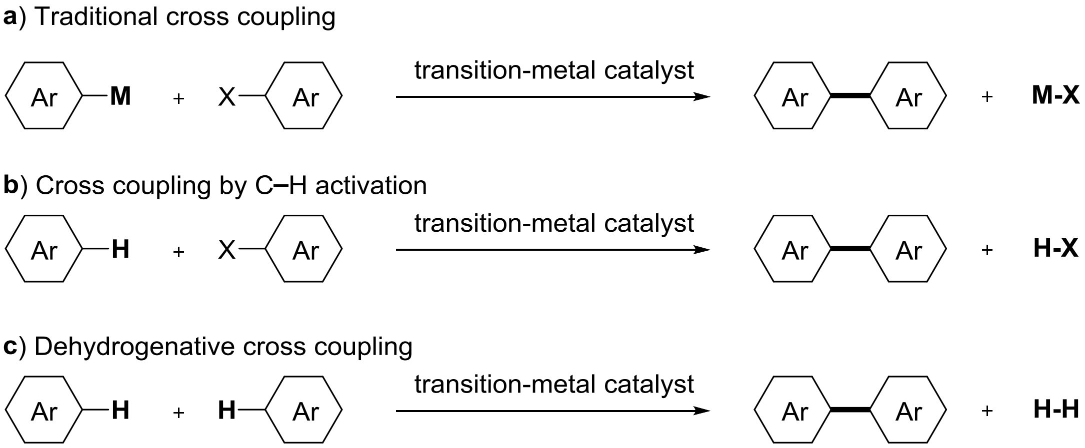
1.1.2 C–H activation

Even though traditional cross couplings are extensively utilised in the construction of aryl–aryl bond, they still encounter several intrinsic disadvantages (**Scheme 1.4**, **a**).

1) Usually several synthetic operations are required for the pre-installation of a metal on the aromatic ring to form the organometallic reagent, which makes the process less efficient. Moreover, it is not atom-economic due to the requirement for stoichiometric amounts of metals to form the organometallic reagents.

2) The heavy metal salts (M-X) formed as waste are in some cases very toxic, such as SnR_3X waste generated in the Stille cross coupling.

Therefore, chemists have sought to develop new and more efficient aryl–aryl bond forming methods in the past decades. As a result, catalytic C–H activation shows its potential to fulfil this requirement as it allows efficient and economical access to myriad known and yet unknown molecules (**Scheme 1.4**, **b**).[6] The replacement of the organometallic reagent with a simple arene makes the reaction more efficient since pre-functionalisation is obviated for this reagent, as well as more environmentally friendly because the waste product is less toxic. The ideal scenario is dehydrogenative cross coupling that does not require pre-functionalisation of either arene, forming aryl–aryl bond in the most efficient way (**Scheme 1.4**, **c**). However, an external oxidant is usually required.



Scheme 1.4 Comparison of tradition cross coupling and C–H activation

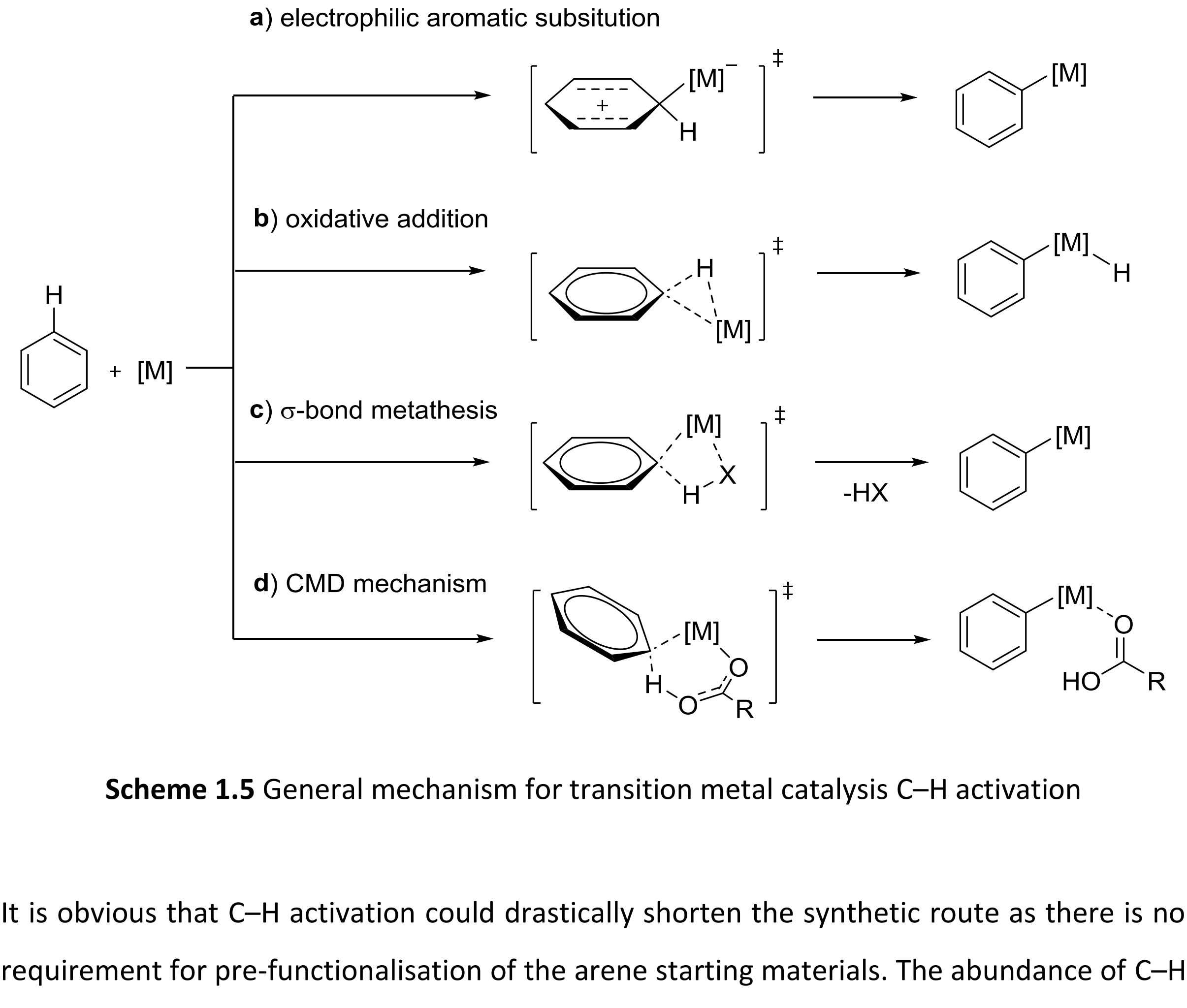
Generally, the main challenge that this type of processes faces is the C–H activation step, due to the intrinsically low reactivity of C–H bonds and the difficulties of controlling the selectivity when many of them are present. There are four major kinds of mechanisms for the transition metal mediated C–H activation (**Scheme 1.5**):[7]

a) Traditional electrophilic aromatic substitution, which usually involves a rate-limiting metalation of the arene to form an unstable Wheland intermediate, followed by a rapid deprotonation step with re-aromatisation to form the metal-aryl intermediate (**Scheme 1.5**, **a**).[8]

b) Oxidative addition, usually takes place with low-oxidation state, electron-rich transition metals to form metal hydride species by the addition of the C–H bond into the metal centre (**Scheme 1.5**, **b**).[9]

c) σ-Bond metathesis, typically through a four-membered cyclic transition state, forming metal-aryl intermediate by the loss of HX (**Scheme 1.5**, **c**).[10]

d) Concerted-metalation-deprotonation (CMD) mechanism which requires the assistance of a carboxylate or carbonate. A six-membered cyclic transition state involving the metal carboxylate (or carbonate) and arene, results in simultaneous cleavage of the C–H bond and formation of a metal-aryl intermediate (**Scheme 1.5**, **d**).[11]



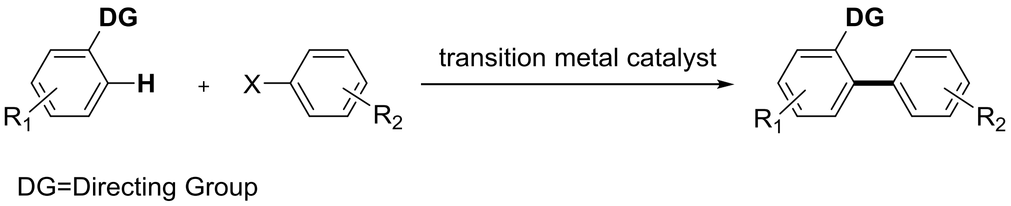
Scheme 1.5 General mechanism for transition metal catalysis C–H activation

It is obvious that C–H activation could drastically shorten the synthetic route as there is no requirement for pre-functionalisation of the arene starting materials. The abundance of C–H bonds in nature provides precedent for developing methodologies that enable the conversion of C–H bonds into valuable functionalised organic molecules. However, there are still significant hurdles to be overcome:

1) Harsh conditions are usually required due to the intrinsic low reactivity of C–H bond (aromatic C(sp^2)–H bond energies are generally in the order of 100 kcal/mol), consequently, resulting in low substituted toleration.
2) Poor chemoselectivity, as most of functional groups present in the molecule may be more reactive than the targeted C–H bond. Thus, undesired products may be generated during the C–H activation.
3) Poor regioselectivity, due to the ubiquitous nature of C–H bonds in organic molecules.

In this thesis, we will focus on the third point in particular for the regioslective functionalisation of aromatic compounds. In this approach, it is obviously necessary to control the regioselectivity while dealing with molecules containing more than one C–H bond. However, to obtain high regioselectivity in the direct arylation of substituted arenes is a big challenge, especially when a requirement for overcoming their 'natural' reactivity controlled by the electronic properties of their substituents is demanded.

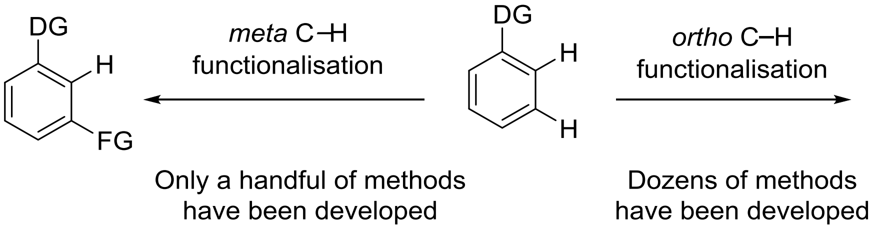
The most common strategy for inducing regioselectivity relies on the use of directing groups (DGs) which coordinate the transition-metal catalyst, forced to activate the proximal C–H bond, consequently achieving the selectivity in both intramolecular and intermolecular direct arylation (**Scheme 1.6**).



Scheme 1.6 C–H activation in the presence of DGs

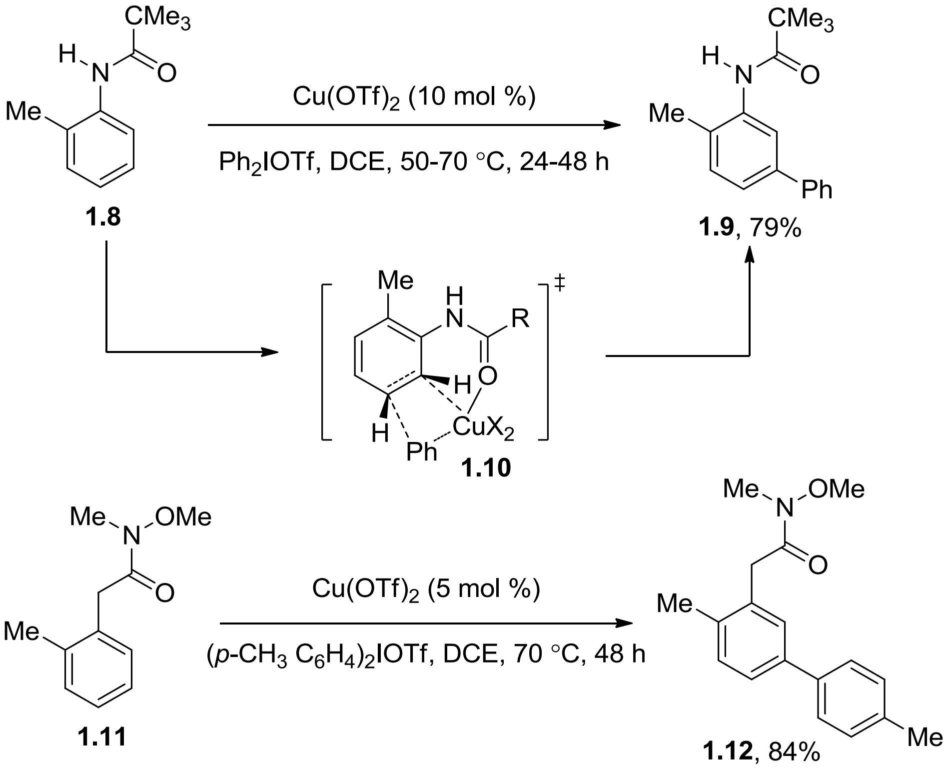
1.1.3 *Meta*-selective functionalisation

Even though the use of DGs for regioselectivity-controlling groups can direct site-selective C–H activation because of its σ-chelating coordination ability, the DGs direct the transition metal into close proximity to the C–H bond to be activated. Moreover, a conformationally rigid five- or six-membered cyclic pre-transition state is usually formed, thus *ortho*-selective C–H activation takes place in most of the cases. Therefore, a great many methods have been reported for *ortho*-selective functionalisation by the use of DGs,[12] whereas *meta*- and *para*-selective functionalisation methods are still significantly underdeveloped (**Scheme 1.7**).[13]



Scheme 1.7 Regioselectivity in C–H functionalisation in the presence of DGs

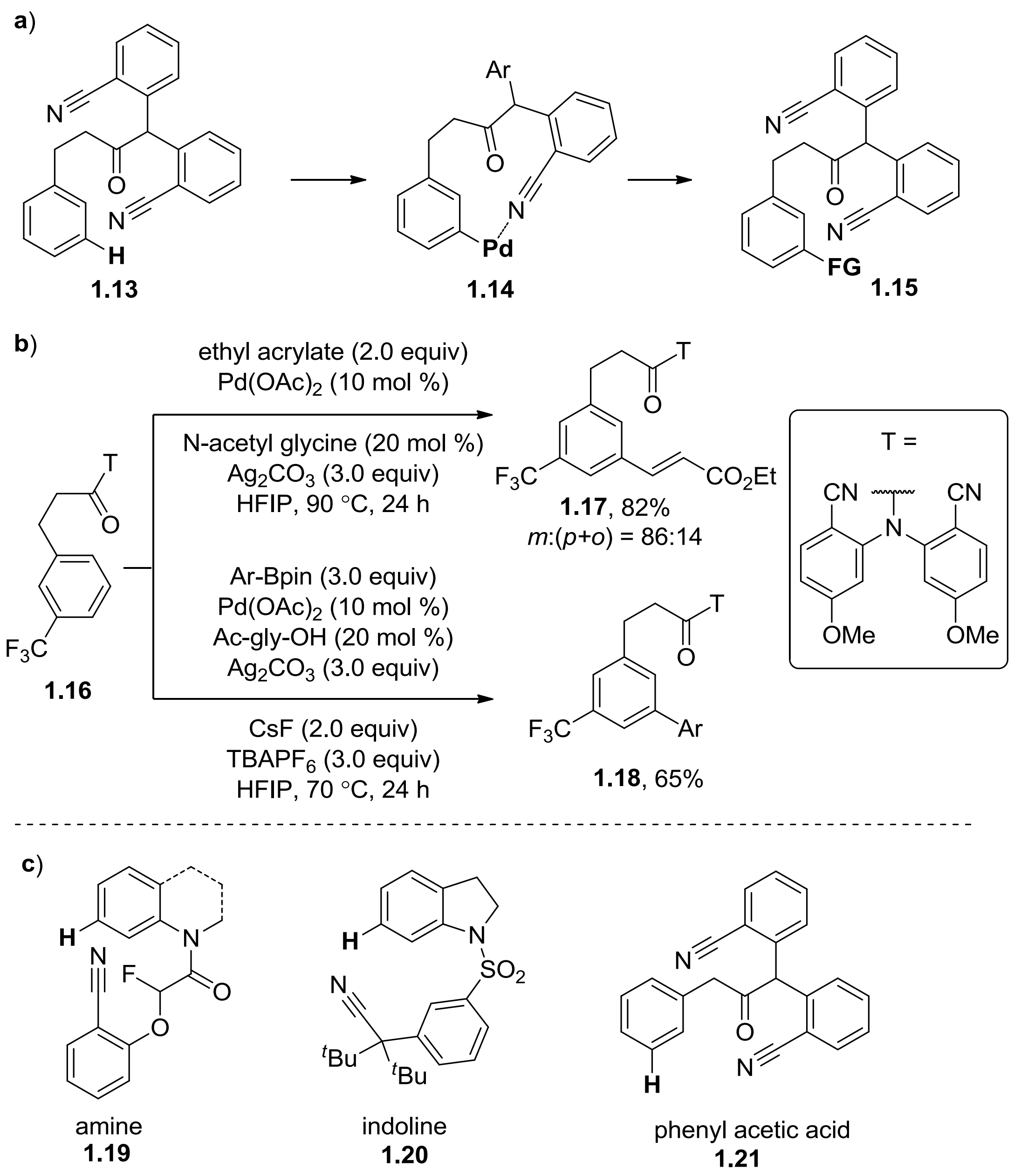
To date, only a handful of methodologies for the *meta* C–H functionalisation have been reported. Pioneering reports by Gaunt and co-workers described the use of acetanilide and acetamide as DGs for *meta*-selective direct arylation under Cu catalysis conditions.[14] The authors proposed an oxy-cupration across the 2,3-positions of the aromatic ring with participation of the carbonyl oxygen. Later on, however, a theoretical study by Wu's group suggested a Heck-like four-membered-ring transition state involving a Cu(III)-Ph intermediate (**1.10**)[15] even though the exact mechanism of the reaction remains unclear. However, the method is limited exclusively to the use of 2-oxo-substituted directing groups, and the non-commercially available Ar_2IOTf species as the coupling partner (**Scheme 1.8**).



Scheme 1.8 Cu-catalysed *meta*-selective arylation

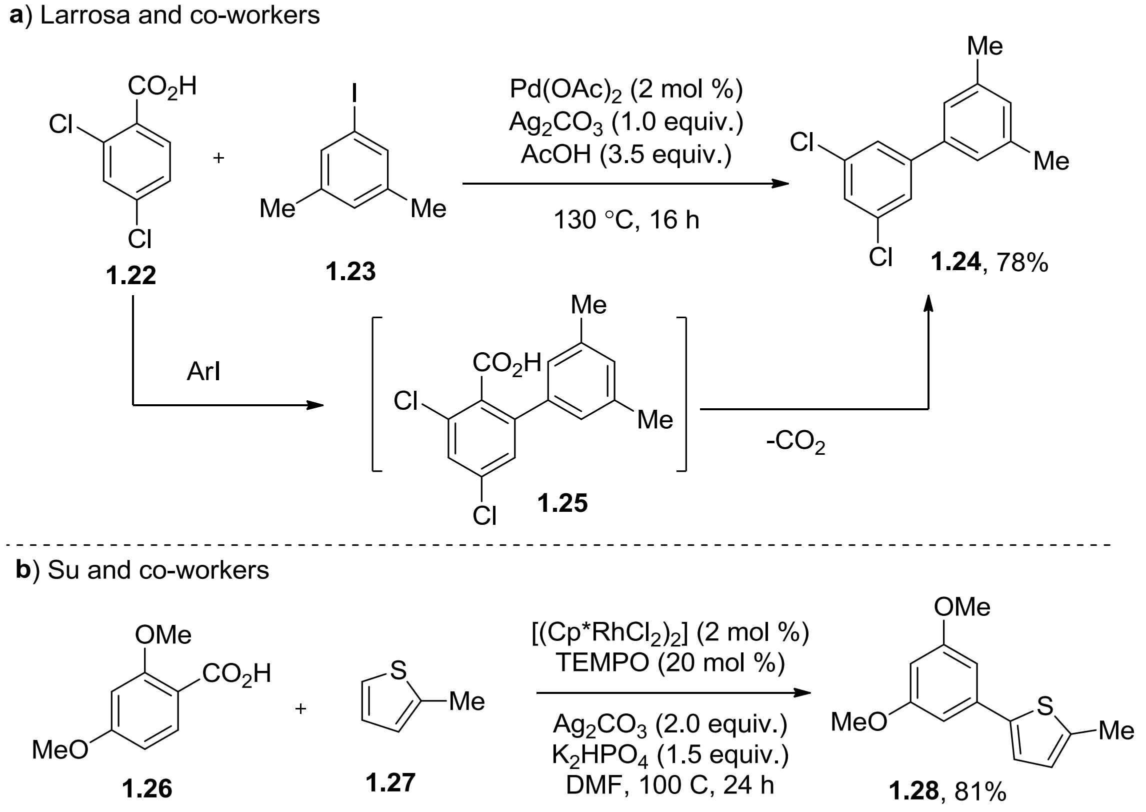
Instead, Yu and co-workers demonstrated a method for *meta*-olefination and arylation assisted by an end-on template (**Scheme 1.9**, **b**).[16] An innovatively designed moiety containing a strategically positioned nitrile group that is able to coordinate a Pd catalyst is installed and therefore directs the functionalisation in the *meta*-position (**Scheme 1.9**, **a**). This strategy was then applied in many other substrates such as phenyl amines **1.19**[17], indolines **1.20**[18] and phenyl acetic acids **1.21**[19], by introducing different precisely designed templates that control the C–H functionalisation at *meta*-position (**Scheme 1.9**, **c**).

However, this method is limited due to the requirement of a covalently attached complex template, which makes the process less atom- and step-economic. The need for a particular template matching each substrate also limits its application.



Scheme 1.9 Template assisted *meta*-selective functionalisation

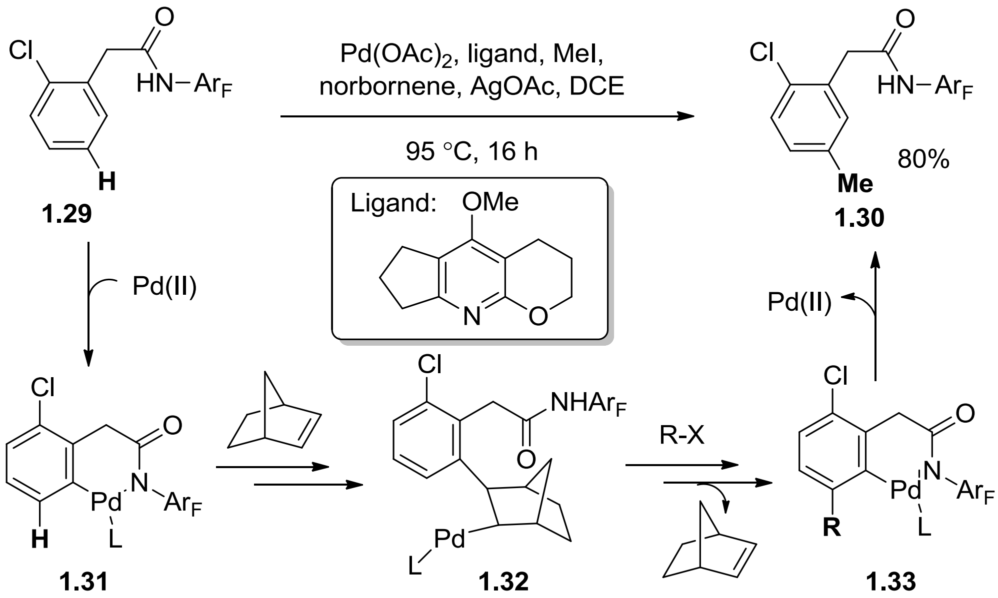
Our group published a method for accessing the *meta*-substituted biaryls by the use of carboxylic acid as a removable *ortho*-directing group. Direct arylation catalysed by Pd in the *ortho*-position of the carboxylic acid group takes place with a subsequent *in situ* protodecarboxylation, forming a *meta*-substituted biaryl (**Scheme 1.10**, **a**).[20] Unlike the previous methods reported by Gaunt's and Yu's groups, where particular directing groups are required, in this method, biaryls with a variety of *meta*-substituents such as -Me, -OMe, -Cl, -F, -NO_2, -CF_3 can be transformed from the corresponding *ortho*-substituted benzoic acids, owing to the loss of the real directing group. Su and co-workers used the same strategy, with Rh(III) catalysed C–H/C–H cross coupling reaction, achieving *meta*-arylation *via* a tandem arylation/decarboxylation process (**Scheme 1.10**, **b**).[21]


a) Larrosa and co-workers

b) Su and co-workers

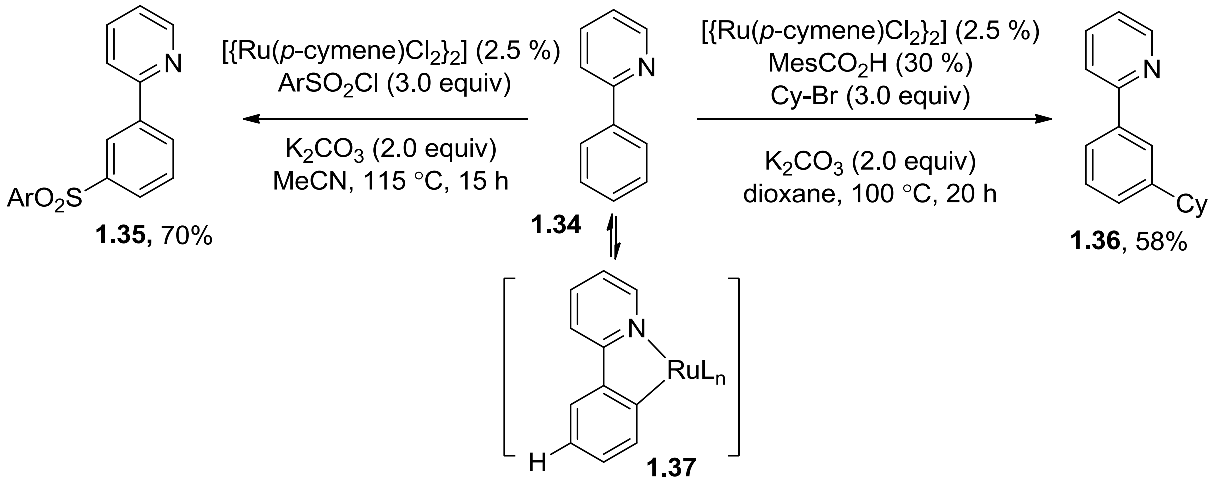
Scheme 1.10 CO_2 as a traceless directing group for accessing the *meta*-substituted biaryls

Very recently, Yu's group has developed a strategy *via* a Catellani-like process[22] (**Scheme 1.11**).[23] The process starts with an *ortho* C–H activation of **1.29**, giving palladacycle **1.31**, followed by the insertion of norbornene to give place to complex **1.32** which contains the Pd centre in the appropriable position for C–H activation of the original *meta* C–H bond. The *meta*-functionalised product **1.30** is therefore generated *via* a stepwise process involving *meta* C–H activation, oxidative addition, reductive elimination and β-carbon elimination of norbornene. The Pd catalyst was regenerated by protodemetallation. It is an attractive method for *meta*-selective functionalisation without any introduction of other regioselectivity-controlling groups by the use of a transient norbornene. However, the reaction scope is currently extremely limited in the iodoarenes coupling partner as is the case in most Catellani-type processes. Later on, Dong and co-workers also reported a method using Pd/norbornene catalysis, which allows *meta*-selective C–H arylation of simple dimethylaniline.[24]



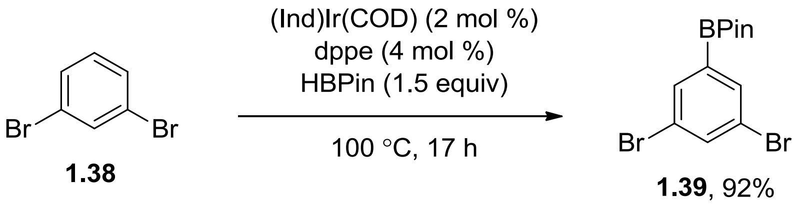
Scheme 1.11 Norbornene as a transient mediator for *meta*-functionalisation

In 2011, Frost *et al*. reported a *meta*-sulfonation taking advantage of the *para*-directing effect of Ru on an electrophilic aromatic substitution (S_EAr) on ruthenacycle **1.37** (**Scheme 1.12**, left).[25] Afterwards, Hofmann and Ackermann applied this method for *meta*-alkylation of 2-phenylpyridines (**Scheme 1.12**, right).[26]



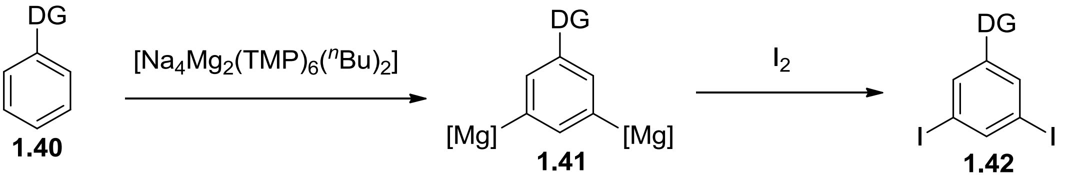
Scheme 1.12 Ru-catalysed *meta* C–H functionalisation

Beyond directing groups, methodologies for *meta*-selective borylation and one-pot borylation/functionalisation of 1,3-disubstituted arenes at C5 position have been reported by Hartwig, Miyaura *et al*. and Smith *et al*.[27] Regioselectivity was shown to be dictated by a minimisation of the steric hindrance around the catalyst (**Scheme 1.13**).



Scheme 1.13 Ir-catalysed borylation of 1,3-disubstituted arene at C5 position

A template base, [$Na_4Mg_2(TMP)_6(^nBu)_2$], directed *ortho-meta*′ and *meta-meta*′ dimetalation (D*om*M, D*mm*M) depending on the directing groups was developed by O'Hara's group (**Scheme 1.14**). The regioselectivity is controlled by the interaction between the template base cage and the directing group (**Figure 1.1**).[28]



DG = NMe_2, N^iPr2, ^{t}Bu

When DG = OMe, CH_2OMe, O^tBu, CF_3 *et al*. *ortho-meta*' demetalation took place

Scheme 1.14 Directed *meta-meta*′ metalation and subsequent electrophilic addition

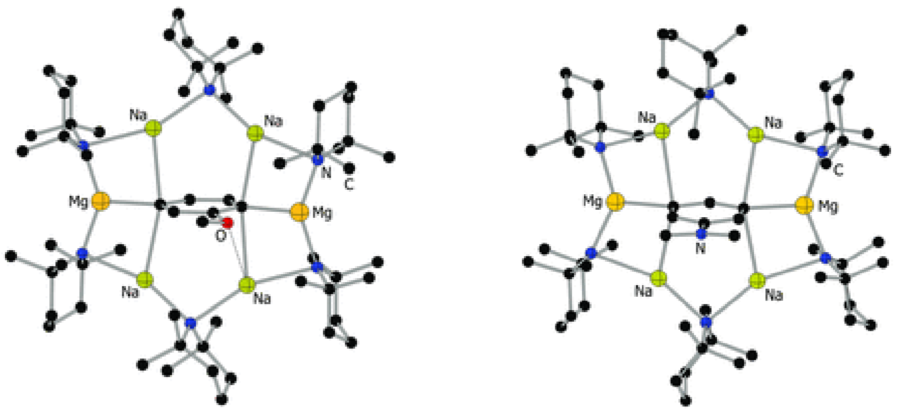


Figure 1.1 Molecular structures: D*om*M (left) and D*mm*M (right)

1.1.4 Conclusions

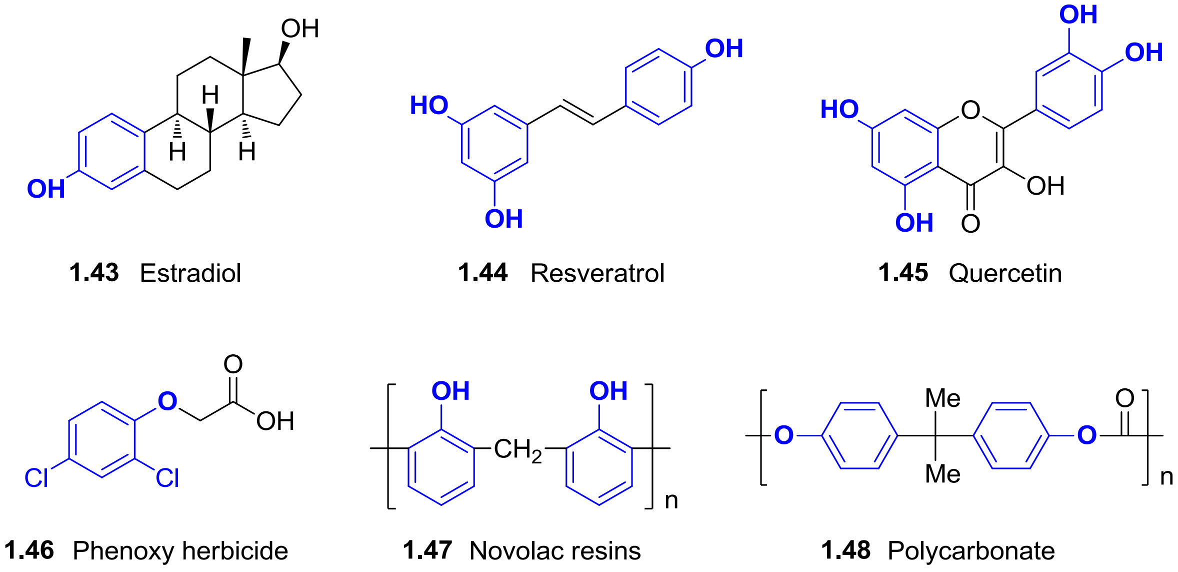
In conclusion, catalytic C–H functionalisation has received great attention due to its simple, and efficient access to myriad known and yet unknown molecules. Over the last decades, an array of methodologies for *ortho* C–H functionalisation compatible with a variety of directing groups have been reported, but there is still a lack of directing groups that can lead to *meta*-selective C–H activation, with the only examples reported by Gaunt and co-workers for Cu-catalysed *meta*-selective arylation of acetanilide and acetamide and Yu and co-workers who developed a series of nitrile containing U-shaped templates that are able to coordinate with Pd catalyst thus control the functionalisation of C–H bond at the *meta*-position. An alternative efficient strategy that allows access to a variety of *meta*-substituted biaryls by the use of a removable directing group was developed by our group. Su and co-workers applied it in a Rh(III) catalysed C–H/C–H cross coupling system. Very recently, Yu's and Dong's groups have developed an efficient methodology for *meta*-functionalisation by the use of norbornene as a transient mediator *via* a Catellani-like process. Beyond directing groups, the work reported by Hartwig and Smith that used Ir-catalysed *meta*-borylation of 1,3-disubstited arenes and O'Hara's work on the template base directed *ortho*-*meta'* and *meta*-*meta'* dimetalation constitute powerful alternatives. However, they are extremely limited to particular substrates.

On the other hand, the low availability of *meta* C–H functionalisation methodologies is striking when compared with the number of *meta*-substituted motifs in pharmaceuticals, biologically active molecules and materials, thus, developing more general *meta*-selective C–H functionalisation methods is highly desired.

1.2 Functionalisation of phenols

1.2.1 Importance of phenols

In this thesis, we targeted the direct functionalisation of phenols as they are important central motifs that are abundant in many natural products, pharmaceuticals and agrochemicals, they are also found in catalysis ligands and polymers. Moreover, the high reactivity of phenol derivatives makes them versatile building blocks for organic synthesis.[29]

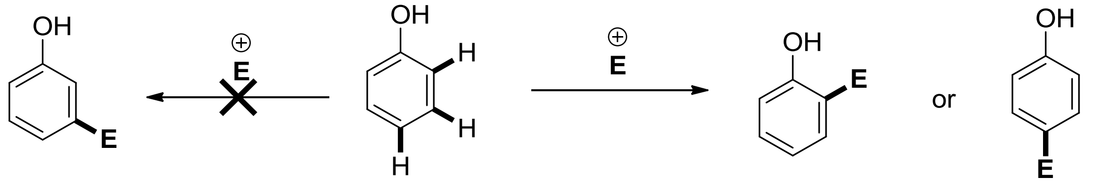


Scheme 1.15 Phenol-containing molecules

For example, Estradiol (**1.43**), is well-known to drive the development of secondary sex characteristics in women. It is not only essential for the development and maintenance of female reproductive tissues, but also vital for keeping men's joints and brains healthy.[30] Another example, Quercetin (**1.45**) is widely distributed in nature, it has been found in many fruits, vegetables and grains,[31] and it is used as a health care product as its powerful antioxidant properties can help protect the body against harmful free radicals. Polymers such as phenol formaldehyde resin and polycarbonate can be used in a variety of areas involving electronic applications, automotives, aircrafts, fiberglass, sound walls and so on, and both are made from the corresponding phenolic precursor.[32]

1.2.2 Site-selective functionalisation of phenols

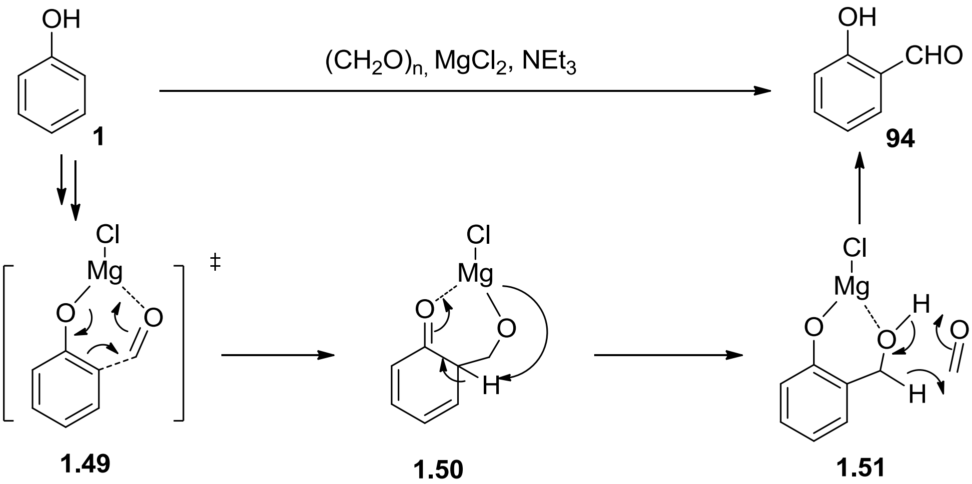
The functionalisation of phenols is of great interest and many efforts have been made in the past generally taking advantage of their nucleophilic character. Due to the well-known electron-donating nature of the hydroxyl group, electrophilic substitution on phenols is highly favoured at the *ortho*- and *para*-positions, as a result, many methodologies for site-selective *ortho*- and *para*-functionalisation of phenols have been reported and commonly exploited. On the other hand, there is no example that could lead to *meta*-functionalised phenols merely by a single synthetic operation from parent phenols to date (**Scheme 1.16**).



Scheme 1.16 Direct functionalisation of phenols is favoured at *ortho*- and *para*-positions

Ortho-functionalisation of phenols

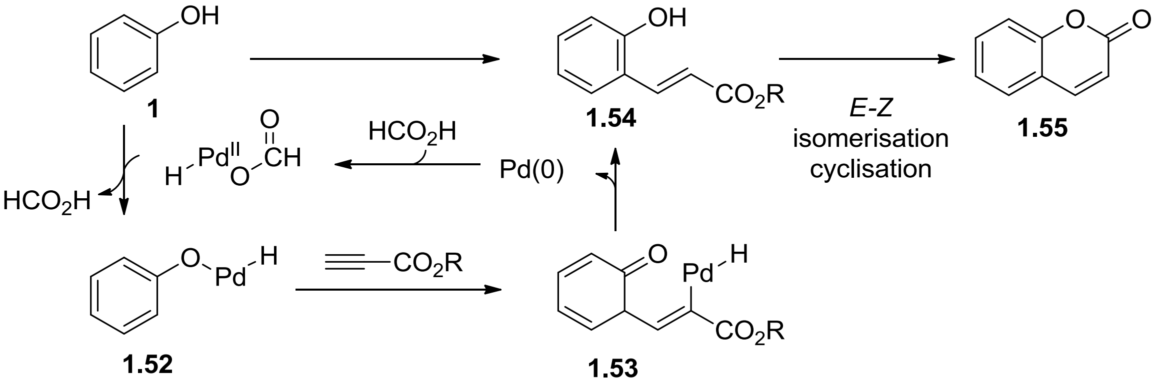
Methodologies for *ortho*-selective functionalisation of phenols are generally based upon an active role of the hydroxyl group, by means of hydrogen bonding or coordination. For example, the selective *ortho*-formylation of phenol was achieved by the assistance of magnesium, which acts as a Lewis acid coordinating both the phenol and the formaldehyde, directing it to the *ortho*-position to form species **1.50** *via* a transition state **1.49**. Re-aromatisation then forms hydroxymethylated phenol magnesium salt (species **1.51**), which is oxidised to aldehyde by hydrogen transfer with a second equivalent of formaldehyde (**Scheme 1.17**).[33] Thus, the coordinating ability of the hydroxyl group with magnesium is essential for this reaction to proceed selectively at the *ortho*-position.



Scheme 1.17 Magnesium-mediated *ortho*-formylation of phenol

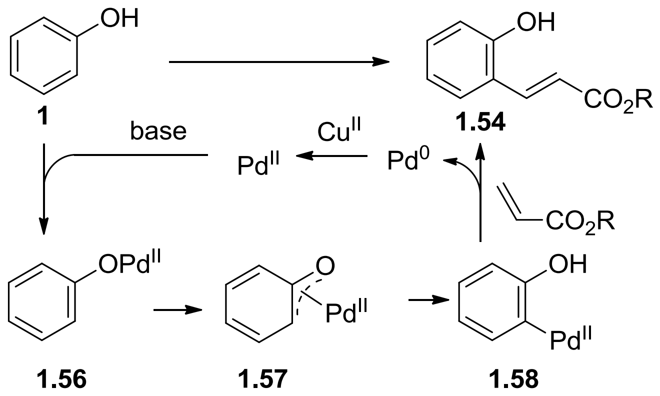
A large amount of work based upon transition metal catalysed *ortho*-functionalisation of phenols has been reported in the past decade. In this area, the participation of the hydroxyl group is also essential for the reaction with regard to both reactivity and regioselectivity.

Pioneering work was reported by Toste and Trost who synthesised coumarins by Pd(0)-catalysed direct *ortho*-olefination of phenols from alkynes in formic acid, followed by nucleophilic attack for cyclisation.[34] From the proposed mechanism in **Scheme 1.18**, the coordination between Pd and the hydroxyl group in the assistance of formic acid is necessary, with the formation of species **1.52**. The insertion of an alkyne leads to **1.53** which followed by reductive elimination to afford *ortho*-olefin phenols **1.54**. Finally, isomerisation cyclisation of **1.54** gives place to coumarin **1.55**.



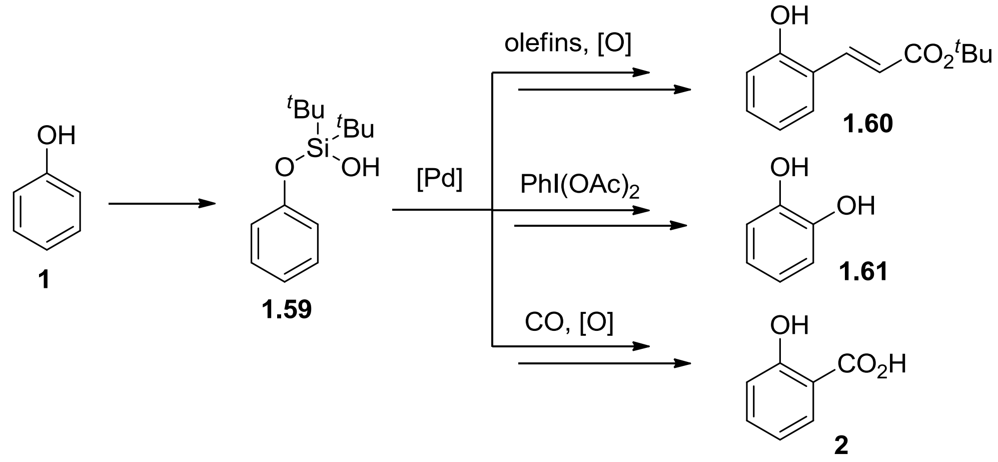
Scheme 1.18 Pd(0)-catalysed direct synthesis of coumarins

Afterwards, Fujiwara and co-workers used Pd(II) catalysis to efficiently activate the *ortho* C–H bond of phenol by the use of TFA.[35] More recently, Malti and Shi's research groups realised that base could accelerate Pd(II)-catalysed *ortho*-couplings of phenol with olefins.[36] In this process, intermediate **1.56** forms by coordinating phenoxide with palladium catalyst in the presence of base, and then Pd 1,3-migration to generate intermediate **1.58** *via* **1.57**, Alkene insertion and β-H elimination releases the alkenylated product (**Scheme 1.19**). Pt[37], Ru[38], Cu[39], Au[40] have also been found to catalyse or mediate *ortho*-alkylation and alkenylation in different manners.



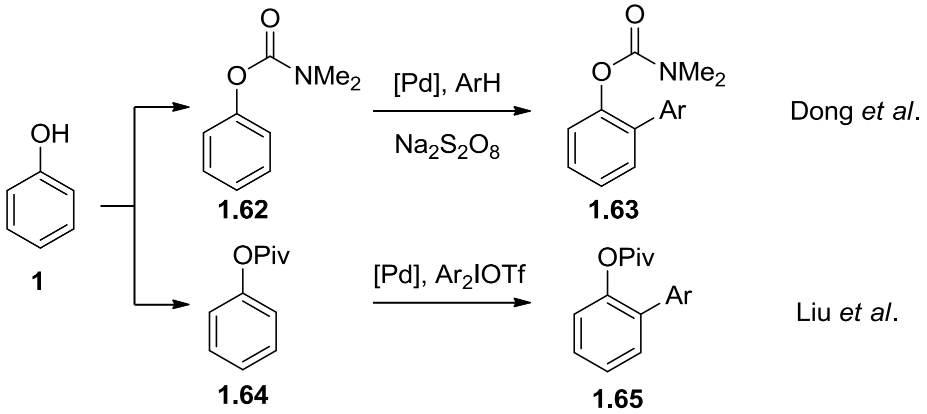
Scheme 1.19 Pd(II)-catalysed direct synthesis of coumarins

However, the ability of the hydroxyl group to act as a directing group is limited, due to unfavourable four-membered metallacycle. As an alternative, the strategy of pre-functionalisation of the hydroxyl group can be used in order to form more stable five- or six-membered metallacycles. For instance, Gevorgyan's group strategically installed a silanol group which could easily coordinate Pd to form a six-membered palladacycle, thus leading to *ortho*-alkenylation, oxygenation and carboxylation of phenol (**Scheme 1.20**).[41]



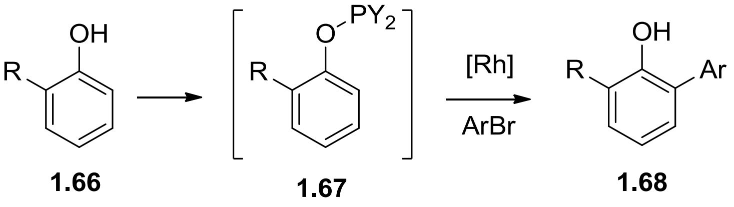
Scheme 1.20 Pd-catalysed silanol directed *ortho*-alkenylation, oxygenation and carboxylation of phenol

This strategy was also used by Dong *et al.*[42] and Liu *et al.*[43] in *ortho*-arylation of phenylcarbamates and phenol esters as well (**Scheme 1.21**). In both cases, a carbonyl motif is contained so that palladium is able to coordinate with the protecting groups, forming a six-membered palladacycle which leads to *ortho*-arylated products.



Scheme 1.21 *Ortho*-arylation of phenol derivatives

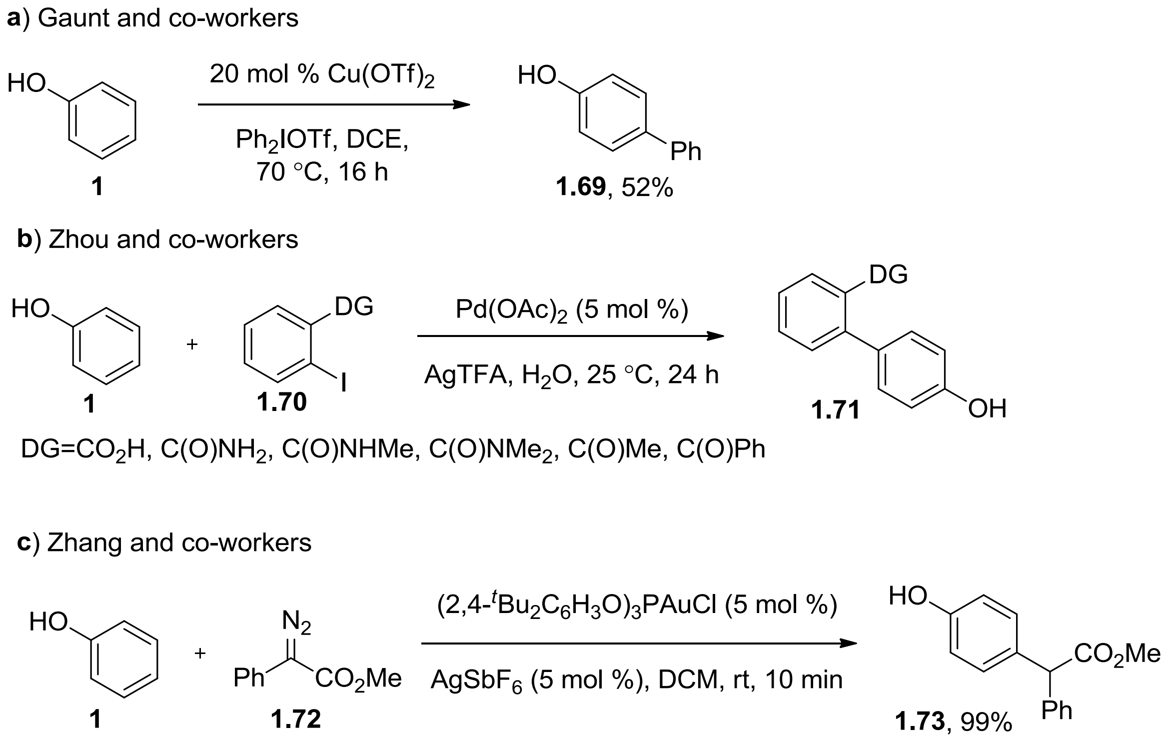
Bedford and co-workers reported the used of a catalytic phosphinite that can transesterify with the substrate phenols *in situ*, then an *ortho*-metalation can occur to give less-strained, five-membered metallacyles (**Scheme 1.22**).[44] The limitation of the reaction is that a bulky group such as *tert*-butyl is required in the *ortho*-position. No activity is observed with simple phenol.



Scheme 1.22 Catalytic arylation of phenols

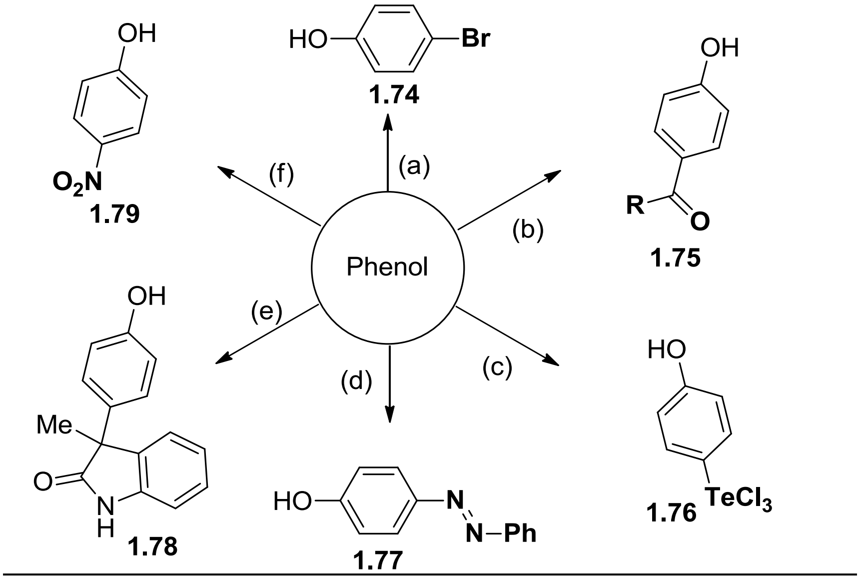
Para-functionalisation of phenols

In terms of the functionalisation of phenols at its *para*-position, there are few examples that have been applied in transition metal-catalysed systems. However, it is also possible to recognise the slightly higher reactivity to achieve high *para*-selectivity in the presence of transition metals. Gaunt and co-workers reported the selective *para*-arylation of phenol, anisole and aniline derivatives in the presence of Cu catalyst (**Scheme 1.23**, **a**). Although the mechanism is unclear, the authors proposed a Cu-catalysed Friedel-Crafts arylation.[45] In 2013, Zhou's group reported a Pd-catalysed *para*-selective arylation of phenols under quite mild and green conditions (**Scheme 1.23**, **b**).[46] The mechanism might involve an electrophilic metalation of the C–H bond of phenol at the *para*-position, followed by oxidative addition of aryl iodide, and reductive elimination affords the desired product. More recently, the group of Zhang used diazo compounds in the presence of a gold complex for highly *para*-selective direct C–H bond functionalisation of phenols (**Scheme 1.23**, **c**). The reaction probably proceeds through an electrophilic addition of the gold-carbene complex, followed by rapid 1,2-hydride migration.[47]



Scheme 1.23 *Para*-selective functionalisation of phenol in the presence of transition metal

However, *para*-selective direct functionalisation of phenols can be achieved *via* Friedel-Crafts processes. Although it is hard to discriminate between the *ortho*- and *para*-positions by minor differences in the electron density, the *para*-position is less hindered compared to the *ortho*-position, so it is still possible to achieve the single *para*-selective functionalised phenol regioisomer. Selected examples of those highly selective *para*-functionalisations of phenol are listed below (**Scheme 1.24**):[48]

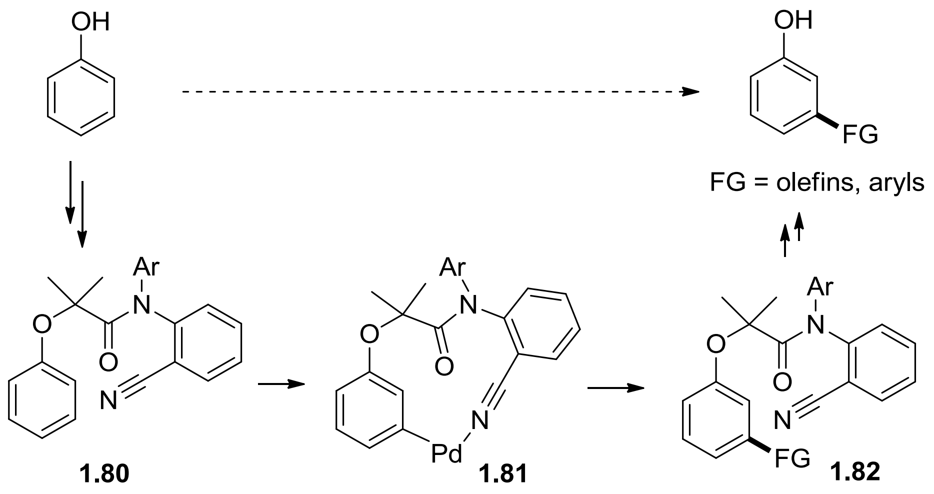


Reactions conditions: (a) KBr (1.0 equiv), $(PhCH_2PPh_3)_2S_2O_8$ (1.0 equiv), MeCN, reflux; (b) AcCl (1.0 equiv), TfOH, 0 °C to rt; (c) $TeCl_4$ (0.1 mol), phenol (1.4 equiv), CCl_4, reflux; (d) Aniline, Clay catalyst, $NaNO_2$, 0-5 °C; (e)3-hydroxy-2-oxindole (0.5 mmol), phenol (3.0 equiv), $Bi(OTf)_3$ (25 mol %), DCM; 45 °C(f) Sodium dodecyl sulfate (SDS) (0.05 M), nitric acid (1.0 M), rt.

Scheme 1.24 Selected examples of *para*-functionalisation of phenol

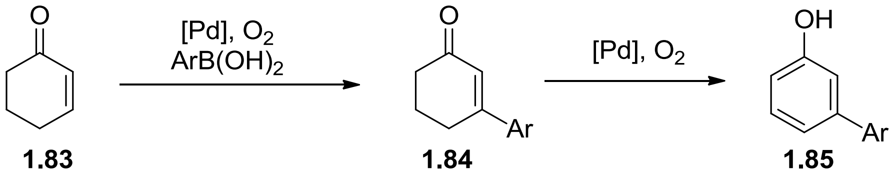
Meta-functionalisation of phenols

Meta-functionalisation of phenols, on the other hand, is a big challenge due to the well-known *ortho*/*para* directing ability of the electron-donating hydroxyl group. Ground-breaking work was reported by Yu's group *via* the strategy discussed in Chapter 1.1.3 (**Scheme 1.9**). *Meta*- olefination[49] and arylation[16] could be achieved by the assistance of the U-shaped template, which can remotely control the *meta*-selective C–H activation *via* a macrometallacycle, (**Scheme 1.25**). However, the requirement of a covalently attached complex template is a substantial drawback for synthetic applications, as it introduces several additional steps.



Scheme 1.25 Template assisted *meta*-functionalisation of phenol

There are no other examples of direct *meta*-functionalisation of phenols existing to date. However, several indirect methodologies have been developed over the past decade. A nice strategy was reported by Stahl and co-workers, who used cyclohexenone as a phenol precursor, through an aerobic oxidative Heck/dehydrogenation process, achieving *meta*-arylated phenols (**Scheme 1.26**).[50] Nevertheless cyclohexenone substitutions **1.83** are extremely limited compared with the variety of readily available phenols.



Scheme 1.26 One-pot oxidative Heck/dehydrogenation

Another approach for the synthesis of *meta*-functionalised phenols is the late-stage installation of hydroxyl group from the corresponding aryl iodide, aryl bromide or aryl boronic acid.[51] However, in this approach, to achieve the *meta*-substituted phenols, the corresponding *meta*-substituted aryl bromide or aryl boronic acid, which are not easily prepared, are required.

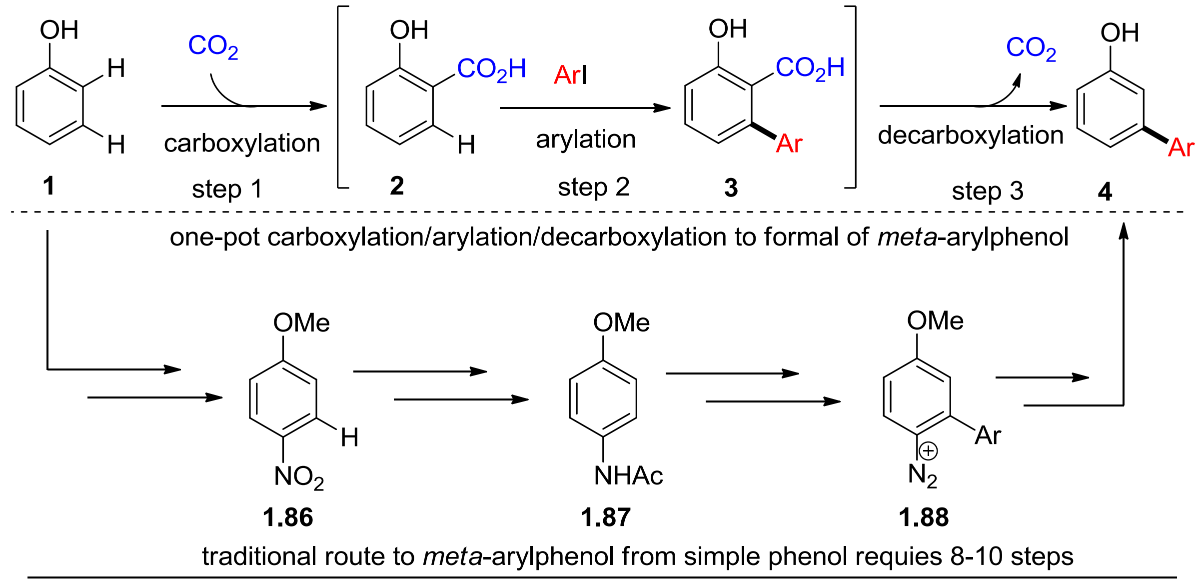
1.3 Conclusions and objectives of this thesis

In conclusion, there are a great variety of methodologies for catalytic *ortho*-functionalisation of phenols. Despite a lack of transition metal catalysed *para*-functionalisation of phenols, there are easily accessible *via* Friedel-Crafts processes so that further functionalisation can be continued. However, there are many areas in which the methodologies could still be improved. For instance, in the catalytic *ortho*-functionalisation of phenols, pre-functionalisation of the hydroxyl group is frequently required, which results in extra independent synthetic operations/purifications including removal of the protecting group to release free phenol. Therefore, the direct functionalisation of free phenols is more attractive.

On the other hand, methodologies for the *meta*-functionalisation of phenols are scarce, so the development of this method is highly desirable. ***We aimed to develop an efficient methodology for meta-arylation of phenols from the wide availability of cheap phenol starting materials.*** Ideally, such methodology would proceed in one step and be highly functional group tolerant, under mild conditions and scalable.

To date, the most common way to achieve the desired *meta*-arylphenols so far employs Suzuki coupling, in which eight to ten synthetic steps are required, involving the protection of the hydroxyl group, installation of a strong *ortho*-directing functionality, such as an amide, in the *para*-position with reference to the hydroxyl group (**1.87**), followed by arylation, removal of the amide and deprotection. Overall, such a synthetic route would need nine steps involving stoichiometric reagents which are not incorporated into the final product (**Scheme 1.27**, bottom route).

We hypothesised that, instead of transforming the hydroxyl group into a *meta*-directing group, a removable directing group (RDG) could be installed at the *ortho*-position of phenols so that the *meta*-arylphenols could be accessible with the cleavage of the directing group after the arylation at *ortho*-position referred to RDG (*meta*-position referred to -OH group). Recently, carboxylic acids have been shown to be useful in transition metal catalysed *ortho*-arylation.[52] In addition, decarboxylation of benzoic acids can also occur in the presence of transition metals.[53] Finally, a variety of methods allow the installation of carboxylic acid in the *ortho*-position of phenols, such as Kolbe-Schmitt carboxylation,[54] carbonylation/ oxidation,[55] and *ortho*-lithiation of suitable *O*-substituted phenols, followed by reaction with CO_2.[56] Based on this work, CO_2H would be an ideal traceless directing group candidate for testing our hypothesis (**Scheme 1.27**, top route).



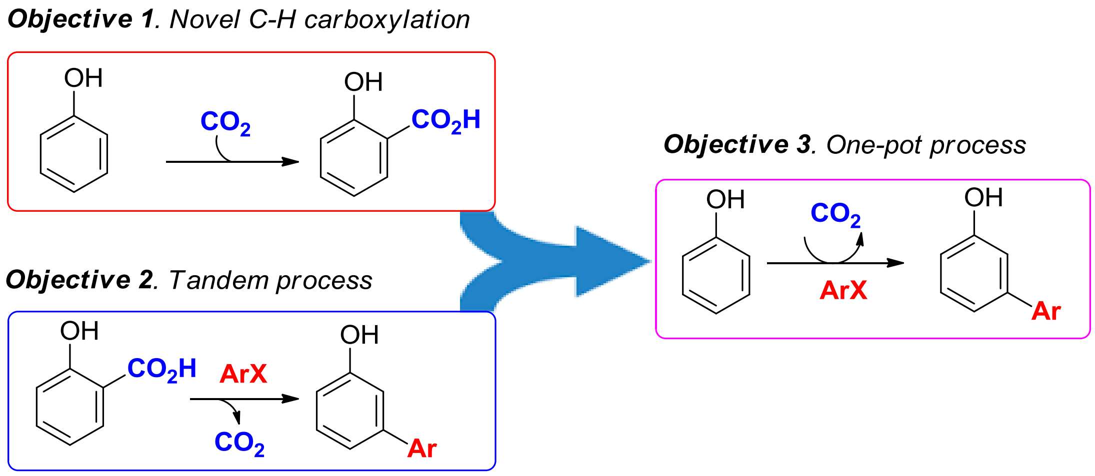
Scheme 1.27 Our hypothesis route and traditional route to access *meta*-arylated phenol

A step-wise approach towards our aim will be applied (**Scheme 1.28**):

Firstly, we aimed to develop a novel method for carboxylation of phenols that would offer a broad scope of salicylic acids under mild reaction conditions. As CO_2 is a green carbon source, highly abundant in the atmosphere and non-toxic, the utility of CO_2 as C1 source for the carboxylation of phenols would be of high interest (**Scheme 1.28**, *Objective 1*).

Secondly, our efforts were directed towards a Pd-catalysed tandem arylation/ protodecarboxylation of salicylic acid in the reaction with aryl iodide coupling parther, to afford the corresponding *meta*-arylated phenol product (**Scheme 1.28**, *Objective 2*).

Finally, we wondered if the combination of these two transformations above could lead to the development of a one-pot process carboxylation/arylation/decarboxylation, achieving *meta*-arylated phenols. If that would be the case, the methodology would provide an efficient alternavtive to *meta*-arylphenol derivatives from the corresponding phenols (**Scheme 1.28**, *Objective 3*).



Scheme 1.28 Objectives of the project

Chapter 2

Chapter 2 Carboxylation of phenols[i]

2.1 Transition metal-catalysed carboxylation

2.1.1 Introduction

CO_2 is a green carbon source, highly abundant in the atmosphere, as well as non-toxic and recyclable. What is more, steadily increasing levels of CO_2 in the atmosphere due to the human activities are associated with 'global warming'. Thus, it is highly attractive to develop methodologies that use CO_2 as a building block in organic synthesis. Of particular interest is the synthesis of carboxylic acids by fixation of $CO_{2.}$ However, due to the thermodynamic stability and high oxidation state of CO_2, to couple with CO_2, energy-rich substrates such as epoxides, aziridines and amines are always required. As a result, the construction of C–O and C–N bonds by the use of CO_2 is widely explored in past decades.[57] The formation of C–C bond by coupling with CO_2, on the other hand, still remains a challenge. The most common strategy applied for the creation of C–C bond by coupling with CO_2 is to use the highly reactive organolithium or Grignard reagents to react with CO_2.[58] However, the low compatibility of functional groups with organolithium or Grignard reagents limits their applications. Therefore, efforts have focused on transition metal-catalysed C–C versions of this process. In this part, state of the art transition metal-catalysed carboxylation, particularly the carboxylation of aromatic compounds, will be presented.

2.1.2 Carboxylation of organometallic reagents

Organotin reagents

As described above, although the fixation of CO_2 into valuable carboxylic acids and their derivatives by the use of highly reactive organolithium or Grignard reagents are well studied

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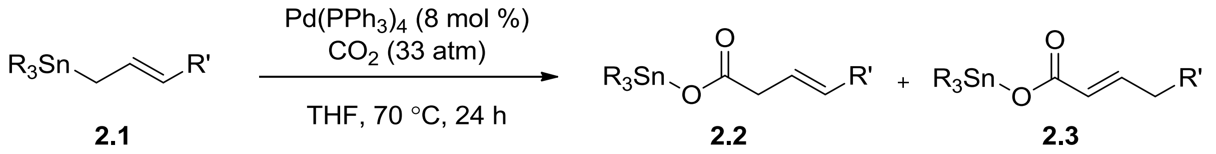
[i] This work was carried out in collaboration with Dr Sara Preciado, the contributions where included will be highlighted in the text.

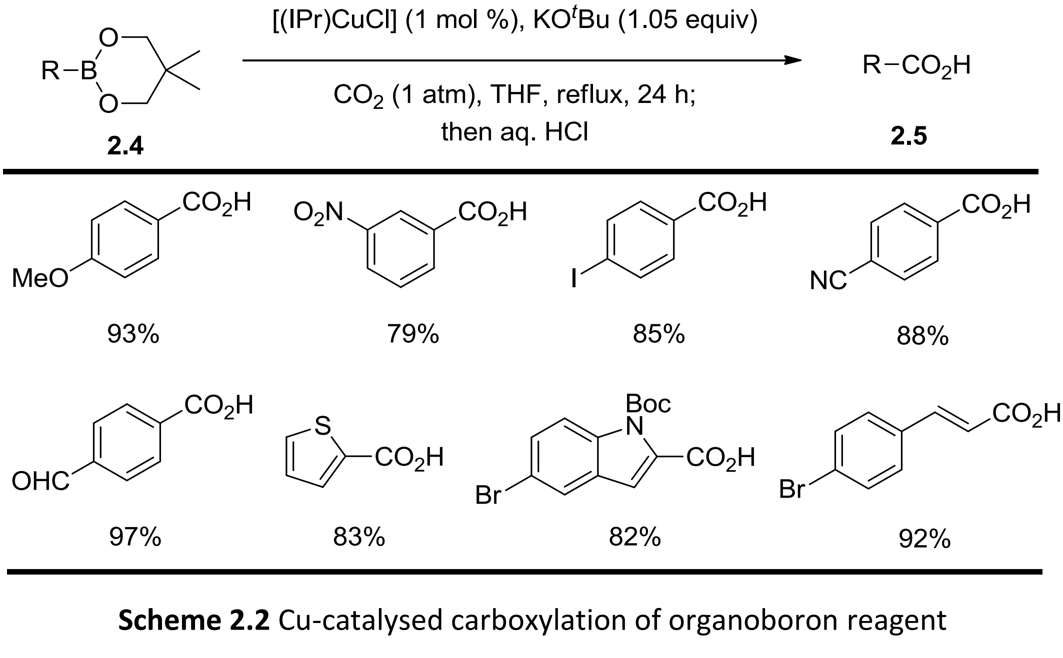
and developed, the low compatibility of functional groups with organolithium or Grignard reagents limits their applications. Thus, many other less reactive organometallic reagents, such as organoboron, organozinc, have been developed. Pioneering work was reported by Nicholas and co-workers in 1997 who inserted CO_2 into Sn–C bond in the presence of a palladium catalyst.[59] The use of high loading catalyst and toxic Sn limit the utility (**Scheme 2.1**).



Scheme 2.1 Pd-catalysed insertion of CO_2 into Sn–C bond

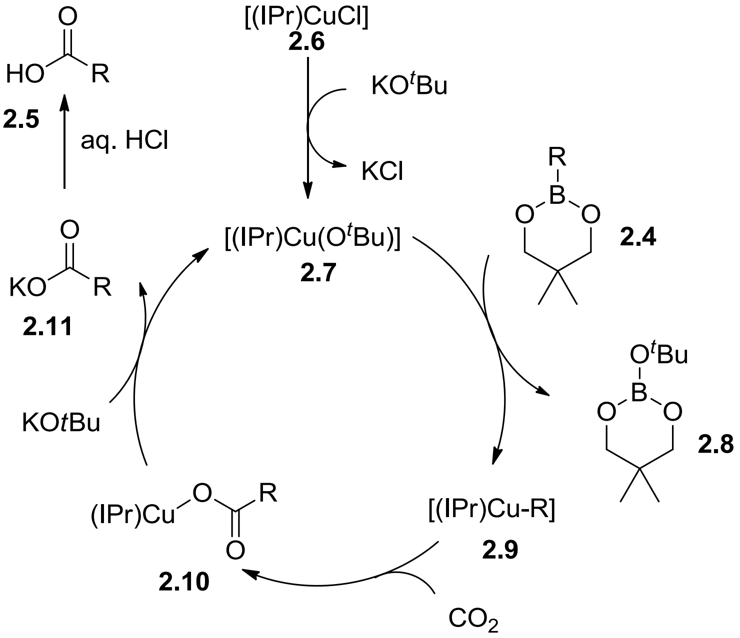
Organoboron reagents

The use of organoboron compounds as nucleophiles has also been explored for the conversion CO_2 into useful molecules. An example is shown in **Scheme 2.2** reported by Hou and co-workers.[60] A variety of functional groups such as cyanide and aldehyde substituted arylboronic and alkenylboronic esters can be transformed to carboxylic acids under CO_2 atmosphere catalysed by [(IPr)CuCl].



Scheme 2.2 Cu-catalysed carboxylation of organoboron reagent

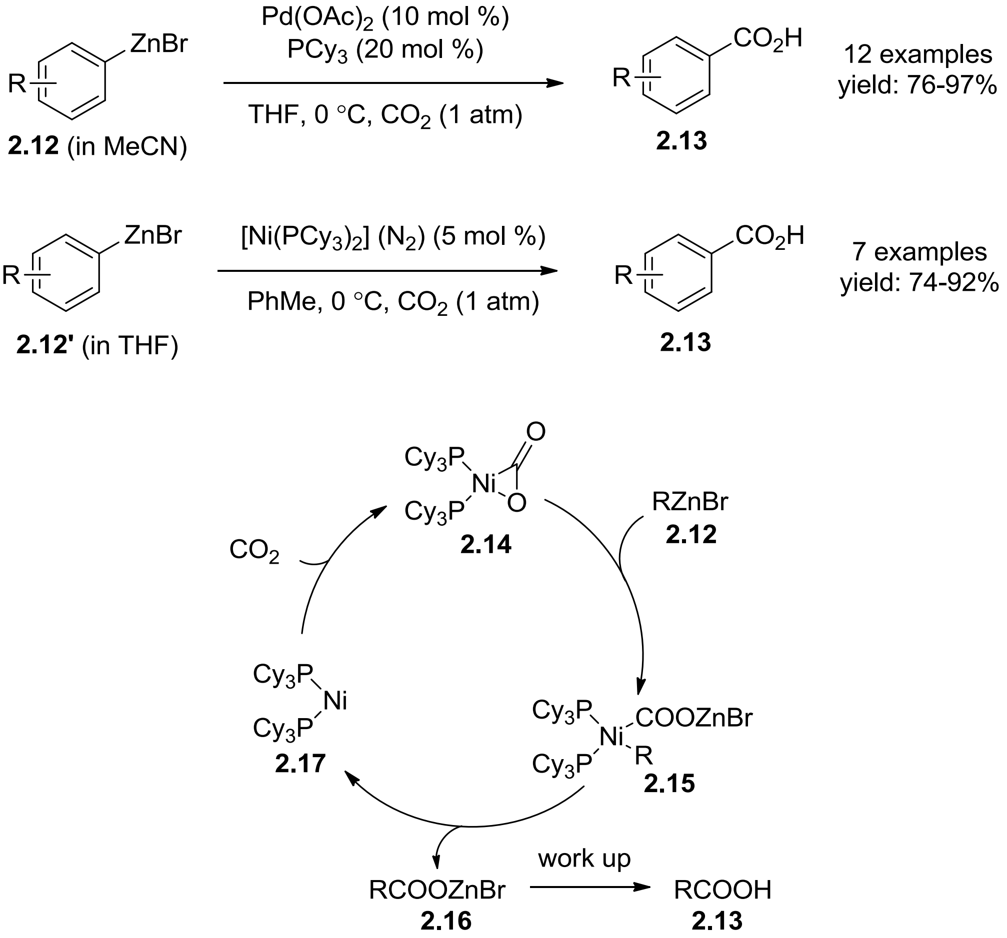
A plausible mechanism for this transformation was proposed by the authors, [(IPr)Cu(O^{t}Bu)] (**2.7**) was initially formed by the ligand exchange between [(IPr)CuCl] (**2.6**) and KO^{t}Bu, and subsequently transmetallation with boronic ester (**2.4**) afforded organocopper complex [(IPr)CuR] (**2.9**). After the insertion of CO_2 into the Cu–C bond to form [(IPr)CuCO$_2$R] complex (**2.10**), the carboxylate copper complex undergoes another ligand exchange with KO^{t}Bu to form potassium salt RCOOK (**2.11**) with concomitant regeneration of the [(IPr)Cu(O^{t}Bu)] catalyst (**2.7**) (**Scheme 2.3**). CuI and [Rh(OH)(cod)]$_2$ were also explored as catalysts, with Iwasawa and co-workers successfully achieving the conversion of boronic ester into carboxylate compounds by.[61]



Scheme 2.3 Proposed catalytic cycle of Cu-catalysed carboxylation of organoboron

Organozinc reagents

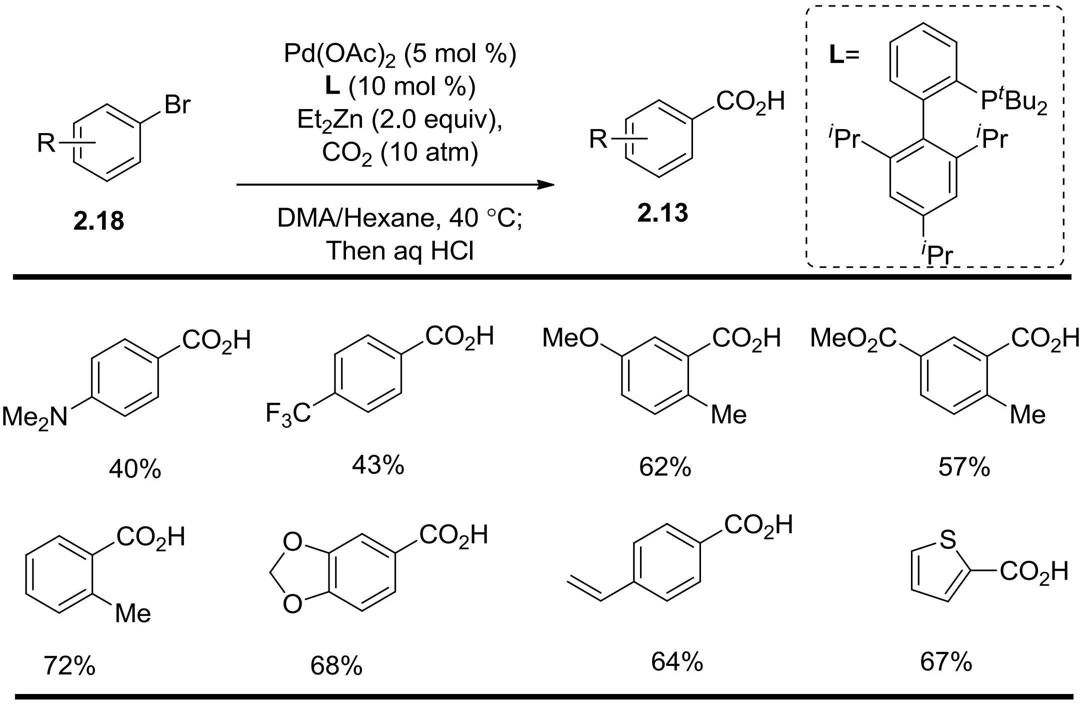
Organozinc compounds have been found to be efficiently transformed to carboxylic acids by Pd and Ni catalysts under mild conditions by Dong and co-workers **(Scheme 2.4)**.[62] This work was inspired by Aresta's complex, Ni(η^2-CO$_2$)(PCy$_3$)$_2$ (**2.14**), which was first reported in 1975.[63] However, no method had been developed for the catalytic transformations with CO_2 using Aresta's complex (**2.14**). The authors hypothesised that Aresta's complex (**2.14**) could transmetallate with organozinc compounds **2.12** to afford species **2.15**, which followed by reductive elimination, affording a zinc carboxylate **2.16** and Ni(PCy_3)$_2$ (**2.17**). Aresta's complex (**2.14**) could regenerate by oxidative cycloaddition of **2.17** with CO_2 (**Scheme 2.4**, below).



Scheme 2.4 Carboxylation of organozinc compounds and proposed mechanism

2.1.3 Carboxylation of aryl halides

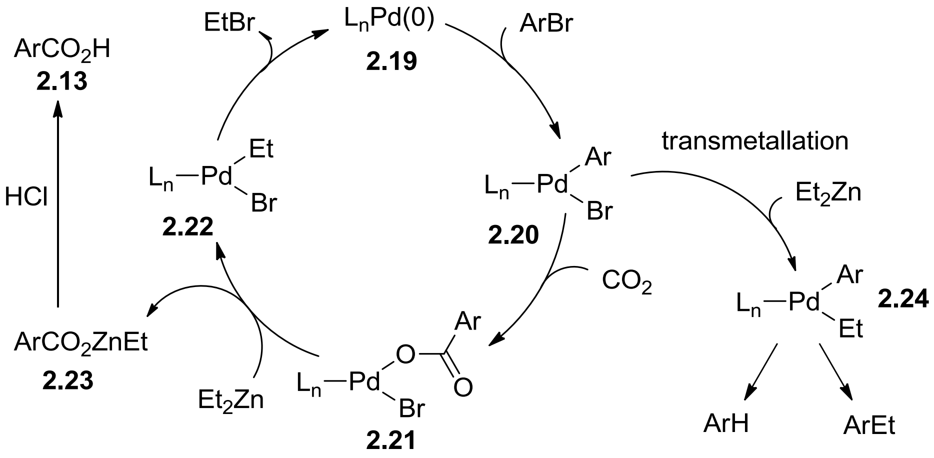
The transition metal-catalysed carboxylation of aryl halides was first reported by Martin and Correa in 2009.[64] In this approach, the readily available aryl bromides were converted into benzoic acids with CO_2 under Pd catalysis in the presence of stoichiometric $ZnEt_2$. A variety of substituted aryl bromides bearing electron withdrawing groups (EWGs) and electron donating groups (EDGs) were tested, and smoothly underwent carboxylation to the corresponding benzoic acids in moderate to good yields (**Scheme 2.5**).



Scheme 2.5 Pd-catalysed carboxylation of aryl bromides

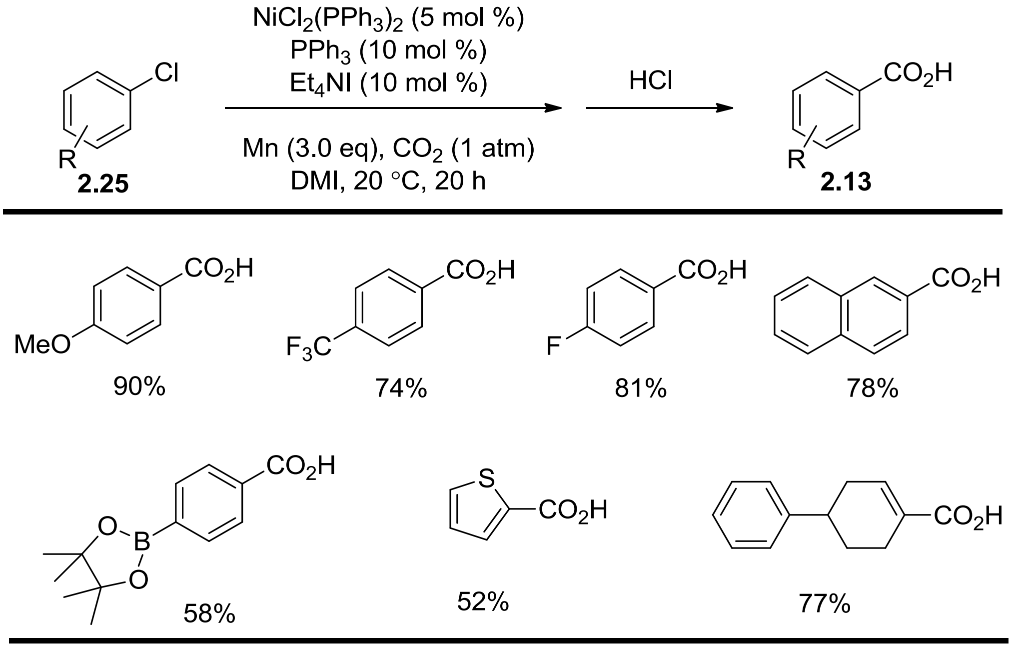
A proposed mechanism is shown in **Scheme 2.6**. Firstly, an oxidative addition of aryl bromides into the Pd centre occurs, which followed by the insertion of CO_2 to generate Pd benzoate **2.21**. After this, species **2.21** undergoes transmetallation with Et_2Zn to produce zinc benzoate **2.23** which produces the benzoic acids after work up, on the other hand, Pd species **2.22** undergoes reductive elimination to regenerate the Pd(0) species.

This methodology is more attractive than the catalytic carboxylation of organometallic reagents, as the aryl halides are readily available starting materials. However, 2.0 equivalents of $ZnEt_2$ were still required and the use of pressured CO_2 gas resulted in the requirement of a special autoclave equipment.



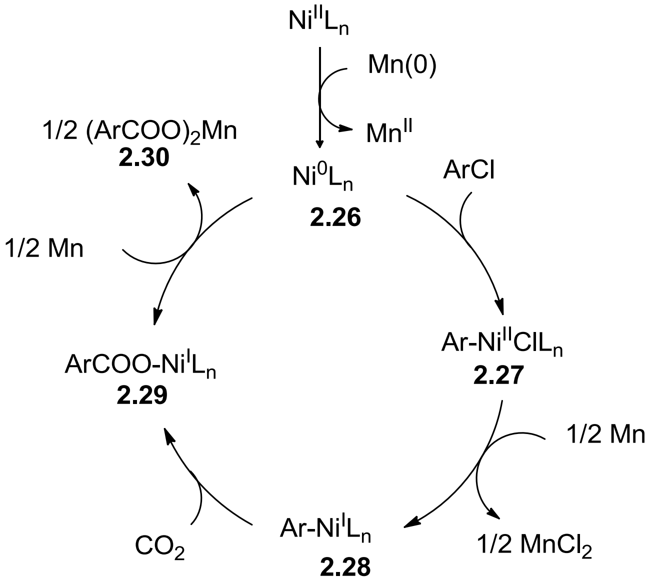
Scheme 2.6 Proposed mechanism for Pd-catalysed carboxylation of aryl bromides

Later on, Tsuji's research group successfully developed a Ni-catalysed carboxylation of aryl and vinyl chlorides at atmospheric pressure CO_2 and room temperature (**Scheme 2.7**).[65]



Scheme 2.7 Ni-catalysed carboxylation of aryl and vinyl chlorides

Ni(I) species was suggested as an active catalyst that plays an important role in the catalytic carboxylation by the group, and Mn powder acts as a the reducing reagent. In the proposed mechanism, Ni(0)L$_n$ (**2.26**) is generated *via* reduction of Ni(II)L$_n$ precatalyst by Mn(0), followed by oxidative addition of aryl chloride to give Ar–Ni(II)Cl intermediate (**2.27**). After this, Ar–Ni(II)Cl (**2.27**) could be reduced by Mn to Ar–Ni(I) species **2.28** which could then react with CO_2 to give the carboxylatonickel intermediate **2.29**, followed by the reduction by Mn(0) to give manganese carboxylate **2.30**, and regenerate Ni(0) catalyst **2.26** simultaneously (**Scheme 2.8**).

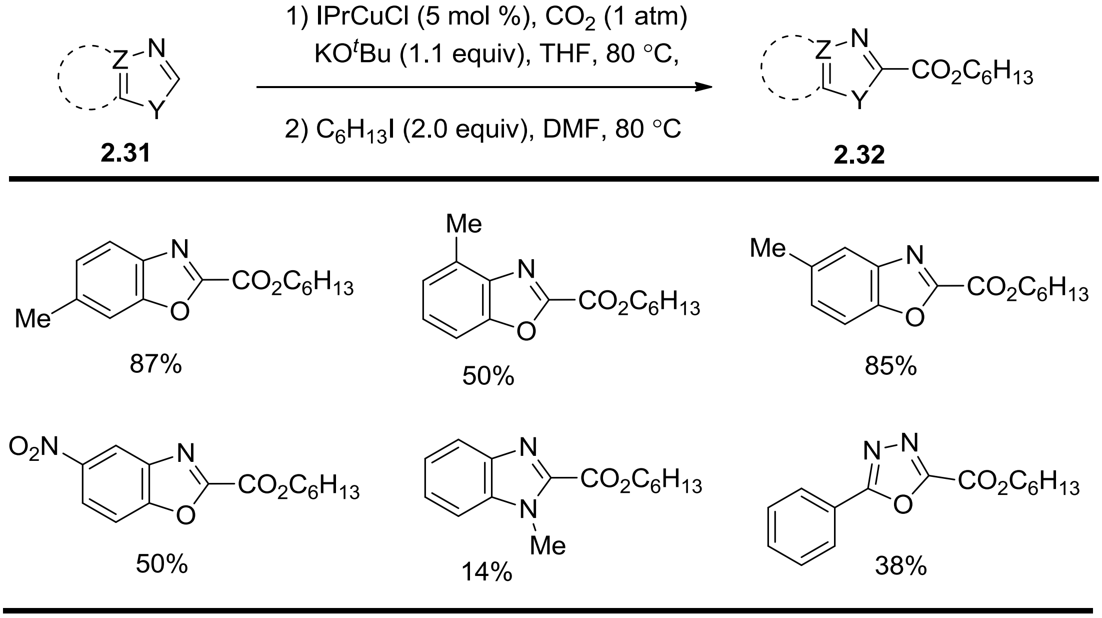


Scheme 2.8 Proposed catalytic cycle for carboxylation of aryl chlorides

In addition to Ni and Pd complexes that have been developed as catalysts for the reductive carboxylation of aryl and vinyl halides, the simple and abundant CuI has also been used as a catalyst for carboxylation of aryl iodides with CO_2.[66] More recently, the research group of Martin reported a methodology that allows benzyl halides to be converted into carboxylic acids under a Ni catalytic system.[67]

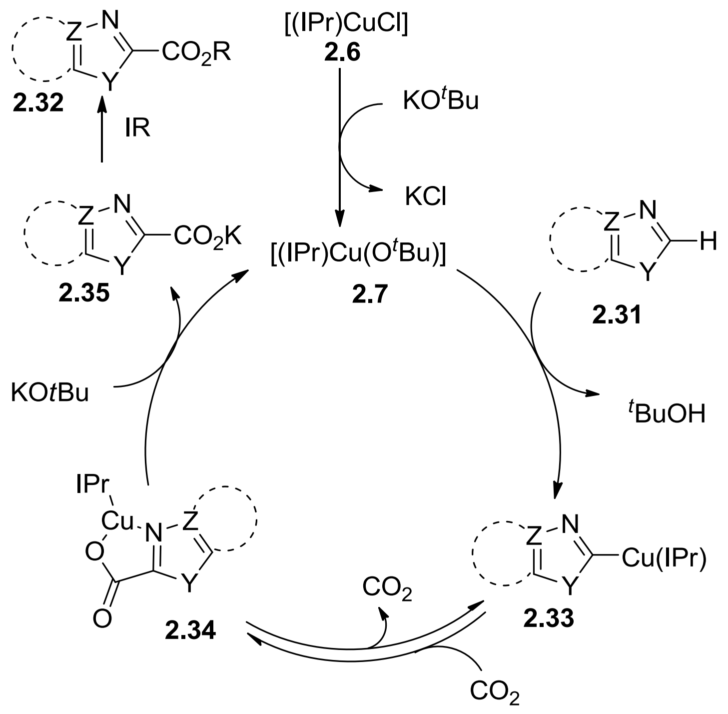
2.1.4 Direct carboxylation of C–H bonds

Similarly to the direct C–H functionalisation described in Chapter 1, the direct carboxylation of C–H bonds is of great significance due to the avoidance of substrate pre-functionalisation. However, given both the stability of CO_2 and C–H bonds, there are few methodologies for direct C–H carboxylation existing to date. In 2009, Hou and co-workers reported a methodology for direct C–H carboxylation of aromatic heterocycles using [(IPr)CuCl] catalyst (**Scheme 2.9**).[68] Various benzoxazole derivatives bearing both electron-donating and electron-withdrawing groups at the aryl unit could carboxylate in good to high yields.



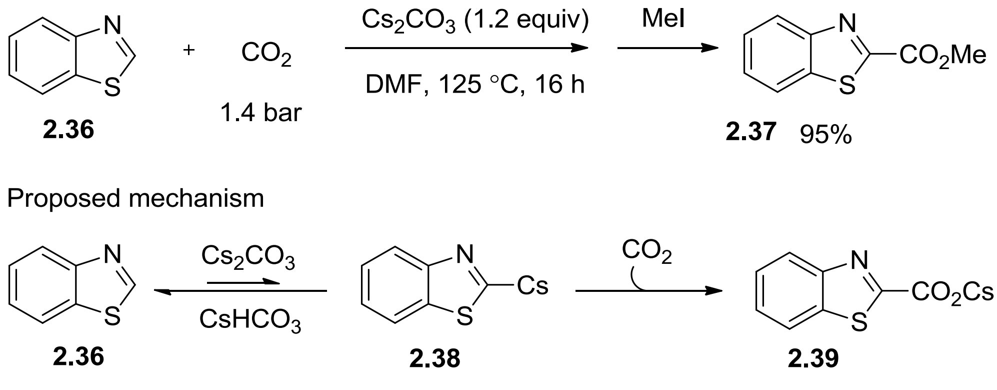
Scheme 2.9 Cu-catalysed direct C–H carboxylation

Crucial intermediates **2.33** and **2.34** in **Scheme 2.10** were isolated by the authors to elucidate the mechanism. Complex **2.34** could be obtained from **2.33** by exposing it to 1 atm of CO_2 at room temperature. A proposed catalytic cycle is shown in **Scheme 2.10**. Initially, ligand exchange between [(IPr)CuCl] (**2.6**) and KO^{t}Bu affords [(IPr)Cu(O^{t}Bu)] (**2.7**), which deprotonates the heterocycle to form **2.33**. CO_2 insertion of **2.33** takes place to afford **2.34** which subsequently reacted with ^{t}BuOK to regenerate [(IPr)Cu(O^{t}Bu)] (**2.7**), and produces the potassium carboxylate **2.35**. Further S_N2 reaction between **2.35** and alkyl iodide affords the ester product **2.32**.



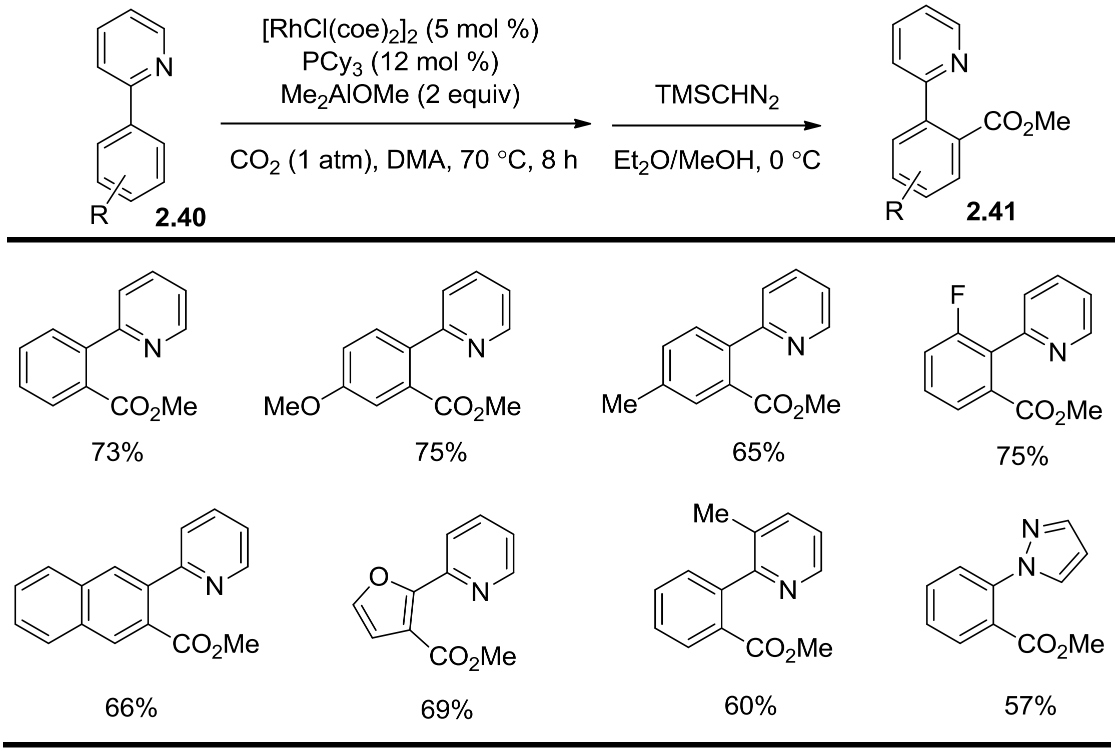
Scheme 2.10 Proposed mechanism for Cu-catalysed C–H carboxylation

The group of Hu reported that carboxylation of benzothioazoles could proceed well using only Cs_2CO_3, although the reaction temperature is much higher compared to the previous methods already discussed.[69] An uphill cleavage of C–H at the C2 position, followed by formation of C–C bond with CO_2 was proposed (**Scheme 2.11**). In the case of partial conversion, benzothiazole and 2-benzothiazolecarboxylate were detected but not the 2-benzothiazolyl anion by NMR. Moreover, benzothioazole was not deprotonated by Cs_2CO_3 in the absence of CO_2.



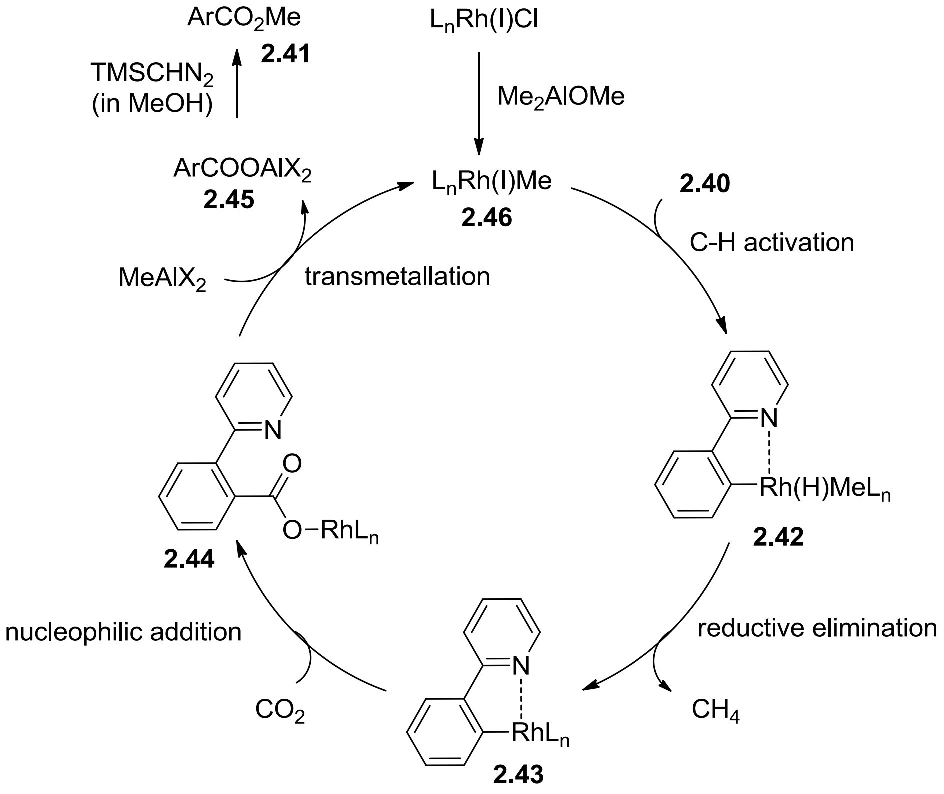
Scheme 2.11 C–H carboxylation by the use of a simple base

Rh(I)-catalysed direct C–H carboxylation of unactivated aryl C–H bond under ambient pressure of CO_2 was achieved *via* chelation-assisted C–H activation.[70] In this method, pyridines and pyrazoles were used and found to be suitable as directing groups. Substitutions with electron-donating and electron-withdrawing groups are both tolerated (**Scheme 2.12**). However, the high loading of expensive Rh catalyst limits the application of this methodology.



Scheme 2.12 Rh-catalysed C–H carboxylation

A reasonable catalytic cycle was proposed to consist of C–H activation by oxidative addition of Rh(I) species **2.46** with 2-arylpyridine to form Rh(III) species **2.42**, which is followed by reductive elimination to give Rh (I) species **2.43**. Subsequently, nucleophilic carboxylation of arylrhodium produces rhodium carboxylate **2.44**, which then undergoes transmetallation with methylaluminium to afford aluminium carboxylate **2.45**, and regenerates methylrhodium catalyst **2.46**. Further reaction of aluminium carboxylate **2.45** with trimethylsilyldiazomethane ($TMSCHN_2$) in methanol affords ester product **2.41** (**Scheme 2.13**).



Scheme 2.13 Proposed catalytic cycle of Rh-catalysed C–H carboxylation

2.1.4 Conclusions

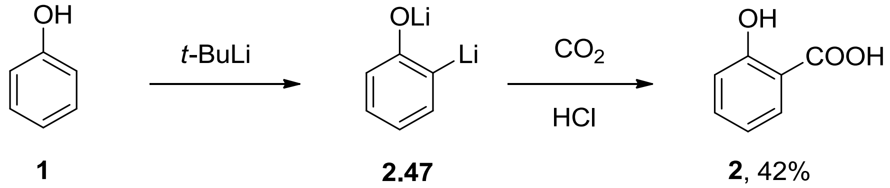
Generally, it is well-known that the reaction between CO_2 and energy-rich substrates, such as epoxides and aziridines, and the synthesis of polycarbonates/polycarbamates and/or cyclic carbonates/carbamates by the use of CO_2 have been widely explored during the past decades. However, to achieve C–C bond formation by the activation of CO_2, highly reactive organolithium or Grignard reagents are generally required, which limits the generality of this method. Fixation of CO_2 into more stable and synthetically useful reagents, on the other hand, still remains a big challenge, particularly the carboxylation of aromatic compounds. Organometallic reagents, including organotin, organoboron and organozinc reagents have been successfully utilised in the transition metal-catalysed carboxylation with CO_2. However, it is obvious that the stoichiometric use of metals is undesirable for both economical and environmental concerns, especially when applying to industrial synthesis.

The carboxylation of simple, general and readily available chemicals is extremely limited. Methods for the carboxylation of aryl halides were reported by Martin and Tsuji using Pd catalyst and Ni complex catalyst, respectively. In terms of the direct C–H carboxylation, despite the perfect performance of carbene metal complexes in the CO_2 activation, the reports have limited substrate scope. Thus, it is highly desirable to develop new methodologies for carboxylation to proceed in simple, mild and generally applicable conditions using readily available starting materials, so that direct C–H carboxylation can meet the requirements for step- and atom-economy.

2.2 The synthesis of salicylic acids and Kolbe-Schmitt reaction

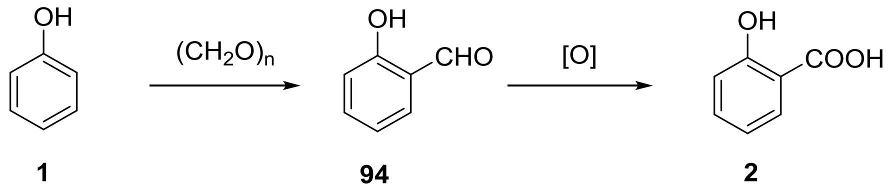
Salicylic acid derivatives are important motifs in pharmaceutically and biologically active compounds, the high reactivity of salicylic acids makes them versatile building blocks for organic synthesis.[71] Therefore, efforts have been made in the past generally using the wide availability of cheap phenol starting materials.

Posner and Canella reported that dilithium cation species **2.47** could undergo carboxylation by treatment of CO_2 to afford salicylic acid in moderate yield (**Scheme 2.14**).[72] However, the use of pyrophoric *tert*-BuLi limits this application. Moreover, lithiation could be directed by many different groups,[73] resulting in low functional group tolerance.



Scheme 2.14 Carboxylation of lithium species

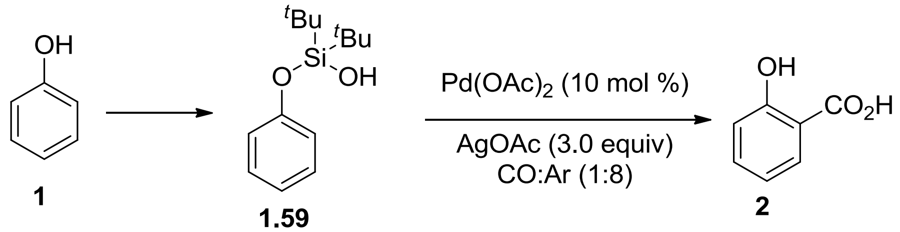
Due to the easy oxidation of salicylaldehydes to the corresponding salicylic acids,[74] as well as the various methodologies for *ortho*-formylation of phenols,[75] the salicylic acid derivatives are accessible by an *ortho*-formylation of phenols with a subsequent oxidation (**Scheme 2.15**).



1 **94** **2**

Scheme 2.15 Synthesis of salicylic acid by *ortho*-formation with subsequent oxidation

More recently, Gevorgyan and co-workers have developed a Pd-catalysed silanol-directed carboxylation by the use of CO.[41] In this approach, a silanol group was firstly installed on the hydroxyl group, then the silanol protected phenol **1.59** could facilitate a Pd-catalysed *ortho* C–H carboxylation in the presence of CO gas (**Scheme 2.16**). However, the high loading of Pd catalyst and the use of 3.0 equivalents of Ag-salts as an oxidant limit the utility.

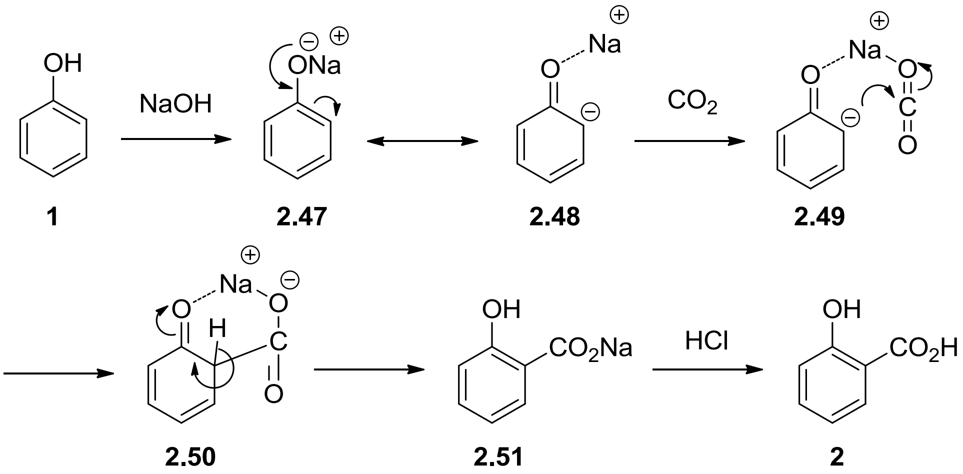


1 **1.59** **2**

Scheme 2.16 Pd-catalysed silanol-directed carboxylation using CO

Kolbe-Schmitt Carboxylation

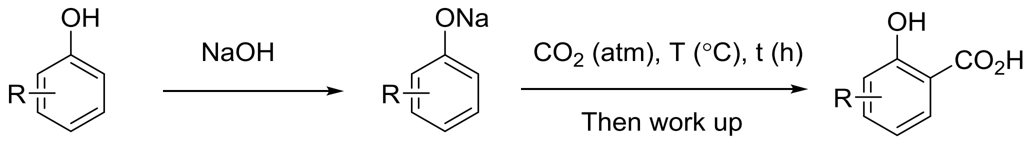
The strategy of direct C–H carboxylation of phenols, on the other hand, provides an efficient alternative to the salicylic acid derivatives. The first example of C–H carboxylation of phenols, Kolbe-Schmitt carboxylation, was developed in the 1860s, and it is still widely used in industry today.[54] The process begins with the preparation of the phenoxide, classically sodium phenoxide (**2.47**). Then, a nucleophilic addition to CO_2 that coordinates with Na^+, gives a non-aromatic cyclohexadienonecarboxylate intermediate **2.50** which is followed by tautomerisation to afford salicylate **2.51**. Simple acidic work up of **2.51** leads to salicylic acid (**2**) (**Scheme 2.17**).

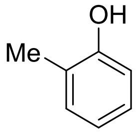
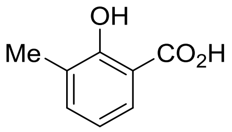
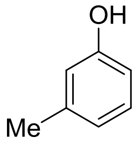
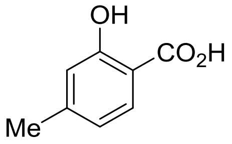
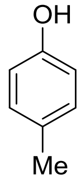
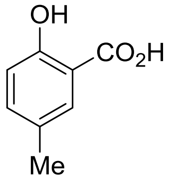
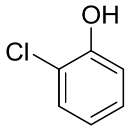
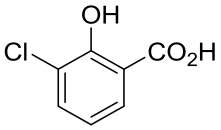
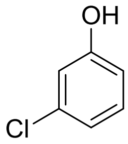
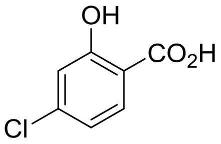
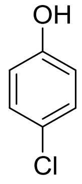
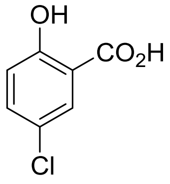
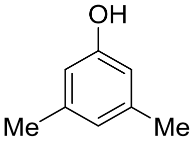
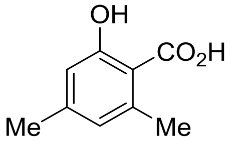
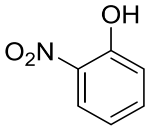
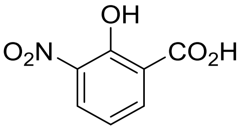


Scheme 2.17 Kolbe-Schmitt carboxylation process

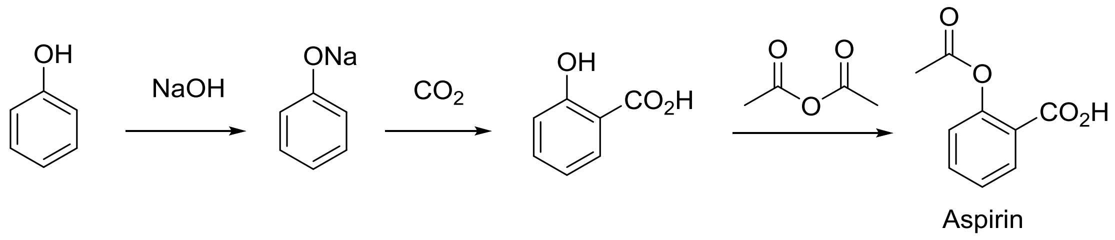
Some typical phenol substrates that have been carboxylated are presented in **Table 2.1**.[76] As we can see, both electron-donating and electron-withdrawing groups at *ortho*-, *meta*- and *para*-positions can undergo carboxylation, affording moderate to good yields. However, the carboxylation of phenols with electron-withdrawing substituents is less efficient than with electron donating substituents. When very strongly electron-withdrawing groups, such as a -NO_2 group, are present on the phenol ring, no carboxylated product was obtained. The sterically hindered substrate 3,5-dimethylphenol, could also be carboxylated, leading to 30% of carboxylated product.

Table 2.1 Kolbe-Schmitt carboxylation



phenols	Conditions			Products	Yield (%)
	CO$_2$ (atm)	T (°C)	t (h)		
	40	200	6		70
	100	125	8		70
	40	200	4		85
	100	150	8		61
	100	175	8		68
	100	175	8		69
	40	200	6		30
	40	210	4		0

The Kolbe-Schmitt process is widely used for the synthesis of acetylsalicylic acid, known as Aspirin, which is one of the most widely used medicines in the world, with an estimated 40,000 tonnes being consumed each year. In the synthetic process, salicylic acid was prepared using the Kolbe-Schmitt reaction. After this, salicylic acid is simply treated with acetic anhydride to afford the acetylsalicylic acid (**Scheme 2.18**).



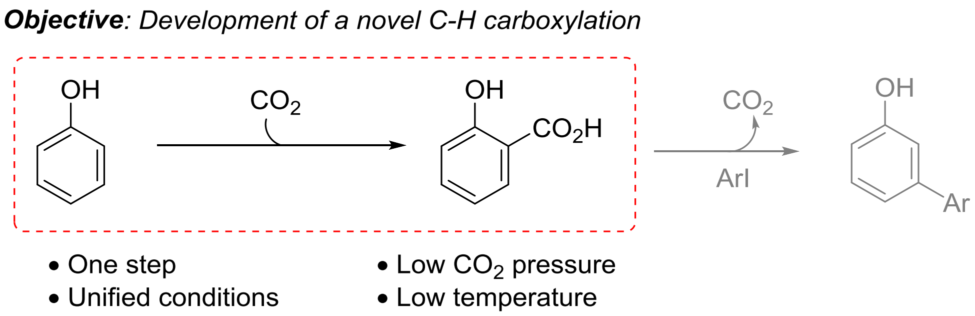
Scheme 2.18 Synthesis of Aspirin

Although a large number of phenol derivatives can be carboxylated using the Kolbe-Schmitt reaction, the reaction conditions are very harsh: The process requires pressurised CO_2 (40-100 atm) and high temperatures (125-210 °C). Moreover, the reaction conditions vary over a wide range depending on the functional groups on the substrate. The preparation of completely dry metal phenoxide is necessary, making the procedure less practical. We therefore aimed to develop a method for carboxylation of phenol under milder conditions compared to the classic Kolbe-Schmitt procedure.

2.3 Aims of the project

To meet with our hypothetical strategy for *meta*-arylation of phenols using CO_2H as a transient directing group described in Chapter 1.2.3, a process of carboxylation of phenols to afford salicylic acid derivatives is necessary. Kolbe-Schmitt carboxylation provides an efficient method for the synthesis of salicylic acid derivatives from the corresponding phenols. However, as described in Chapter 2.2, there are many problems that need to be improved.

At the first stage of our project, we aimed to develop a mild version of the Kolbe-Schmitt carboxylation, ideally, this process could proceed under atmospheric CO_2 and low temperature. Additionally, unlike the conditions of classic Kolbe-Schmitt that vary over a wide range depending on the starting alkali metal phenoxide as well as the substituents functional groups, we aimed to achieve the carboxylation of phenols under a simple set of unified conditions (**Scheme 2.19**).



***Objective**: Development of a novel C-H carboxylation*

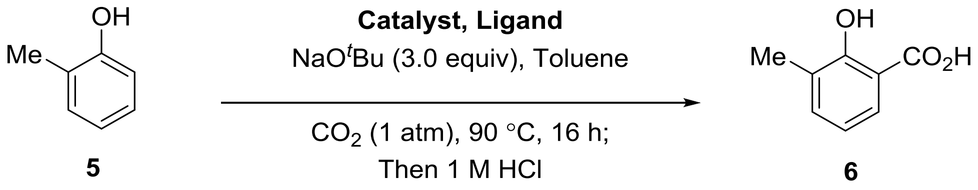
- One step
- Unified conditions
- Low CO_2 pressure
- Low temperature

Scheme 2.19 Aim of the project

2.4 Previous results

As described in the introduction, transition metal catalysis plays an important role in CO_2 fixation with many different substrates such as organozinc, organoboron aryl halides, etc. Sara Preciado in our group started to explore the possibility of phenol carboxylation using Pd catalysis. With an extensive screening of solvents, ligands and bases, a maximum 10% yield was obtained when 10 mol % of $Pd(OAc)_2$, 20 mol % of PCy_3 and 3.0 equivalents of NaO^tBu were used in the reaction (**Table 2.2**, entry 1). An electron-rich phosphine proved important to this reaction: replacing of PCy_3 with PPh_3 resulted in no reactivity (**Table 2.2**, entry 2). The reaction did not work in the absence of Pd and ligand (**Table 2.2**, entry 3), suggesting that the transition metal catalyst together with the phosphine ligand were necessary for the carboxylation of phenols. These results demonstrate that it is possible to carboxylate phenol with CO_2 under mild conditions by the use of a transition metal catalyst. However, we still face the challenge to find the optimum conditions.

Table 2.2 Pd-catalysed carboxylation of phenols



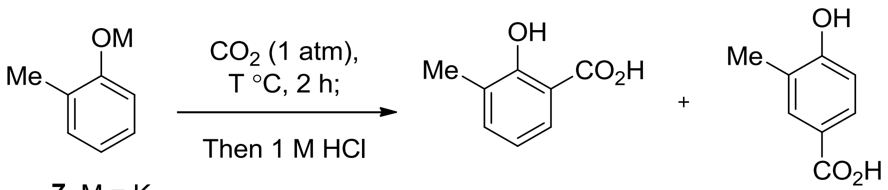
Entry	Catalyst (10 mol %)	Ligand (20 mol %)	Yield of **6** (%)
1	$Pd(OAc)_2$	PCy_3	10
2	$Pd(OAc)_2$	PPh_3	0
3	-	-	0

2.5 Modification of Kolbe-Schmitt carboxylation

2.5.1 Attempts towards Kolbe-Schmitt carboxylation at atmospheric CO_2 pressure

We altered our attention towards the Kolbe-Schmitt carboxylation, aiming to develop a method for carboxylation of phenols at low pressure. Initially, we tested the classic Kolbe-Schmitt carboxylation procedure under atmospheric CO_2 pressure (**Table 2.3**). We were pleased to find the alkali metal 2-methylphenolate (**7** and **8**) underwent carboxylation at atmospheric CO_2 pressure, affording 2-hydroxy-3-methylbenzoic acid (**6**) and 4-hydroxy-5-methylbenzoic acid (**9**). The higher temperature was found to be necessary to improve the reactivity (**Table 2.3**, entries 1 vs 2 and 3 vs 4). Moreover, the sodium 2-methylphenolate (**8**) was found to be more selective compared to the potassium 2-methylphenolate (**9**), allowing the carboxylation at the *ortho*-position (**Table 2.3**, entries 1 vs 3 and 2 vs 4). Although low reactivity was obtained when carrying the Kolbe-Schmitt carboxylation at atmospheric CO_2 pressure, it encouraged us to further improve the process.

Table 2.3 Kolbe-Schmitt carboxylation at atmospheric CO_2 pressure[a]



7, M = K
8, M = Na

6

9

entry	M	T (°C)	Yield **6** (%)	Yield **9** (%)
1	K	160	12	9
2	K	185	11	18
3	Na	160	16	2
4	Na	185	24	2

[a] Unless otherwise noted, all reactions were carried out using 0.25 mmol of **7**; Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard after acidify work up.

2.5.2 Screening of bases

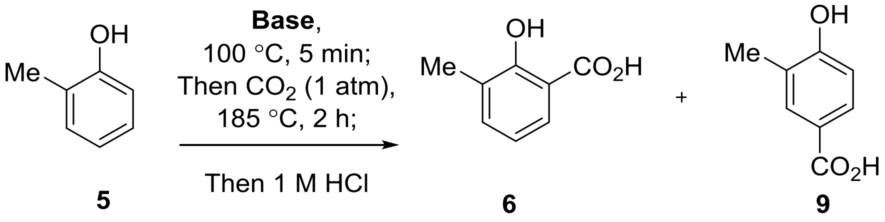
Despite the Kolbe-Schmitt carboxylation proceeding at atmospheric CO_2 pressure, we wanted to do the carboxylation from simple phenols, avoiding the preparation of completely dry metal phenoxide. Therefore, we tried the carboxylation reaction by simply mixing *o*-cresol and KOH, heating at 100 °C for 5 min in order to form the potassium 2-methylphenolate, and then heating the mixture at 185 °C for 2 h under atmospheric CO_2 pressure. Unfortunately, there was no desired product **6** obtained (**Table 2.4**, entry 1). The use of NaOH resulted in no reactivity either (**Table 2.4**, entry 2). The formation of water during the deprotonation of phenols may quench the reaction, as water has been demonstrated to be disastrous for the Kolbe-Schmitt carboxylation.[77]

Marasse developed a modification of Kolbe-Schmitt carboxylation, in which the phenols could undergo carboxylation in the presence of excess of anhydrous K_2CO_3 under high pressured CO_2 (50-100 atm) and elevated temperature.[78] Importantly, the preparation of the completely dry metal phenolate is avoided in this method. Thus, the Marasse method was tried under atmospheric CO_2 pressure, unfortunately, only 1% of desired product **6** was obtained (**Table 2.4**, entry 3). Na_2CO_3 turned out to lead to no reactivity at all (**Table 2.4**, entry 4).

NaH is a strong base that is commonly used for deprotonation of phenol derivatives. Importantly, unlike KOH or NaOH in which water is formed during the deprotonation of phenols, NaH deprotonates phenols to produce easily removed H_2. Gratifyingly, 32% of *ortho*-carboxylated product **6** and 2% of *para*-carboxylated product **8** was obtained when 1.0 equivalent of NaH was used (**Table 2.4**, entry 5).

Increasing the amount of NaH to 2.0 equivalents gave a higher yield of 38% (**Table 2.4**, entry 6). However, no improvement in the yield was observed with a further increase in the amount of NaH to 3 equivalents (**Table 2.4**, entry 7). When the reaction time was prolonged to 4 h, and still 39% of carboxylated product was obtained (**Table 2.4**, entry 8), probably because the reaction has stopped after 2 h.

Table 2.4 Screening of base[a]



entry	Base (equiv)	Yield **6** (%)	Yield **9** (%)
1	KOH (1.0)	0	0
2	NaOH (1.0)	0	0
3[b]	K_2CO_3 (1.0)	1	0
4[b]	Na_2CO_3 (1.0)	0	0
5	NaH (1.0)	32	2
6	NaH (2.0)	38	2
7	NaH (3.0)	39	3
8[c]	NaH (2.0)	39	2

[a] Unless otherwise noted, all reactions were carried out using 0.25 mmol of **5**, yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] The reactions were performed at elevated temperature from 100 °C to 185 °C. [c] The reaction was performed for 4 h.

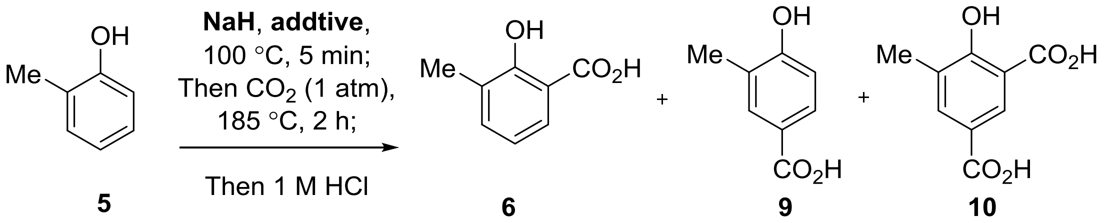
2.5.3 Screening of phenol derivatives as additives

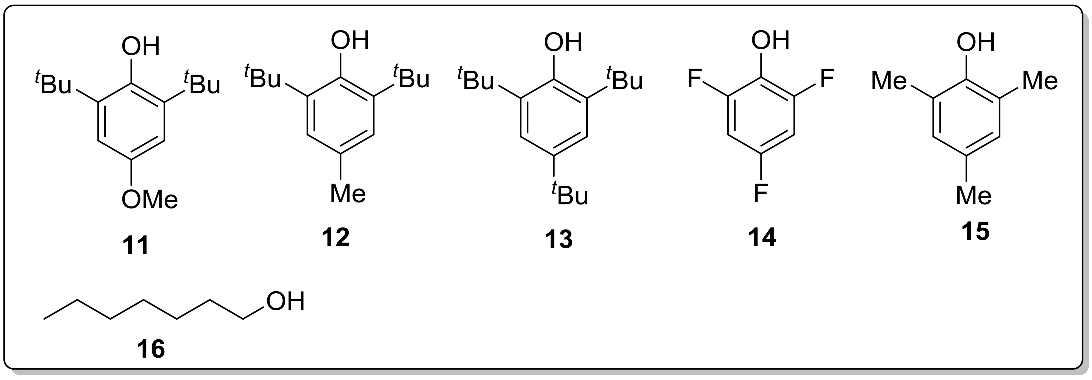
Given that CO_2 could be captured by a metal phenolate through weak coordination between the alkali metal and CO_2, we speculated that the carboxylation could be promoted by the use of an extra phenolate, as more CO_2 could be absorbed into the solid phase. However, this phenolate should not undergo carboxylation to consume the absorbed CO_2. We investigated whether 2,4,6-trisubstituted phenolates would be suitable due to having the *ortho*- and *para*-positions blocked.

Similar to the formation of sodium 2-methylphenolate (**5**), the 2,4,6-trisubstituted phenolate could be formed *in situ* by a simple mixture of the corresponding phenol additive and NaH. Initially, we tested the effect of the phenolate additive by adding 1 equivalent of the corresponding phenol additive and 2 equivalents of NaH respect to the phenol additive. Gratifyingly, an improvement in the yield was obtained by the addition of 2,6-di-*tert*-butyl-4-methoxyphenol (**11**), affording 53% of the desired *ortho*-carboxylated product **6**, 5% of *para*-carboxylated product **9** and small amount of dicarboxylated product **10** (**Table 2.5**, entry 2). Encouraged by this, different substituted phenols with *tert*-butyl at both *ortho*-positions **12**, **13** were tested but no improvement in the yield was observed (**Table 2.5**, entries 3 and 4). A substrate with an electron-withdrawing group, 2,4,6-trifluorophenol (**14**) was also tested and afforded a similar result to the reaction when only NaH was used (**Table 2.5**, entry 5). An aliphatic alcohol, 1-octanol (**16**), was also tested and no improvement in the yield was obtained (**Table 2.5**, entry 6).

Finally, 2,4,6-trimethylphenol (**15**) was found to significantly improve the yield of *ortho*-carboxylated product **6** to 84%, as well as *para*-carboxylated product **9** to 12% (**Table 2.5**, entry 7). Decreasing the use of NaH (**15**) from 4 equivalents to 3 equivalents gave a lower yield 74% (**Table 2.5**, entry 8), suggesting that an extra 2.0 equivalents of NaH respect to the phenol additive were required when the phenol additive was used. Decreasing the amount of the phenol additive **15** to 0.5 equivalents was also found to be less efficient in comparison with 1.0 equivalent (**Table 2.5**, entry 9).

Table 2.5 Screening of phenol derivatives as additives[a]





entry	NaH (equiv)	Additive (equiv)	Yield **6** (%)	Yield **9** (%)	Yield **10** (%)
1	2.0	-	38	2	1
2	4.0	**11** (1.0)	53	5	2
3	4.0	**12** (1.0)	37	3	1
4	4.0	**13** (1.0)	36	2	1
5	4.0	**14** (1.0)	40	5	3
6	4.0	**16** (1.0)	40	5	2
7	4.0	**15** (1.0)	84	12	7
8	3.0	**15** (1.0)	74	12	5
9	3.0	**15** (0.5)	76	11	6

[a] Unless otherwise noted, all reactions were carried out using 0.25 mmol of **5**, yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

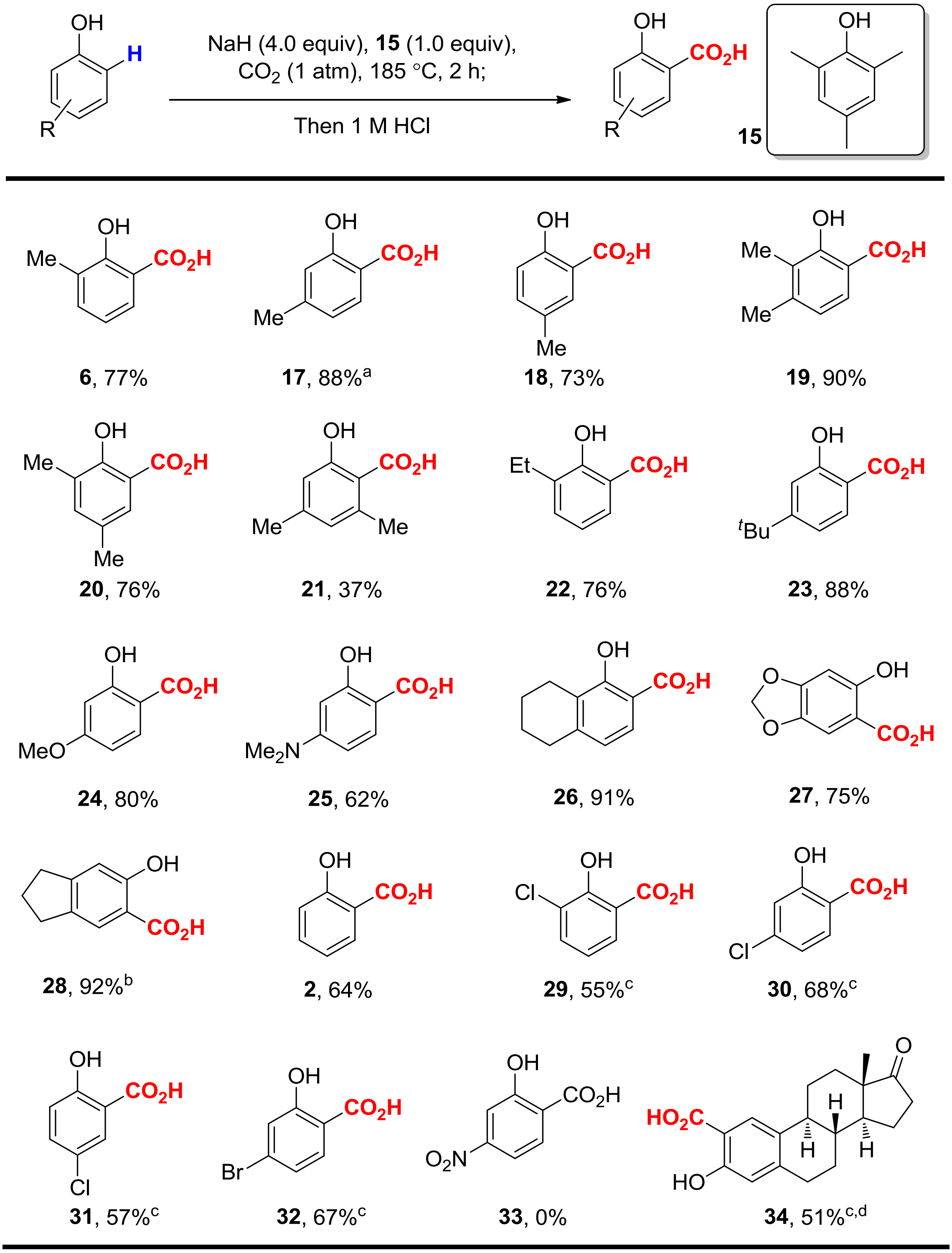
2.6 Scope of the phenol carboxylation

Different phenol substrates were examined to further demonstrate the feasibility of our process (**Scheme 2.20**). Substrates with a small methyl substituent at the *ortho*-, *meta*- and *para*-positions were all *ortho*-carboxylated in good yields (**Scheme 2.20**, **6**, **17** and **18**). However, in terms of *m*-cresol, a mixture of C6 and C2 carboxylated products in 85:15 ratio was obtained (**Scheme 2.20**, **17**). Dimethyl substituted phenols were found to be compatible (**Scheme 2.20**, **19** and **20**), with even the highly hindered 3,5-dimethylphenol affording 37% of carboxylated product (**Scheme 2.20**, **21**).

Different substituents, -Et, -^{t}Bu and -OMe were all found to be compatible with this method, leading to good yields (**Scheme 2.20**, **22-24**). *N*-containing phenols, 3-(dimethylamino)phenol could also be converted into the corresponding salicylic acids in 62% yield (**Scheme 2.20**, **25**).

Cyclic substituted phenols, such as 5,6,7,8-tetrahydro-1-naphthol and sesamol could undergo carboxylation to afford the corresponding salicylic acids in 91% and 75% of yields, respectively (**Scheme 2.20**, **26** and **27**). Similar to the carboxylation of *m*-cresol (**17**), when 5-indanol was used, a mixture of C6 and C4 carboxylated products in 79:21 ratio were obtained, with a 92% of total yields (**Scheme 2.20**, **28**). Simple phenol was also tested and carboxylated, affording 64% of salicylic acid which is the precursor of aspirin (**Scheme 2.20**, **2**).

For phenols substituted with electron-withdrawing groups, slightly higher CO_2 pressure was required, and the carboxylation of halophenols satisfyingly afforded the desired products when employing 5 atm of CO_2 (**Scheme 2.20**, **29-32**). However, a substrate containing the strongly electron-withdrawing -NO_2 group did not work at all (**Scheme 2.20**, **33**). Interestingly, the steroid hormone estrone can be conveniently converted to the corresponding *ortho*-carboxylated product in 51% yield (**Scheme 2.20**, **34**).



Yields are of the isolated pure material. [a] The product was formed as a 85:15 ratio of regioisomers (C6:C2). [b] The product was formed as a 79:21 ratio of regioisomers (C6:C4). [c] Reactions were carried out at 5 atm of CO_2. [d] Reactions were carried out for 12 h.

Scheme 2.20 Scope of ambient pressure carboxylation of phenols

2.7 Conclusions and Future work

This chapter describes the development of a novel carboxylation methodology, which efficiently allows the synthesis of salicylic acids with a range of functionalities, such as alkyl, alkoxy, amine, and halogens, under ambient CO_2 pressure from the corresponding phenols. The trisubstituted phenol additive plays an important role in this ambient pressure carboxylation methodology. However, it is still unclear how this trisubstituted phenol additive helps the reaction.

The process proceeds at much lower pressure, representing an important improvement compared to the classic Kolbe-Schmitt carboxylation which usually requires high pressures. Moreover, the avoidance of phenoxide isolation also improves the current Kolbe-Schmitt procedures in terms of operational simplicity.

Despite the above, there are still some challenges that need to be addressed:

1) The current method requires high temperatures which should be avoided. The aim of these transformations should be to develop a reasonable temperature or room temperature C–H carboxylation protocol, which would consequently tolerate a wide range of sensible groups.

2) Developing methodologies for C–H carboxylation of general aromatic compounds. These methodologies should be able to carboxylate aromatic compounds with different functionalities *via* C–H cleavage, converting to benzoic acid derivatives.

Chapter 3

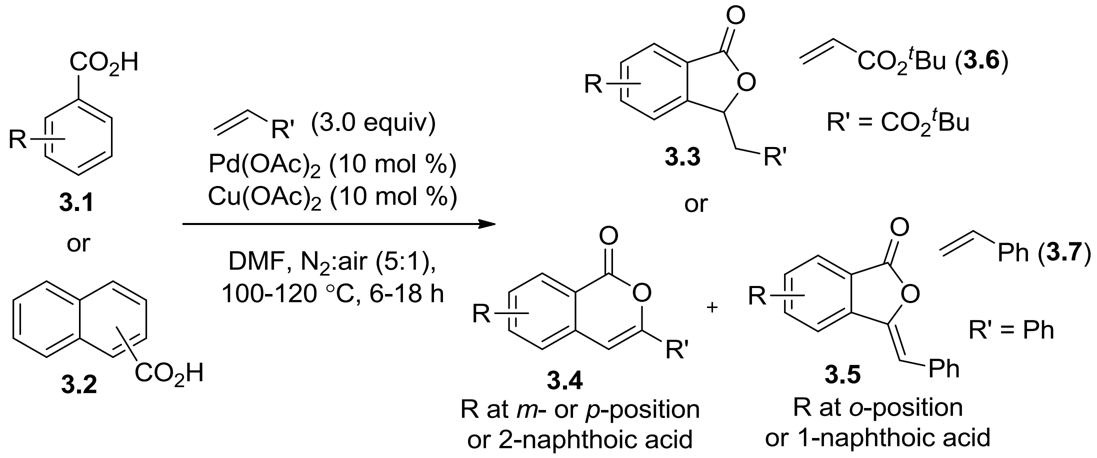
Chapter 3 *Meta*-selective arylation of phenols

3.1 Introduction

As described in Chapter 1, our objective is to develop an efficient methodology for the *meta*-arylation of phenols. We hypothesised that installation of a directing group at the *ortho*-position of phenol would facilitate arylation in the *ortho*-position to the directing group. The *meta*-arylated phenol could then be obtained *via* the cleavage of the directing group. Our attention has been turned to the carboxylic group which has been widely used as the directing group in C–H activation.[79] We wondered whether the carboxylated phenol could undergo arylation and subsequent decarboxylation to provide the *meta*-arylated phenol. A brief overview of carboxyl directed C–H activation and decarboxylation, based on existing literature, will be presented first in this chapter.

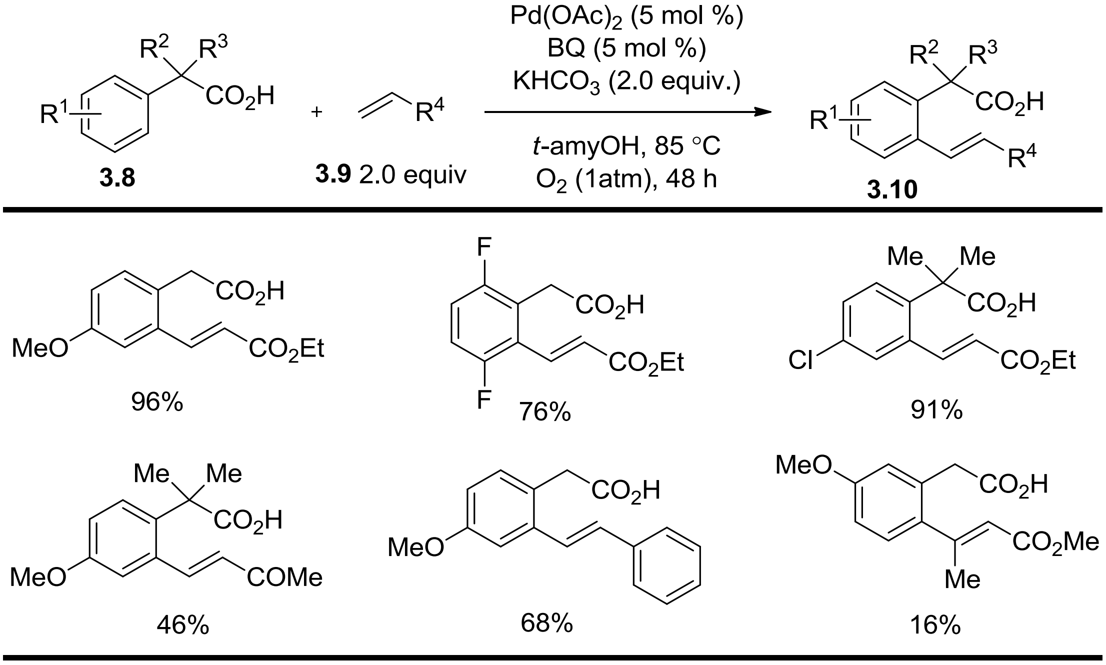
3.1.1 Carboxyl directed C–H functionalisation

A variety of methodologies for carboxyl group directed C–H functionalisation has been developed in the past years.[1] Pioneering work was made in 1998 by Miura and co-workers who established the protocol for Pd(II)-catalysed *ortho*-olefination of benzoic acids **3.1** and naphthoic acids **3.2** (**Scheme 3.1**).[80] In this work, phthalide **3.3** was formed exclusively when butyl acrylate (**3.6**) was used *via* an *ortho*-vinylation followed by nucleophilic cyclisation. The use of styrene **3.7**, on the other hand, could afford phthalides **3.5** or isocoumarin **3.4** *via ortho*-vinylation/Wacker-type oxidation depending on the benzoic acid used. The authors stated that *ortho*-substituted benzoic acids or 1-naphthoic acids resulted in the formation of phthalides **3.5** potentially due to the low steric hindrance between the *ortho*-substituent and the carbonyl group, while unsubstituted or *meta* and *para* substituted benzoic acids or 2-naphthoic acids led to isocoumarin **3.4** formation or mixtures of both phthalides **3.5** or isocoumarin **3.4**.



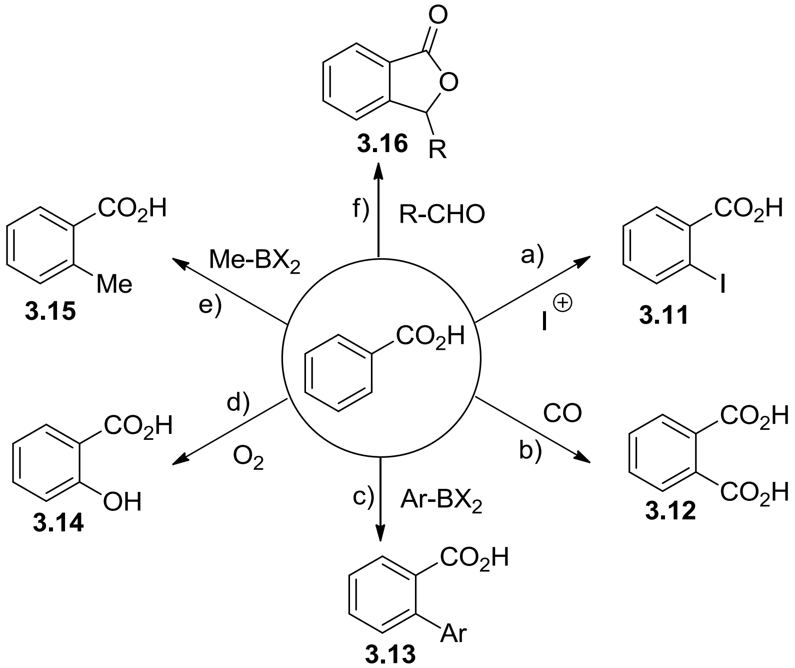
Scheme 3.1 Pd-catalysed *ortho*-olefination of benzoic acids

Carboxylic acid directed olefinations in the presence of Pd has been extensively investigated by Yu and co-workers who developed an efficient method for *ortho*-vinylation of phenylacetic acids **3.8** using an *N*-protected amino acid (**Scheme 3.2**).[81] The authors stated that the *N*-protected amino acid not only enhances the reactivity, but also controls the site-selectivity in C–H activation with two approximately electronically equivalent *ortho* C–H bonds. Besides Pd, Ru[82], Ir[83] and Rh[84] have also been explored as effective catalysts in carboxyl directed *ortho*-olefination.



Scheme 3.2 Pd-catalysed *ortho*-olefination of phenylacetic acids

Beside the carboxyl directed C–H functionalisation with olefins, carboxylic acid directed *ortho* a) halogenation,[85] b) carboxylation,[86] c) arylation[87] d) hydroxylation[88] and e) alkylation[89] were also explored, as well as *ortho*-functionalisation with aldehydes and subsequent intramolecular cyclisation to afford phthalide derivatives[90] (**Scheme 3.3**).

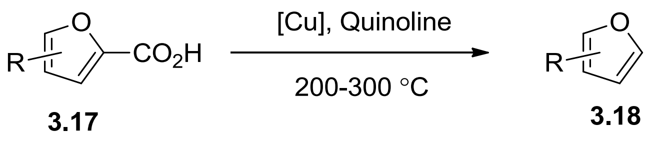


Scheme 3.3 Carboxyl directed *ortho* C–H functionalisation

3.1.2 Decarboxylation

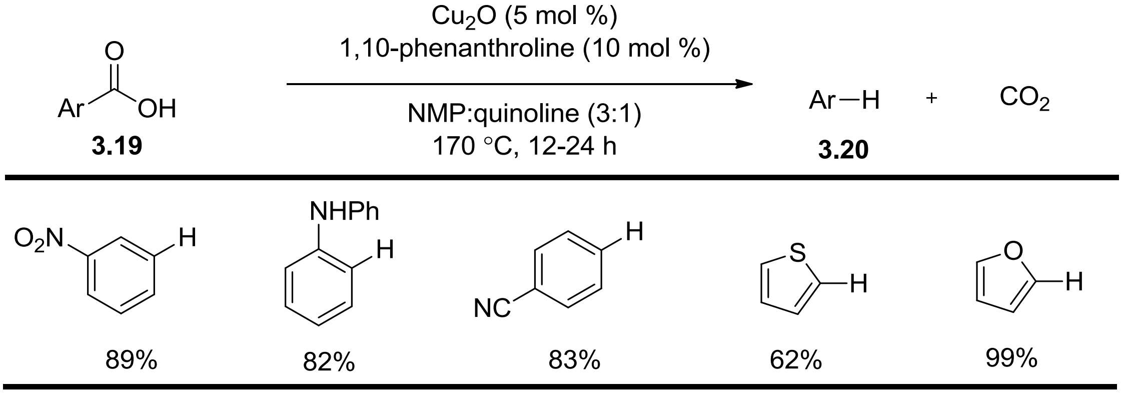
Despite the fact that benzoic acids have been demonstrated to serve as commonly used directing groups for a variety of synthetically useful transformations, the application is limited when the carboxylic acid group is not needed in the target molecule. Therefore, the development of methodologies for the removal of a carboxylic acid is of high interest.

The first study on the metal-mediated protodecarboxylation of benzoic acids was reported by Shepard in 1930 (**Scheme 3.4**).[91] The use of stoichiometric Cu-salts led to decarboxylation of furoic acids (**3.17**) at high temperature. Subsequently, Nilsson[92] and Sheppard[93] reported that benzoic acids could undergo protodecarboxylation under similar conditions.



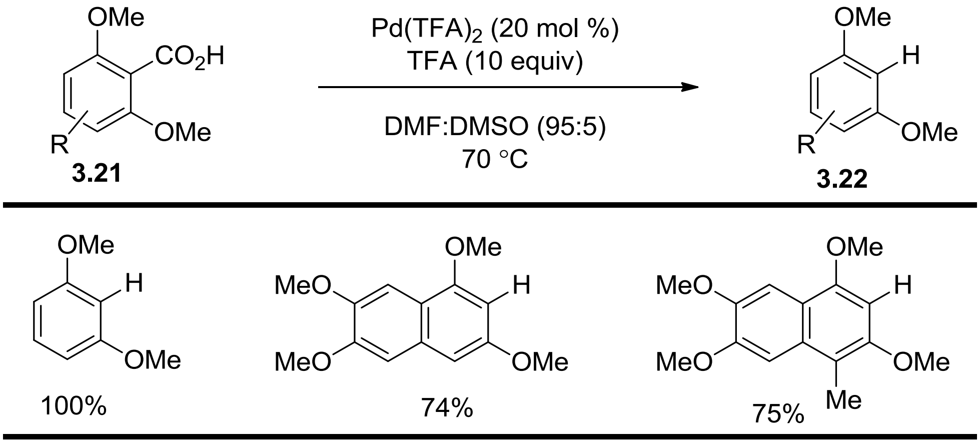
Scheme 3.4 Decarboxylation of furoic acids in the presence of Cu-salts

However, Cu-catalysed decarboxylation of aromatic carboxylic acids has not been developed until 2007, Goossen and co-workers used catalytic Cu_2O for decarboxylation of a wide variety of aromatic carboxylic acids **3.19** in the presence of 1,10-phenanthroline as a ligand (**Scheme 3.5**). [94] Mechanistic studies suggested that the formation of aryl-Cu species as intermediates which upon protonation afford the decarboxylated products **3.20**.



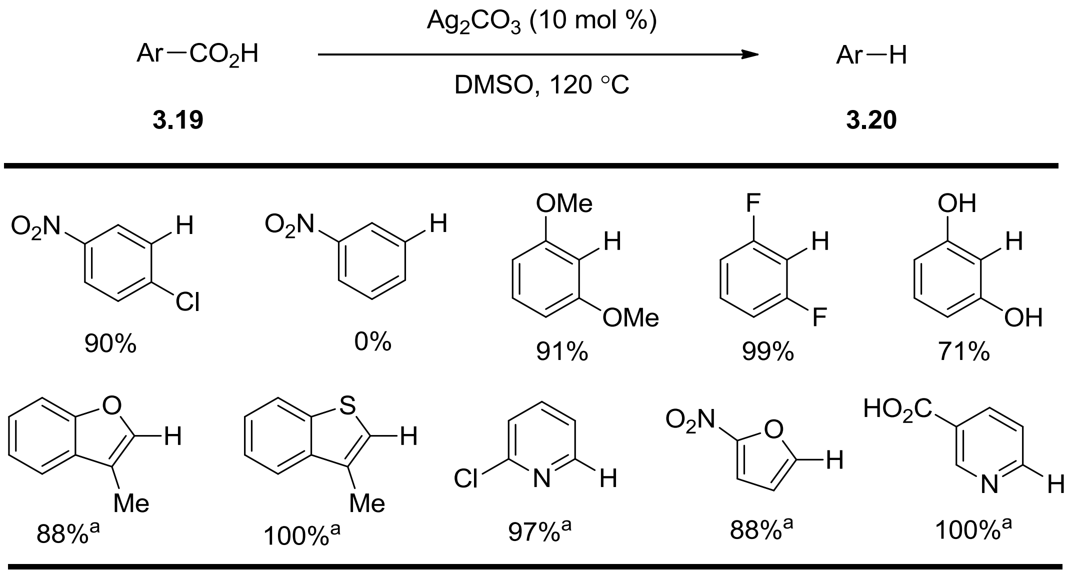
Scheme 3.5 Cu-catalysed protodecarboxylation

Cu is not the only transition metal capable of mediating or catalysing the decarboxylation process. A Pd-catalysed decarboxylation of highly electron-rich trimethoxy-substituted benzoic acids has also been reported by Myers et al.[95] Subsequently, Kozlowski and co-workers developed a protocol for Pd-catalysed protodecarboxylation of benzoic acids (**Scheme 3.6**). [96] However, this methodology for Pd-catalysed decarboxylation is extremely limited as the substrates must contain two or more electron-donating -OMe groups.



Scheme 3.6 Pd-catalysed protodecarboxylation of dimethoxy-substituted benzoic acids

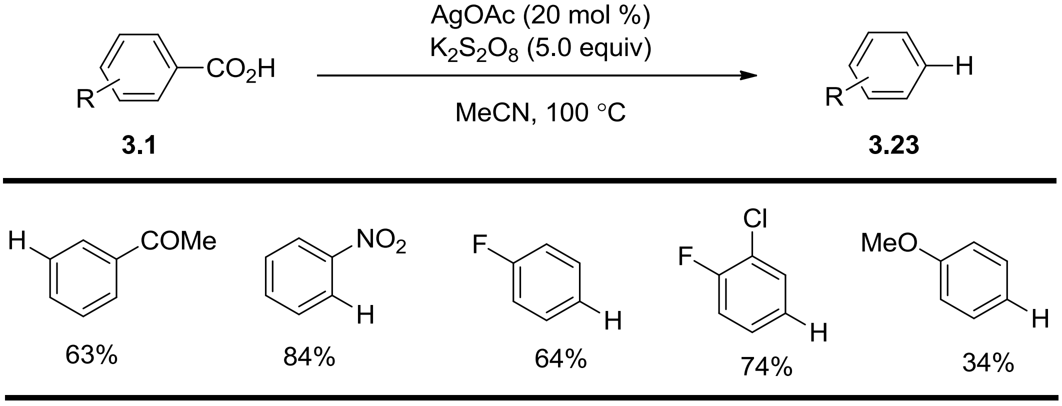
Our group developed a Ag-catalysed protodecarboxylation of a range of *ortho*-substituted benzoic acids,[97] and heteroaromatic carboxylic acids in the presence of AcOH (**Scheme 3.7**).[98] Additionally, selective monoprotodecarboxylation of (hetero)aromatic dicarboxylic acids was performed. Mechanistic studies demonstrated that *ortho*-substituted benzoic acids could lead to a much lower activation energy barrier for protodecarboxylation compared to their *meta*- and *para*-counterparts due to steric and electronic effects.[99] At the same time, Goossen and co-workers reported a Ag-catalysed decarboxylation of *ortho*-substituted (hetero)aromatic carboxylic acid in the presence of K_2CO_3.[100] However, these Ag-catalysed decarboxylation methods are all limited in the substrate scope to *ortho*-substituted carboxylic acids.



[a] 5 mol % of AcOH were added.

Scheme 3.7 Ag-catalysed protodecarboxylation of (hetero)aromatic carboxylic acids

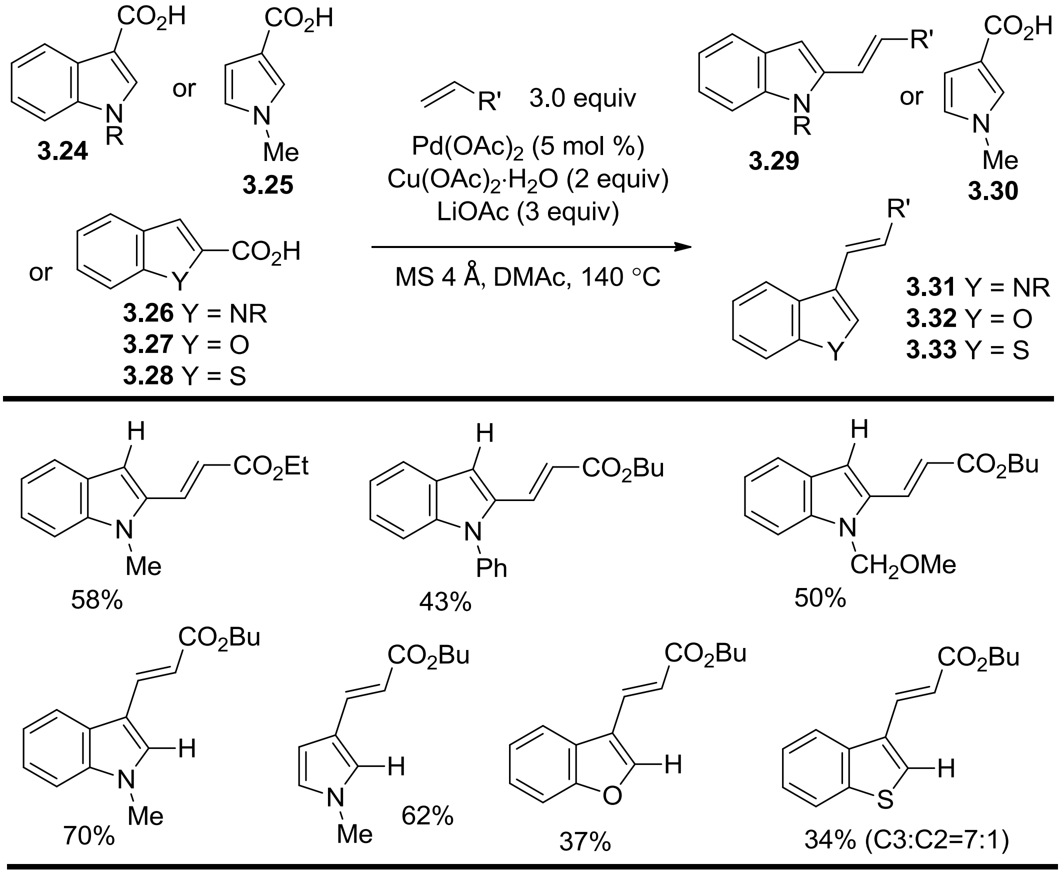
The research group of Greaney developed an oxidative radical process to decarboxylate a variety of benzoic acids.[53] Importantly, this protocol expands the substrate scope, allowing not only the *ortho*-substituted benzoic acids but also the *meta*- and *para*-substituted benzoic aicds to undergo decarboxylation (**Scheme 3.8**).



Scheme 3.8 Ag-catalysed oxidative radical decarboxylation of benzoic acids

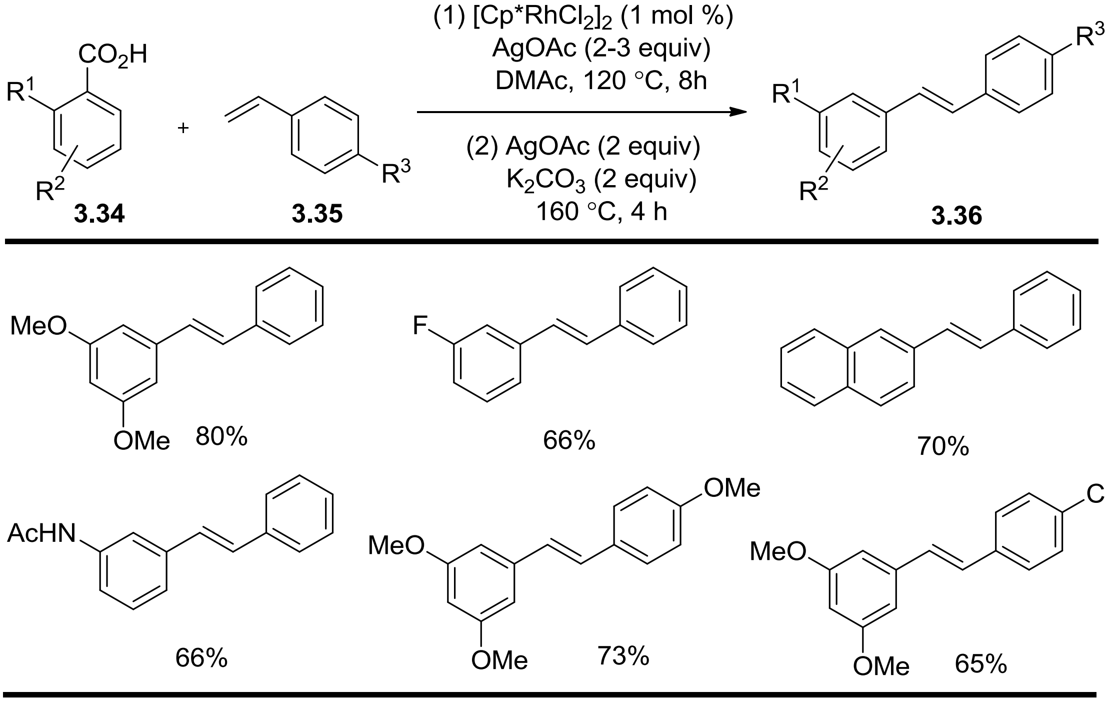
3.1.3 Carboxyl group as a removable directing group in C–H activation

Pioneering work in this area was reported by Miura who developed a Pd-catalysed method for direct C–H vinylation of indole-3-carboxylic acids **3.24** and indole-2-carboxylic acids **3.26**, followed by a decarboxylation process to give the corresponding vinylindoles **3.29** and **3.31**.[101] This method is also applicable for selective C3-olefination of *N*-methylpyrrole-2-carboxylic acid (**3.25**), benzofuran-2-carboxylic acid (**3.27**) and benzothiophene-2-carboxylic acid (**3.28**) (**Scheme 3.9**).



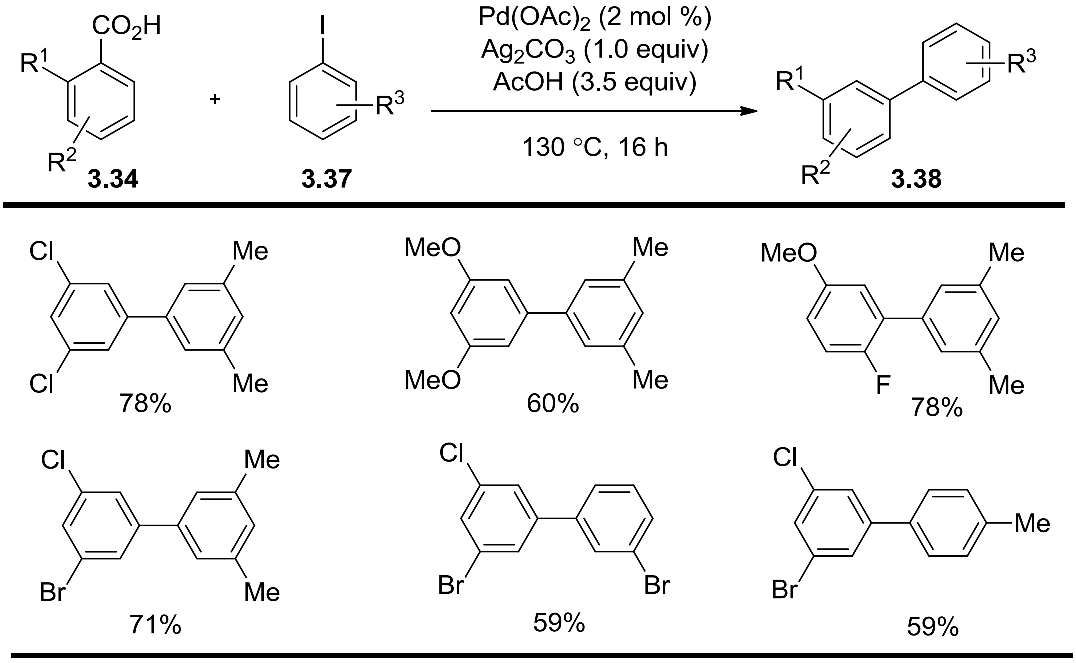
Scheme 3.9 Pd-catalysed olefination/decarboxylation of heteroaromatic carboxylic acids

In 2010, the same group demonstrated that *ortho*-substituted benzoic acids **3.34** can be transformed to the corresponding *meta*-vinylated products **3.36** in the presence of Rh catalyst *via ortho*-olefination and decarboxylation step in one-pot (**Scheme 3.10**).[102] However, the use of the large excess of Ag-salts limited this methodology.



Scheme 3.10 Rh-catalysed *ortho*-olefination/decarboxylation of benzoic acids

An extension of this work was presented by our group in 2011. We showed that the formation of *meta*-substituted biaryl compounds can be achieved under Pd catalysis *via* arylation of the *ortho*-substituted benzoic acids **3.34** and subsequent protodecarboxylation (**Scheme 3.11**). A broad range of functionalities at both benzoic acid and iodoarene coupling partners were found to be compatible, affording a variety of *meta*-substituted biaryl **3.38**.[20] Unlike Miura's work, where the vinylation and protodecarboxylation did not occur at the same time (**Scheme 3.10**), in this work, the arylation of benzoic acids and the protodecarboxylation of the arylated benzoic acid intermediates occur in a tandem process, which makes the method more efficient.



Scheme 3.11 Tandem *ortho*-arylation/decarboxylation process lead to *meta*-biaryls

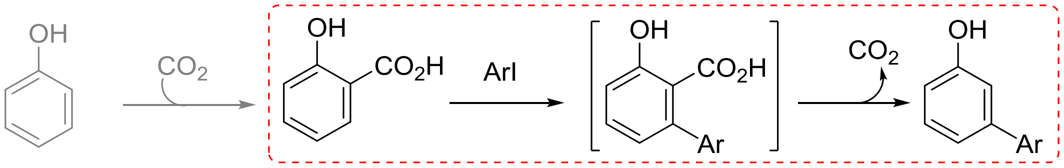
3.2 Tandem arylation/decarboxylation of salicylic acids

3.2.1 Objectives

As described in the introduction, the carboxyl group has been commonly used as an *ortho*-directing group to control site-selective C–H functionalisation. Moreover, the development of catalytic decarboxylation of benzoic acids has also been explored. This dual functionality of the carboxyl group has been exploited by Miura's and our group for *meta*-functionalisation of substituted aromatic compounds.

Phenol derivatives are commonly found in many natural products, pharmaceuticals and agrochemicals.[26] However, due to the high reactivity of phenol derivatives, most of the methodologies for carboxyl group-directed C–H functionalisation are not compatible with free phenol substrates. Thus, at this stage of our research, we wanted to explore whether the salicylic acids could undergo an arylation/protodecarboxylation process to afford *meta*-arylphenol derivatives (**Scheme 3.12**).

Objective: *Tandem arylation/decarboxylation of salicylic acid leads to meta-arylphenol*



Scheme 3.12 Aim of the project

3.2.2 Optimisation of reaction conditions

Preliminary optimisation

With this aim in mind, we started to investigate suitable reaction conditions. Initially, the reaction of salicylic acid **2**, was submitted into the 'formal' *meta*-arylation conditions reported by our group,[20] employing 5-iodo-*m*-xylene **36** as the coupling partner. Fortunately, 35% of *meta*-arylphenol **37** was obtained (**Table 3.1**, entry 1). On the other hand, the non-protodecarboxylated product **38** was not observed in any of the reactions.

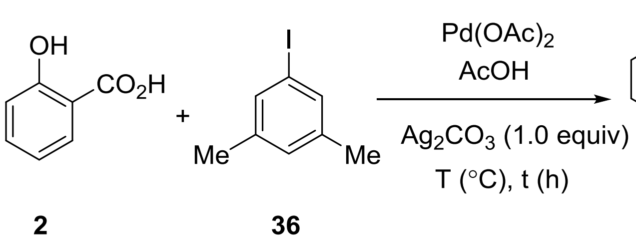
As the solids were not completely soluble in the reaction above, an increased amount of AcOH was used, and it turned out to improve the yields (**Table 3.1**, entries 2 and 3). Due to the well-known ability of DMSO to dissolve many salts, as well as its coordinating ability, we hoped that the yield could be improved by the use of DMSO in the reaction. However, not even a trace of product was obtained when a 1:1 mixture of AcOH and DMSO was used as co-solvent (**Table 3.1**, entry 4).

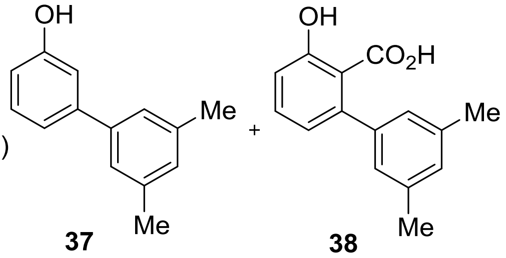
The test for the effect of water showed that the reaction was not sensitive to water, with no decrease of the yield being observed when 5.0 equivalents of water were added into the reaction (**Table 3.1**, entry 5).

The increase of temperature from 130 °C to 140 °C gave slightly higher yield (**Table 3.1**, entry 6). On the other hand, we noted that the decrease of temperature resulted in lower yields (**Table 3.1**, entries 7 and 8).

There was a significant improvement in the yield when the reaction time was prolonged to 60 h, affording 63% of *meta*-arylated product **37** (**Table 3.1**, entry 9). A higher loading of $Pd(OAc)_2$ (5 mol %) afforded similar yield to 2 mol % (**Table 3.1**, entry 10). On the other hand, an increased 45% yield was obtained when reducing the amount of $Pd(OAc)_2$ (to 1 mol % (**Table 3.1**, entry 11). Interestingly, no further reaction was obtained when prolonged the reaction in the presence of 1 mol % of $Pd(OAc)_2$ to 60 h (**Table 3.1**, entry 12). This was perhaps because the catalyst would deactivate during the long reaction time, consequently, a high loading of catalyst was required for further reaction.

Table 3.1 Preliminary results[a]





Entry	T (°C)	t (h)	AcOH (equiv)	$Pd(OAc)_2$ (mol %)	Yield of **37** (%)
1	130	16	3.5	2	35
2	130	16	7.0	2	42
3	130	16	10.5	2	44
4[b]	130	16	3.5	2	0
5[c]	130	16	3.5	2	28
6	140	16	7.0	2	50
7	110	16	3.5	2	32
8	120	16	3.5	2	35
9	130	60	3.5	2	63
10	130	16	3.5	5	36
11	130	16	3.5	1	45
12	130	60	3.5	1	45

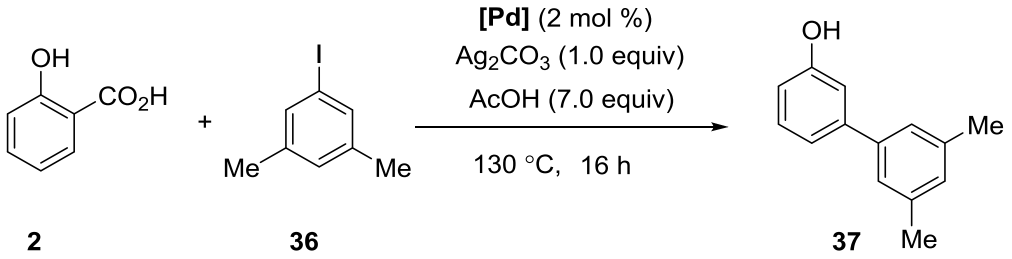
[a] Unless otherwise noted, all reactions were carried out using 1.0 equiv of **2**, 3.0 equiv of **36** and 1.0 equiv of silver carbonate, yields were determined by ^1H NMR analysis using mesitylene as an internal standard. [b] 200 µL of DMSO were also added. [c] 5.0 equiv of water were also added.

Screening of Pd sources

To improve the yield of the tandem arylation/protodecarboxylation of salicylic acid process, different Pd sources were tested (**Table 3.2**). In terms of Pd(0) sources, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were found to be compatible with the reaction, affording 51% and 47% yields, respectively (**Table 3.2**, entries 2 and 3). These yields are slightly higher in comparison with $Pd(OAc)_2$ (**Table 3.2**, entry 1).

Different Pd(II) sources were also examined (**Table 3.2**, entries 4-7), and it was found that PEPPSI-IPr and PEPPSI-IPent afforded the best results, achieving 57% and 61% yields, respectively (**Table 3.2**, entries 6 and 7). The use of $Pd(OAc)_2$ together with NHC ligands did not give as good yield as PEPPSI catalyst (**Table 3.2**, entries 8 and 9).

Table 3.2 Palladium catalysts screening[a]



Entry	[Pd] (2 mol %)	Yield of **37** (%)
1	$Pd(OAc)_2$	42
2	$Pd_2(dba)_3$[b]	51
3	$Pd(PPh_3)_4$	46
4	$Pd(TFA)_2$	42
5	$Pd(MeCN)_2Cl_2$	46
6	PEPPSI-IPr	57
7	PEPPSI-IPent	61
8	$Pd(OAc)_2$[c]	45
9	$Pd(OAc)_2$[d]	38

[a] Unless otherwise noted, all reactions were carried out using 1.0 equiv of **2**, 3.0 equiv of **36**, 1.0 equiv of silver carbonate and 200 μL (7.0 equiv) of AcOH for 16 hours at the temperature of 130 °C, yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] 1 mol % of $Pd_2(dba)_3$ was used. [c] 2 mol % of IMesCl were also added. [d] 2 mol % of IPrCl were also added.

Systematic screening using PEPPSI catalyst

Although PEPPSI-IPent provided the highest yield of the product (61%), PEPPSI-IPr, which afforded 57% of product, was selected for the further optimisation on the basis of its much lower cost.

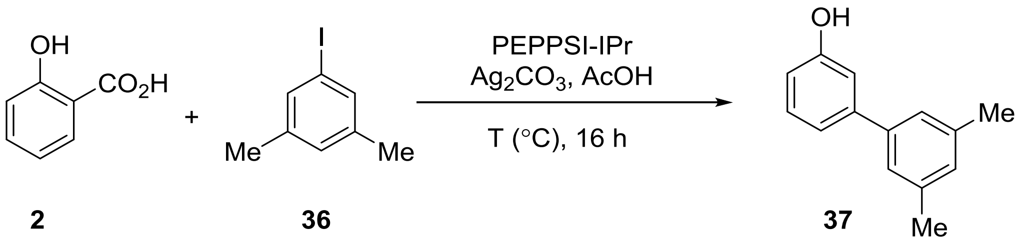
Different amounts of PEPPSI-IPr loading were tested. The reaction in the presence of 1 mol % of PEPPSI-IPr gave 51% of *meta*-arylated product **37** (**Table 3.3**, entry 1). Increased the catalyst to 2 mol % gave a slightly higher yield 57% (**Table 3.3**, entry 2), which seemed to be optimal for the reaction as the reactions in the presence of 3 mol % and 4 mol % of catalysts led to the similar yields (**Table 3.3**, entries 3 and 4).

Temperature screening was also carried out and it was found that decreasing the temperature from 130 °C to 120 °C led to a lower yield 48% (**Table 3.3**, entry 5). On the other hand, an improvement in yield was obtained when increasing the temperature (**Table 3.3**, entries 6-9), and it was found that 150 °C seemed to be most suitable for this method, affording 70% *meta*-arylated product **37** (**Table 3.3**, entry 7). The yield was reduced to 49% upon further heating to 180 °C (**Table 3.3**, entry 9). Increasing the amount of solvent, AcOH, from 7.0 equivalents to 14.0 equivalents slightly improved the yield from to 70% to 74% (**Table 3.3**, entry 10).

Considering that the function of the Ag-salt in this method is presumably as an iodide abstractor we investigated if the Ag-salt could be reduced to 1.0 equivalent. Satisfyingly, a significant improvement in yield to 83% was obtained when the amount of Ag_2CO_3 was reduced to 0.5 equivalents (**Table 3.3**, entry 11).

It has been found that κ^1-coordination (crucial for *ortho* C–H cleavage) between Pd(II) and the carboxyl group is favoured in the presence of inorganic counter cations such as K, Cs, and ammonium salts.[88,103] Therefore, the addition of inorganic salts, K_2CO_3 and Cs_2CO_3, was investigated which satisfyingly improved the yields to 92% and 90% of *meta*-arylated product **37**, respectively (**Table 3.3**, entries 12 and 13).

Table 3.3 Optimisation of the formal *meta*-arylation using PEPPSI-IPr[a]

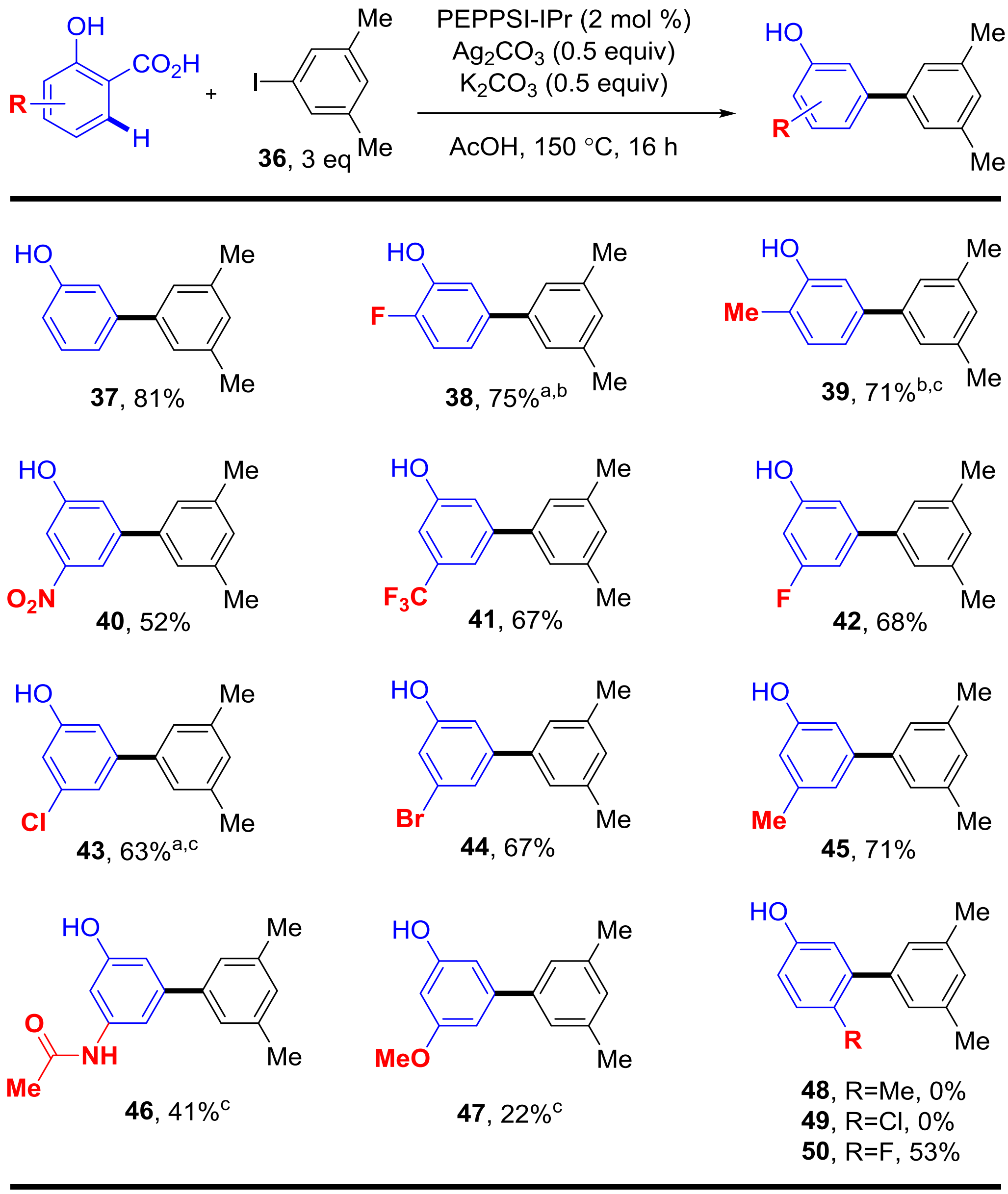


Entry	T (°C)	Ag_2CO_3 (eq)	AcOH (eq)	PEPPSI-IPr (mol %)	Yield of 3a (%)
1	130	1.0	7.0	1	51
2	130	1.0	7.0	2	57
3	130	1.0	7.0	3	57
4	130	1.0	7.0	4	56
5	120	1.0	7.0	2	48
6	140	1.0	7.0	2	66
7	150	1.0	7.0	2	70
8	160	1.0	7.0	2	68
9	180	1.0	7.0	2	49
10	150	1.0	14.0	2	74
11	150	0.5	14.0	2	83
12[b]	150	0.5	14.0	2	86
12[c]	150	0.5	14.0	2	92
13[d]	150	0.5	14.0	2	90

[a] Unless otherwise noted, all reactions were carried out using 1.0 equiv of **2**, 3.0 equiv of **36**, 2 mol% of PEPPSI-IPr, ran for 16 hours, yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] PEPPSI-Ipent was used instead of PEPPSI-IPr. [c] 0.5 equiv of K_2CO_3 were used in the reaction. [d] 0.5 equiv of Cs_2CO_3 were used in the reaction.

3.2.3 Scope of tandem arylation/protodecarboxylation of salicylic acids

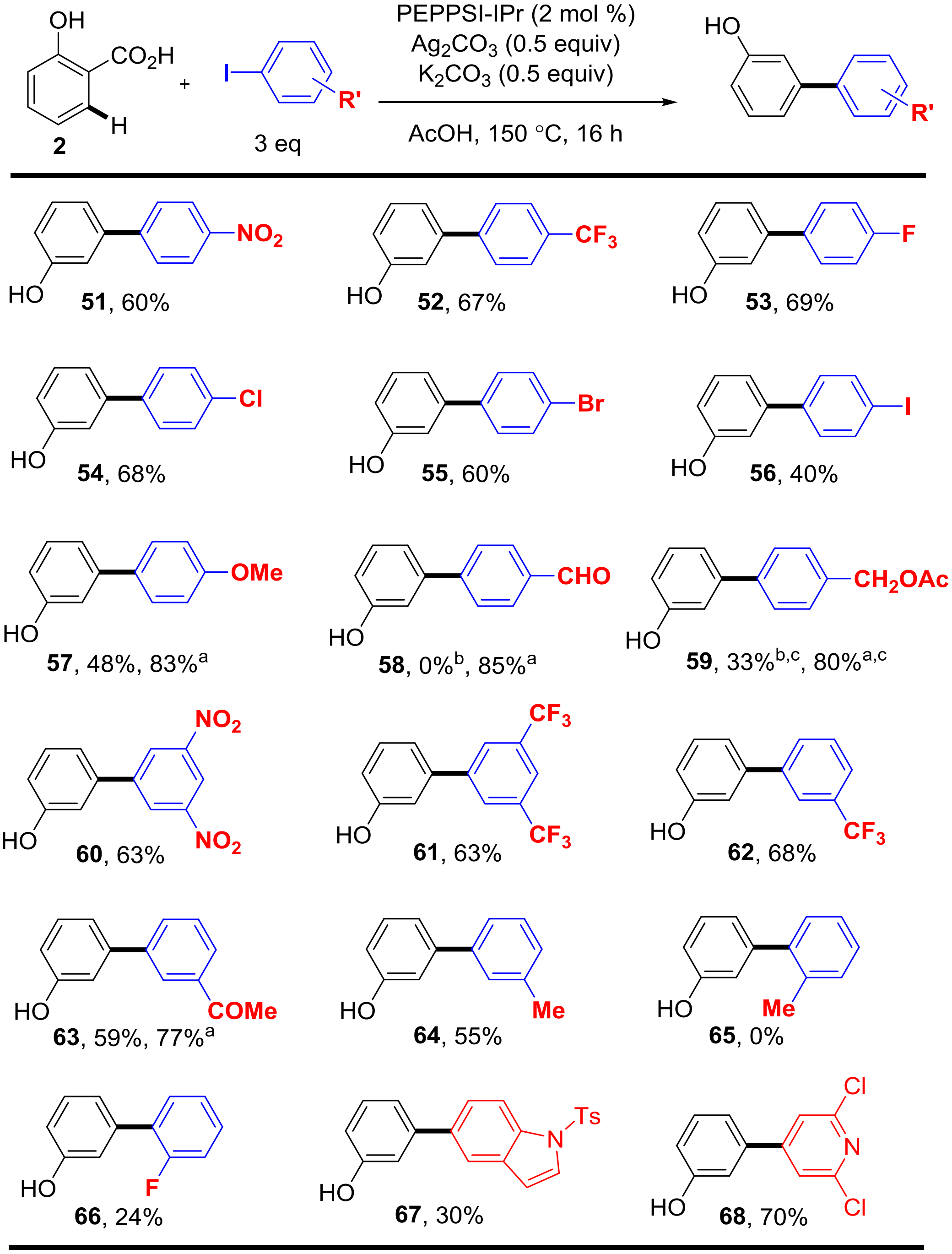
After finding the optimised conditions for this tandem arylation/protodecarboxylation of salicylic acids, a number of substituted salicylic acids were examined. Gratifyingly, many functional groups involving both electron-withdrawing (**Scheme 3.13**, **38**, **42**-**44**) and electron-donating groups (**Scheme 3.13**, **39**, **45**) were tolerated at the C3 or C4 positions of the salicylic acids. Strong electron-withdrawing groups -NO_2 and -CF_3 were found to be compatible, giving 52% and 67% yields, respectively (**Scheme 3.13**, **40** and **41**). On the other hand, when a strong electron-donating -OMe group was present at the C4 position of the acids, only 22% of desired product was obtained (**Scheme 3.13**, **47**). This is due to the competitive decarboxylation of the starting material as a large amount of 4-methoxyphenol was observed. A substrate bearing an amide group at the C4 position also reacted smoothly, affording 41% of the desired product (**Scheme 3.13**, **46**). In this case, although the amide group has been shown to be a good *ortho*-directing group,[104] the carboxyl group is out competing under our conditions as no other regioisomer was obtained. However, a low yield was obtained due to competive decarboxylation of the starting material as mentioned with a -OMe substituted substrate. Finally, different substitutions at the C5 of salicylic acids were tested and found to be poorly tolerated with only a small -F substituent at the C5 position allowed the arylation to proceed, giving 53% of the desired product (**Scheme 3.13**, **50**). -Me and -Cl substitutents at the C5 position did not react at all presumably due to steric hindrance proximity to the activated C–H bond (**Scheme 3.13**, **48** and **49**).



Yields are of isolated products. [a] The reaction was carried out at 160 °C. [b] 1.0 mL of AcOH were used. [c] K_2CO_3 was not used.

Scheme 3.13 Scope of the tandem arylation/protodecarboxylation process on substituted salicylic acids

A variety of substituted aryl iodides were then tested and both electron-withdrawing (**Scheme 3.14**, **51**-**56**, **60**-**63**) and electron-donating groups (**Scheme 3.14**, **57**, **65**) were found to be compatible in both *meta*- and *para*-positions, leading to the corresponding *meta*-arylated phenols in moderate to good yields. Interestingly, only the monoarylated product was obtained selectively from *p*-diiodobenzene as a coupling partner (**Scheme 3.14**, **56**). An aldehyde substituent was found to be unreactive under the standard conditions. But the desired product **58** could be obtained in 85% yield when an excess of salicylic acid was used in the reaction (**Scheme 3.14**, **58**). This is potentially due to the weak coordinating ability of the aldehyde group to the Pd, thus inhibiting the Pd to coordinate to the carboxyl directing group in the presence of large excess of aldehydes. Similarly to the aldehyde substituted iodoarene, the aryl iodides containing a weak coordinating group, *p*-OMe, *p*-CH_2OH and *m*-COMe, proceeded in better yields when excess of salicylic acids were used (**Scheme 3.14**, **57**, **59** and **77**). O*rtho*-substituted iodoarenes were also tested and found to not be well tolerated, with only the small F substituent giving 24% yield (**Scheme 3.14**, **66**), again highlighting one of the limitations of this method. Finally, iodoindole and idodpyridine were tested and found to be compatible with the process, affording the desired products **67** and **68** in 30% and 70% yields, respectively (**Scheme 3.14**, **67** and **68**).

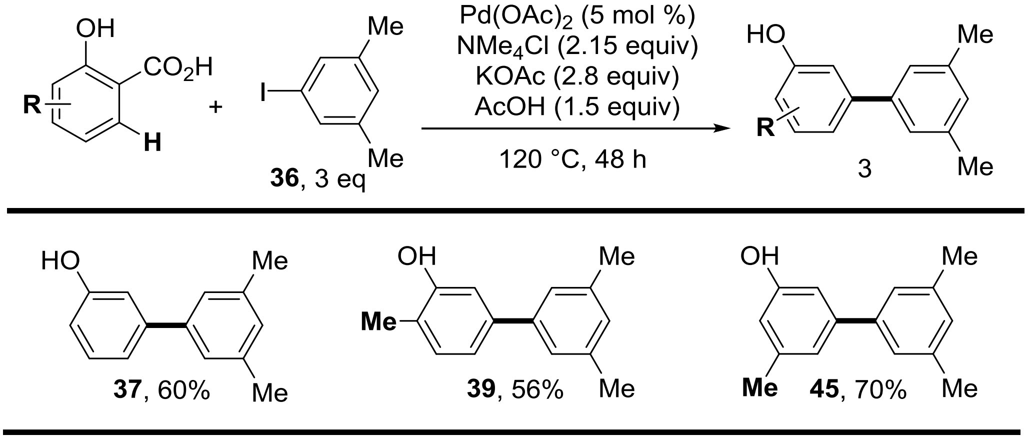


Yields are of isolated products. [a] The reaction was carried out with 0.5 mmol of **1** and 0.167 mmol of aryl iodide at 130 °C. [b] Yield determined by ^{1}H NMR analysis using an internal standard. [c] *p*-iodobenzyl alcohol was used as starting material.

Scheme 3.14 Scope of the tandem arylation/protodecarboxylation process on substituted iodoarenes

3.2.4 Ag-free method for tandem arylation/decarboxylation of salicylic acids

One drawback of the methodology is the need for the stoichiometric use of a Ag-salt as they are expensive and not environmentally friendly, especially when applying the methodology for a large scale synthesis and industrial processes. Recently, our group demonstrated that a cheap and readily available organic salt, Me_4NCl, could be a highly efficient iodide abstractor.[105] Therefore we tested if the Ag_2CO_3 in this present methodology could be replaced with Me_4NCl. Three typical substrates were submitted to the standard Ag-free conditions that we reported before, and gratifyingly, good yields of desired *meta*-arylphenols were obtained without any additional optimisation (**Scheme 3.15**).



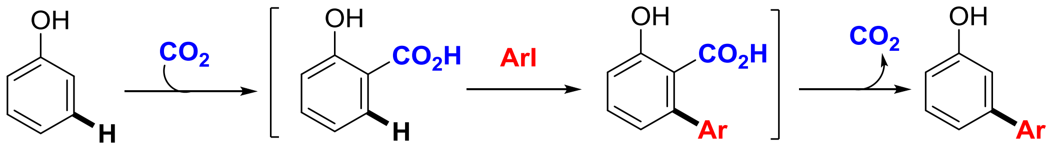
Scheme 3.15 Ag-free method for tandem arylation/protodecarboxylation of salicylic acids

3.3 One-pot *meta*-selective arylation of phenols

3.3.1 Objectives

In the previous section, we showed that various salicylic acids underwent a tandem arylation/protodecarboxylation process under Pd catalysis. Moreover, in the second chapter, we described a methodology allowing the carboxylation of phenols at atmospheric CO_2 pressure. Considering that phenols are more commonly used starting materials and much cheaper in comparison to salicylic acid derivatives, we wondered if we could *meta*-arylate phenols in a one-pot process. Carboxylation of phenol would give salicylic acid which then undergoes arylation/protodecarboxylation to afford *meta*-arylphenols (**Scheme 3.16**).

***Objective**: One-pot meta-arylation of phenols using CO_2 as a traceless directing group*

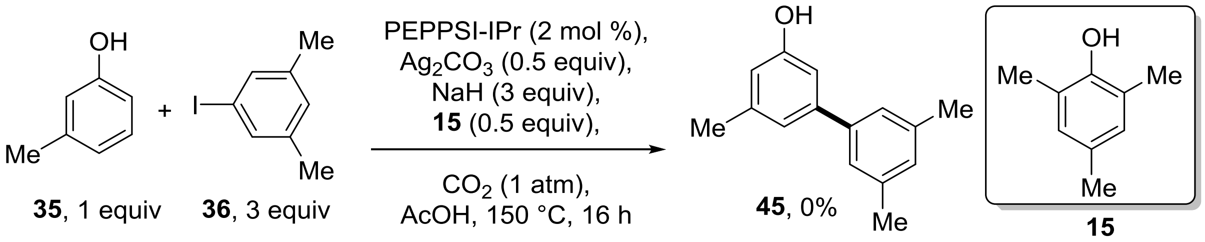


Scheme 3.16 Aim of the project

3.3.2 Optimisation of *meta*-arylation of phenols

Meta-arylation of phenols *via* a tandem carboxylation/arylation/decarboxylation process

Initially, we attempted to combine the method for carboxylation of phenols described in Chapter 2, and the tandem arylation/protodecarboxylation reaction of salicylic acids described in the previous section. We took as a starting point the reaction between *m*-cresol (**35**) and 5-iodo-*m*-xylene (**36**), with 2 mol % of PEPPSI-IPr, 0.5 equivalents of Ag_2CO_3, 3.0 equivalents of NaH and 0.5 equivalents of 2,4,6-trimethylphenol (**15**) in AcOH with a CO_2 balloon, heated at 150 °C for 16 h. Unfortunately, the reaction did not work, with only starting material *m*-cresol (**35**) being observed by NMR analysis (**Scheme 3.17).**

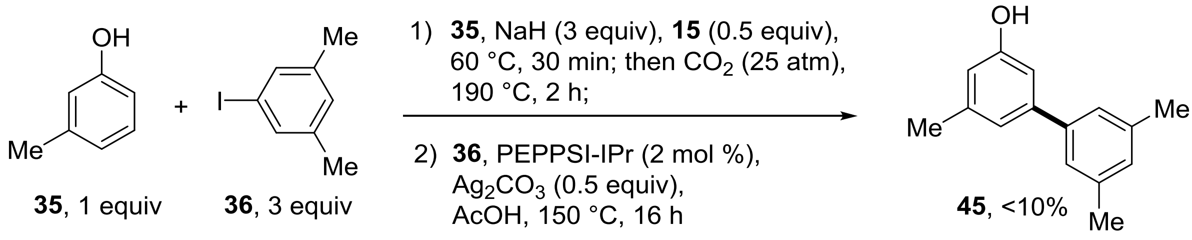


The reactions used 0.5 mmol of **35**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, and confirmed by GCMS analysis.

Scheme 3.17 Tandem carboxylation/arylation/decarboxylation process

One-pot process for *meta*-arylation of phenols

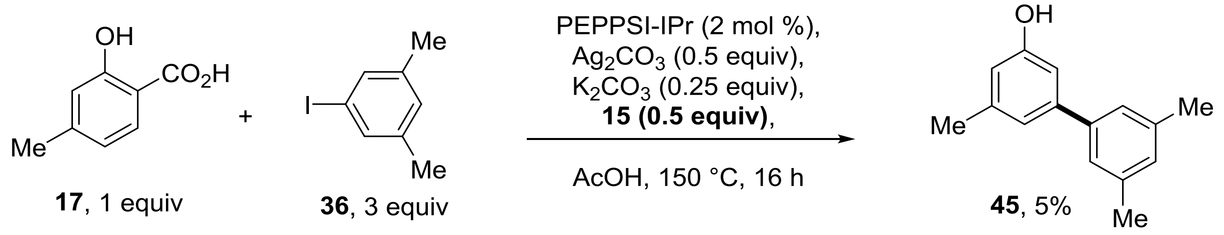
We believed that the addition of large excess of AcOH would shut down the carboxylation process as the carboxylate phenol process requires basic conditions. Therefore, instead of running the reaction as a tandem process, we began to attempt the *meta*-arylation of phenols in a one-pot procedure. Carboxylation of *m*-cresol (**35**) in the presence of 3.0 equivalents of NaH and 0.5 equivalents of 2,4,6-trimethylphenol (**15**). After that time, PEPPSI-IPr, Ag_2CO_3, iodoarene **36** and AcOH were then added into the system, and heated for 150 °C for 16 h. Fortunately, about 10% of *meta*-arylated product was obtained (**Scheme 3.18**). This result was encouraged us to carry on with further optimisation.



The reaction used 0.5 mmol of **35**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.18 One-pot *meta*-arylation of phenols (1)

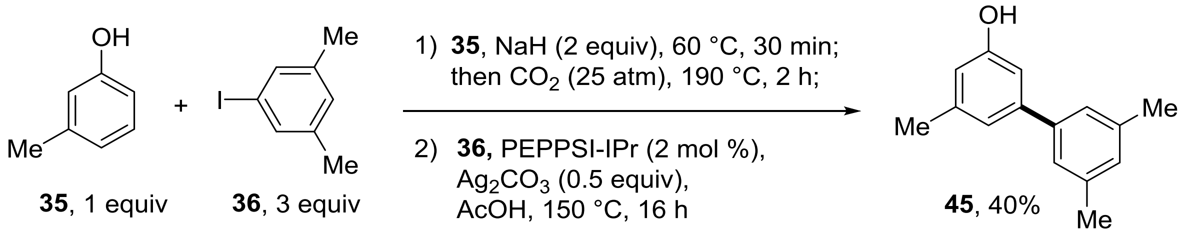
To find the reason why the reaction above afforded low yield, we tested the effect of 2,4,6-trimethylphenol (**15**) in the arylation/decarboxylation of 4-methylsalicylic acid (**17**) reaction. It was found that the addition of 2,4,6-trimethylphenol (**15**) reduced the arylation/decarboxylation of 4-methylsalicylic acid (**17**) from 71% (**Scheme 3.13**, **45**) to 5% (**Scheme 3.19**). We thought this was probably due to the strong coordinating ability of 2,4,6-trimethylphenol (**15**) to the Pd, which prevented the Pd catalyst from coordinating with the carboxyl group.



The reaction used 0.5 mmol of **17**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.19 Investigation of the effect of 2,4,6-trimethylphenol (**15**)

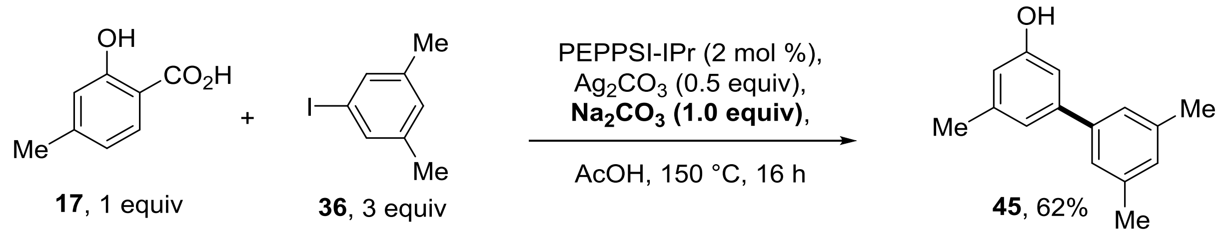
Therefore, we tried the one-pot *meta*-arylation without using 2,4,6-trimethylphenol (**15**), and remarkably, the yield was improved to 40% (**Scheme 3.20**), highlighting that 2,4,6-trimethylphenol (**15**) is not compatible with the standard arylation/protodecarboxylation of salicylic acids.



The reaction used 0.5 mmol of **35**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.20 One-pot *meta*-arylation of phenols (2)

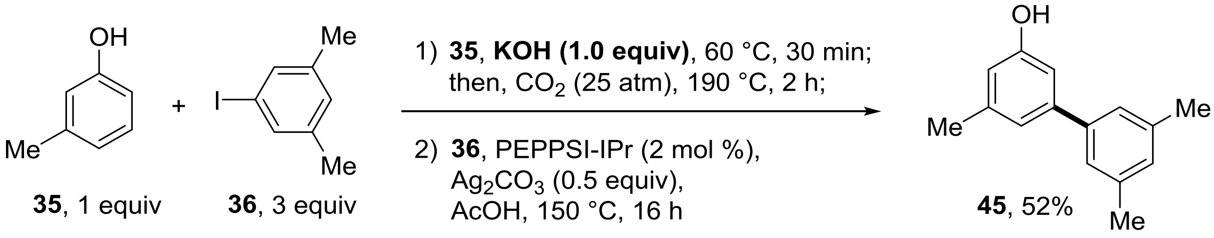
The effect of Na-salt was also tested in the standard arylation/decarboxylation of 4-methylsalicylic acid (**17**). As NaH reacts vigorously with AcOH, we decided to use Na_2CO_3 instead, as both would react with the large excess of AcOH to form NaOAc. The result showed that in the presence of Na_2CO_3 the final product was obtained in a lower yield 62% (**Scheme 3.21**), in comparison with K_2CO_3 where the *meta*-arylated phenol was afforded in 71% (**Scheme 3.13**, **45**).



The reaction used 0.5 mmol of **17**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.21 Investigation of the metal cation for the reaction.

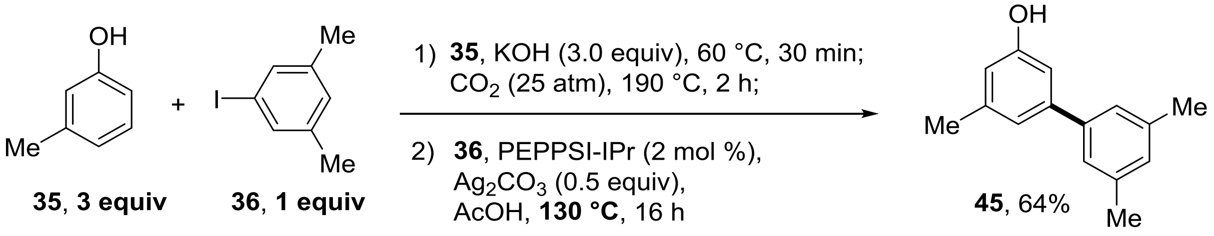
Based upon the experiment above, we decided to replace NaH with KOH in the carboxylation step. To avoid the separate operation for the preparation and desiccation of potassium phenoxide in the classic Kolbe-Schmitt carboxylation procedure, we simply mixed the phenol starting material **35** and KOH in toluene, and heated for 30 minutes. And then toluene was removed in a stream of argon, water that generated from the reaction between phenols and base, on the other hand, was also removed due to the binary azeotrope with toluene, and consequently avoided the need for desiccation of potassium phenoxide. After that time, the reaction flask was submitted into an autoclave at 25 atm of CO_2 pressure for carboxylation, followed by a Pd-catalysed arylation/protodecarboxylation process. Gratifyingly, an increase of yield was achieved, with 52% of the desired *meta*-arylphenol product (**Scheme 3.22**).



The reaction used 0.5 mmol of **35**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.22 One-pot *meta*-arylation of phenols (3)

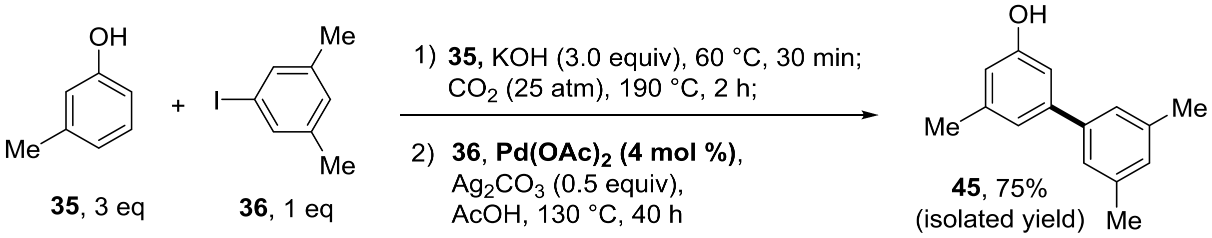
Considering that the Kolbe-Schmitt carboxylation did not give excellent yields, we wondered whether the yield could be improved by using the iodoarene as a limiting reagent instead of phenol. Gratifyingly, the *meta*-arylated phenol product **45** was improved to 64% when using 5-iodo-m-xylene (**36**) as a limiting reagent and 3.0 equivalents of *m*-cresol (**35**) (**Scheme 3.23**). In this case, the temperature can be reduced from 150 °C to 130 °C in the arylation/protodecarboxylation step. Additionally, the use of iodoarenes as limiting reagents makes the method of lower cost as iodoarenes are much more expensive than the phenol starting materials.



The reaction used 0.167 mmol of **36** and 0.5 mmol of **35**. Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.23 One-pot *meta*-arylation of phenols (4)

Further improvement of the yield was successfully obtained by stirring the reaction for 40 h and adding in total 4 mol % of $Pd(OAc)_2$ in two 2 mol % batches. The corresponding *meta*-arylated product **45** was obtained in 75% yield (**Scheme 3.24**). In this case, there was no improvement in yield was obtained when using PEPPSI-IPr.

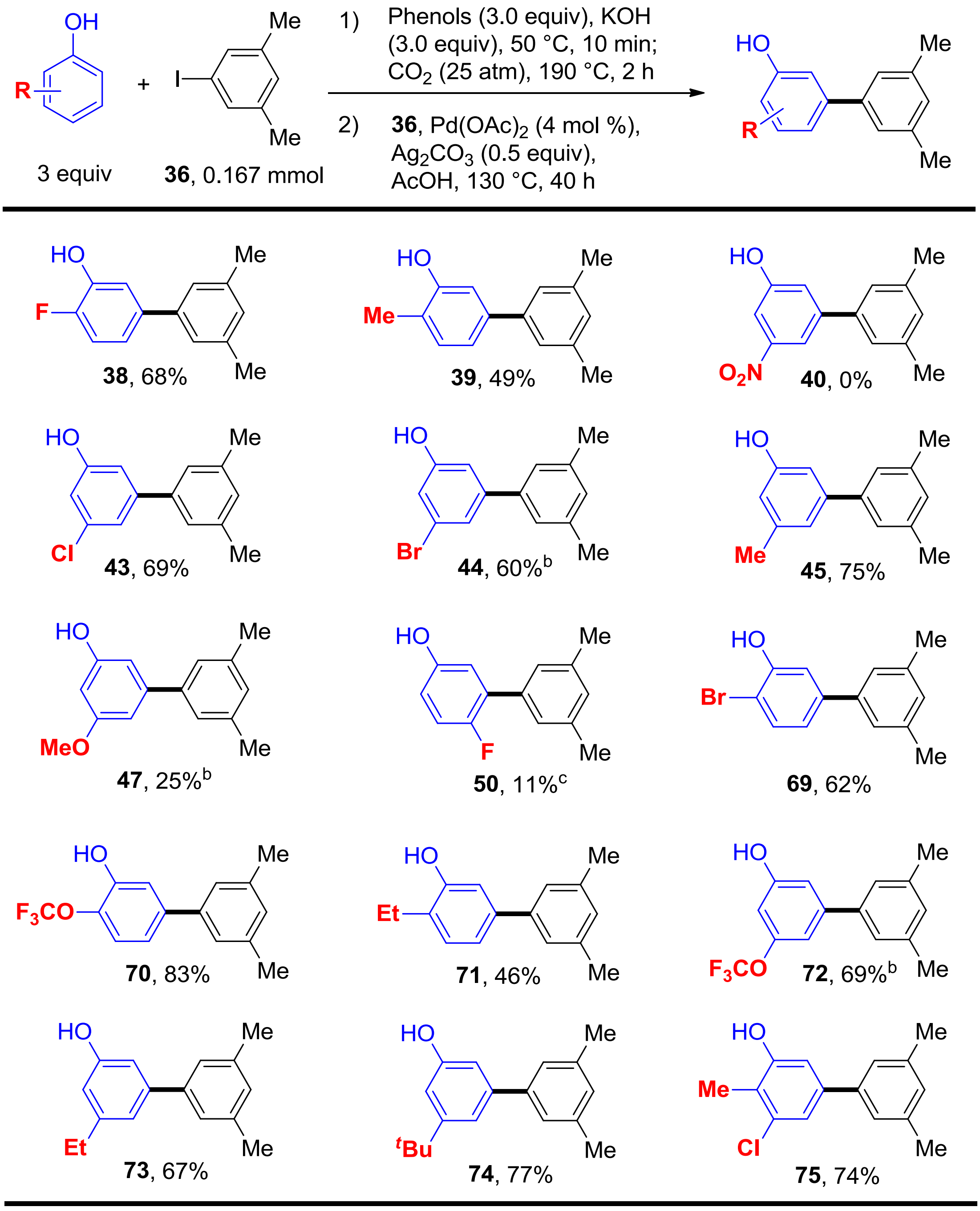


The reaction used 0.167 mmol of **36** and 0.5 mmol of **35**, $Pd(OAc)_2$ was added in two batches.

Scheme 3.24 One-pot *meta*-arylation of phenols (5)

3.3.3 Substrate scope

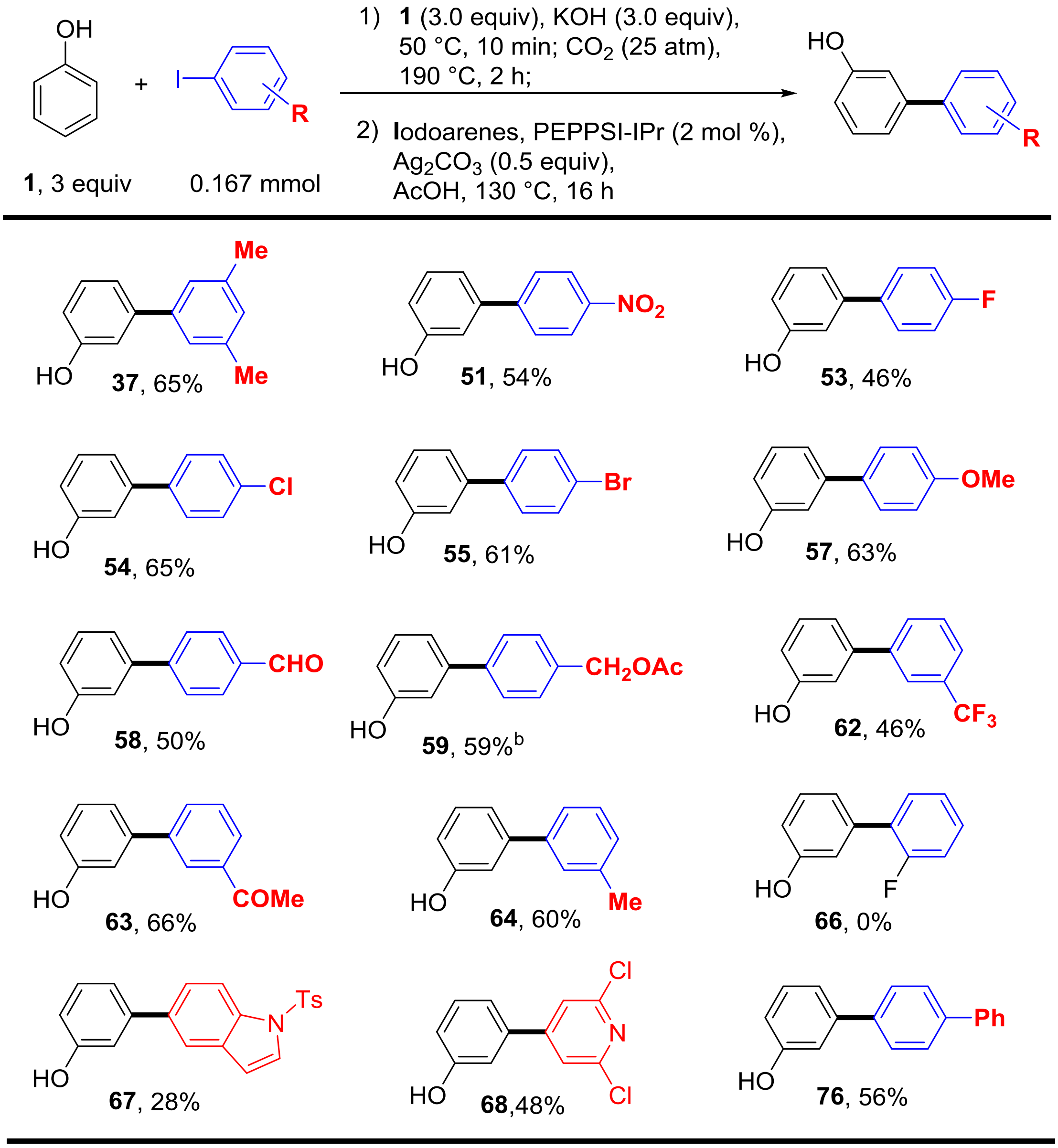
Having found suitable conditions for the one-pot *meta*-arylation of phenols, we started to test the scope of substituted phenols (**Scheme 3.25**). Most of the *meta*-arylated phenol derivatives that were made by using the tandem arylation/protodecarboxylation process of salicylic acids could be directly accessed from the parent phenols with this protocol. (**Scheme 3.25**, **38**, **39**, **43**-**45**, **47**, **50**). Furthermore, taking advantage of the myriad of readily available phenol starting materials, many more new *meta*-arylphenol derivatives were also synthesised by this methodology (**Scheme 3.25**, **69**-**75**). Gratifyingly, many functional groups involving both electron-withdrawing (**Scheme 3.25**, **38**, **43**, **44**, **69**) and electron-donating groups (**Scheme 3.25**, **39**, **45**, **70**-**74**) were tolerated at the *ortho*- or *meta*-positions of the phenols, as well as *ortho*- and *meta*-disubstituted substrate, affording 74% of the desired product **75** (**Scheme 3.25**, **75**). However, in terms of the strongly electron-withdrawing -NO_2 group substituted on the phenol, the desired product was not obtained, due to the prevention of the carboxylation step (**Scheme 3.25**, **40**). On the other hand, the substrate containing a strong electron-donating -OMe group, a low 25% yield was obtained potentially due to the decarboxylation of the salicylic acid derivative intermediate (**Scheme 3.25**, **47**). The replacement of a -OMe group with a less electron-donating -OCF_3 group afforded 69% of desired product (**Scheme 3.25**, **72**). *Para*-substituted phenols were found not to be compatible, with only *para*-fluorophenol giving 11% of *meta*-arylated product analysed by NMR (**Scheme 3.25**, **50**).



[a] Yields are of pure isolated product. [b] 2 mol % PEPPSI-IPr, was used instead of $Pd(OAc)_2$ and the reaction stirred for 16 h. [c] Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.25 Scope of *meta*-arylation of phenols on substituted phenols

Substituents on aryl iodides were then examined by coupling with simple phenol (**Scheme 3.26**). In this case, the reaction using 4 mol % of $Pd(OAc)_2$ for 40 h led to the same yield with the procedure using 2 mol % of PEPPSI-IPr for 16 h. Regarding the reaction time, all the substituted iodoarenes were tested under the conditions in the presence of 2 mol % PEPPSI-IPr and heated for 16 h. Most of the iodoarenes substrates, which were compatible with the tandem arylation/protodecarboxylation process of salicylic acids, were found to be suitable for this one-pot *meta*-arylation of phenols methodology. Substituted aryl iodides containing both electron-withdrawing (**Scheme 3.26**, **51**, **53**-**55**, **62**, **63**, **76**) and electron-donating groups (**Scheme 3.26**, **37**, **57**, **64**) were found to be compatible at both *meta*- and *para*-positions, leading to the corresponding *meta*-arylphenols in moderate yields. The easily oxidised aldehyde functionality was found to be tolerated, affording desired product in 50% (**Scheme 3.26**, **58**). The iodoarene containing benzylic alcohol functionality was also found to be compatible, with an *in situ* acetylation occurred, leading to the acetyl ester **59** in 59% (**Scheme 3.26**, **59**). Iodoindole and iododpyridine were tested and afforded the desired products **67** and **68** in 28% and 48% yields, respectively (**Scheme 3.26**, **67** and **68**). O*rtho*-substituted iodoarenes were also tested and found to be not well tolerated, nor was the small F substituent (**Scheme 3.26**, **66**), which is a limitation of this method.



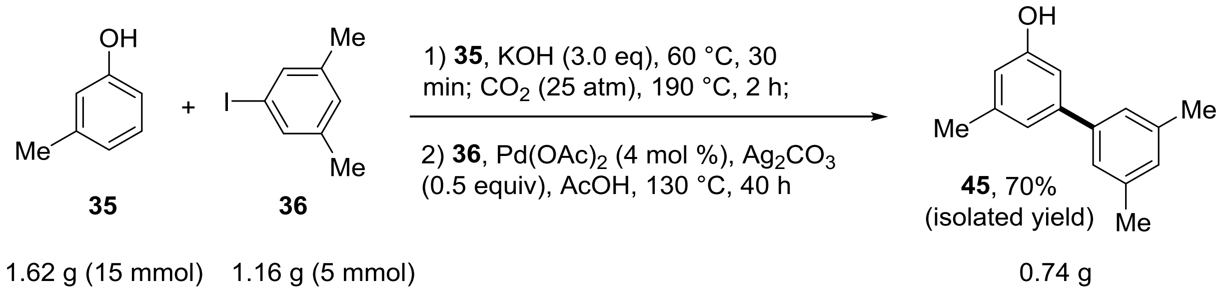
[a] Yields are of pure isolated product. [b] *para*-Iodobenzyl alcohol was used as starting material.

Scheme 3.26 Scope of *meta*-arylation of phenols on substituted iodoarenes

3.3.4 Applications

Scale up reaction

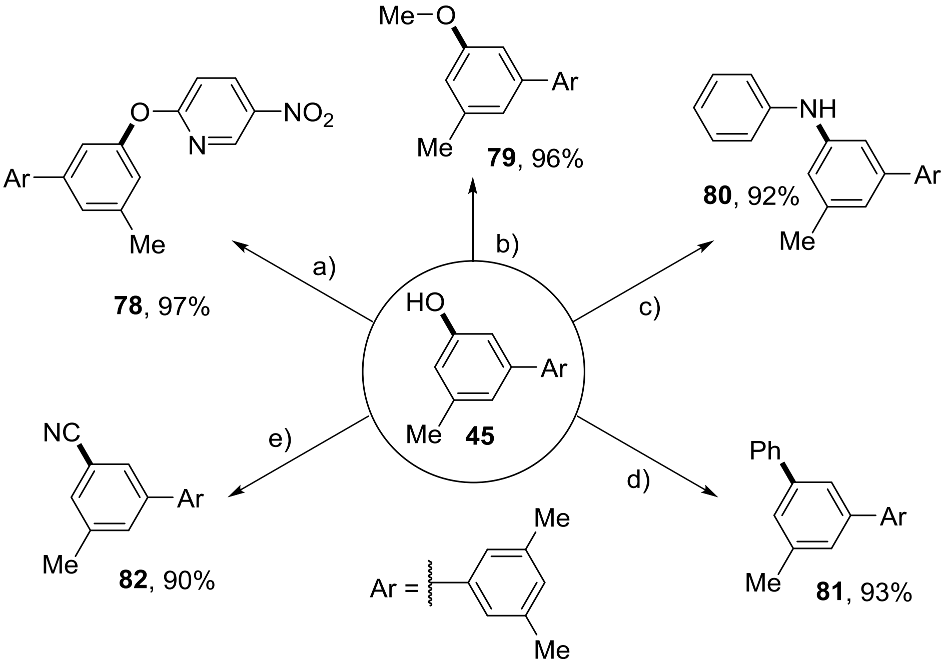
Next, we set up the reaction in gram level scale, and 70% of *meta*-arylated product was obtained under the standard conditions without any modification (**Scheme 3.27**), suggesting that this methodology can be easily scalable.



Scheme 3.27 One-pot *meta*-arylation of phenols in a gram scale

Transformations

A variety of *meta*-functionalised biaryls are easily accessed from the *meta*-arylphenols (**Scheme 3.28**): a) A diarylether subunit was achieved by simply mixing **45** and chloroarene in the presence of base (**Scheme 3.28**, **78**);[106] b) Similarly to the formation of diarylether, *O*-alkylation occurs in the presence of base, leading to 96% of **79** (**Scheme 3.28**, **79**);[107] c) Amine functionality can be introduced *via* Buchwald-Hartwig amination of aryl triflate, which prepared from the corresponding phenol **45** (**Scheme 3.28**, **80**);[108] d) The Suzuki coupling of aryl triflate led to the unsymmetrical *meta*-triaryls **81** (**Scheme 3.28**, **81**);[109] e) Finally, a cyano group was also introduced, giving the product in 90% yield by tosylatation of **45**, followed by Pd-catalysed coupling reaction (**Scheme 3.28**, **82**).[110]

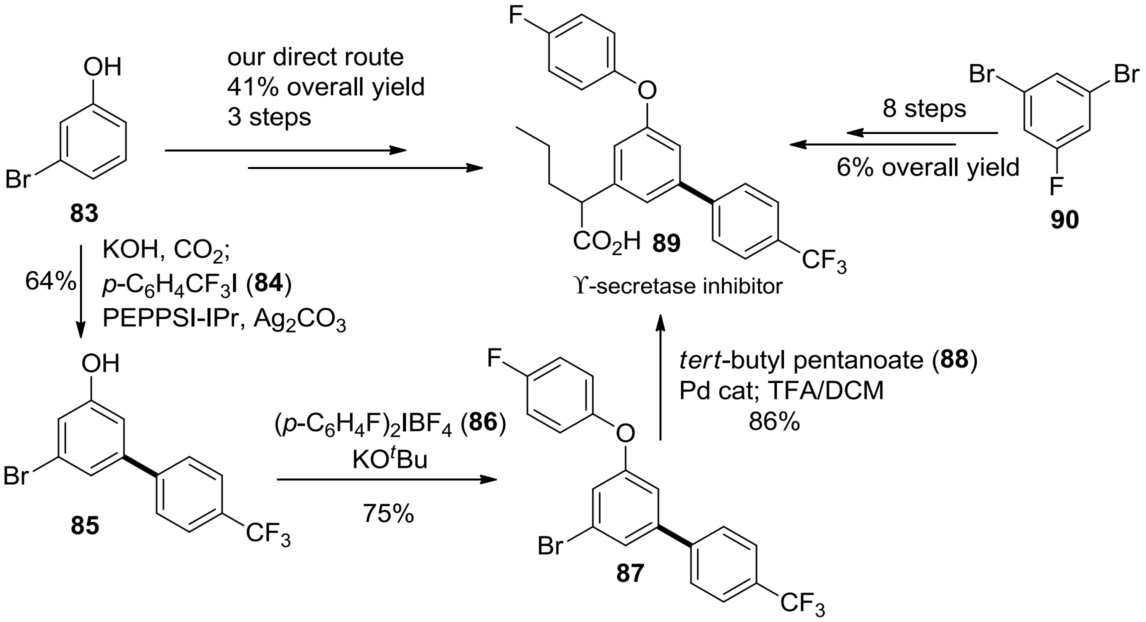


Reagents and conditions: a) 2-chloro-5-nitropyridine, NaH, DMF, rt, 16 h; b) MeI, K_2CO_3, acetone, rt, 16 h; c) Tf_2O, Pyridine, DCM, rt, 1 h; Then, aniline, $Pd(OAc)_2$, BINAP, Cs_2CO_3, PhMe, 120 °C, 16 h; d) Tf_2O, Pyridine, DCM, rt, 1 h; Then, $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, monoglyme/H_2O, 95 °C, 2.5 h; e) TsCl, Et_3N, MeCN, rt, 1 h; Then, $Pd(OAc)_2$, cm-Phos, $K_4[Fe(CN)_6]\bullet 3H_2O$, K_2CO_3, ${}^{t}BuOH/H_2O$, 80 °C, 18 h.

Scheme 3.28 Transformations of **45** into a variety of *meta*-functionalised biaryls

Synthesis of ϒ-secretase inhibitor 89

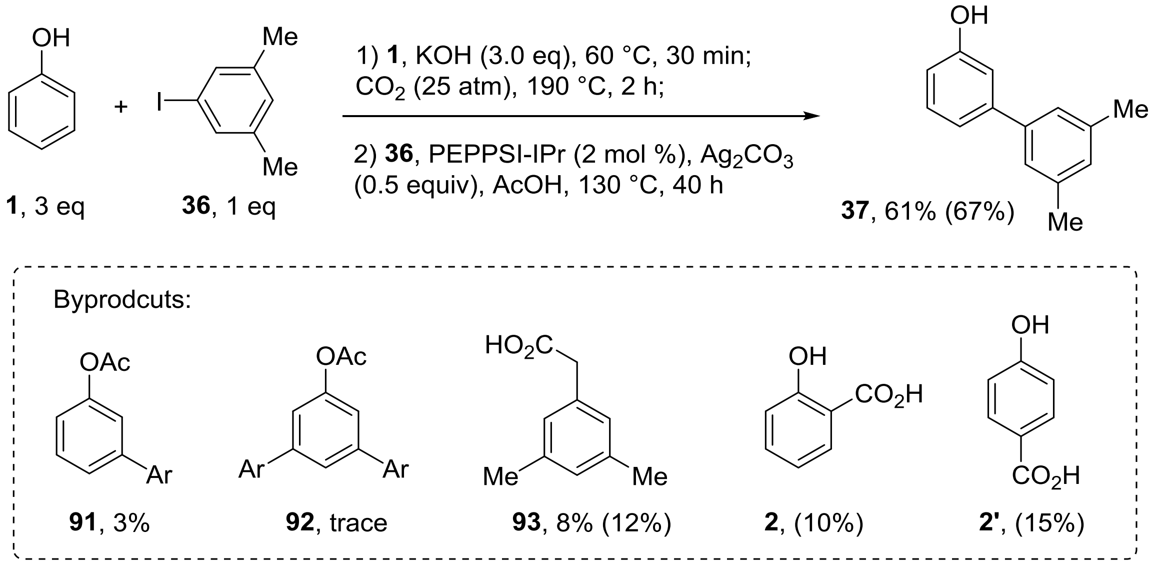
We also synthesised the ϒ-secretase inhibitor **89**, which was studied for the treatment of Alzheimer's disease.[111] The previous synthesis of **89** required eight separate reaction steps and purifications starting from 1,3-dibromo-5-fluorobenzene **90**, with 6% overall yield. We envisaged that our traceless directing group strategy will be applicable to the development of other useful one-pot *meta*-functionalisation processes. The whole synthetic process was accomplished in only three steps from 3-bromophenol (**83**), with the key *meta*-arylation step using **84** as coupling partner, forming **85** in 64% isolated yield. And subsequently *O*-arylation[112] of **85** with diaryl iodonium salt **86**, affording **87** which followed by α-alkylation[113] afforded the ϒ-secretase inhibitor **89**, with 41% overall yield after only three steps (**Scheme 3.29**).



Scheme 3.29 Synthesis of Ɣ-secretase inhibitor **89**

3.3.5 Reaction studies

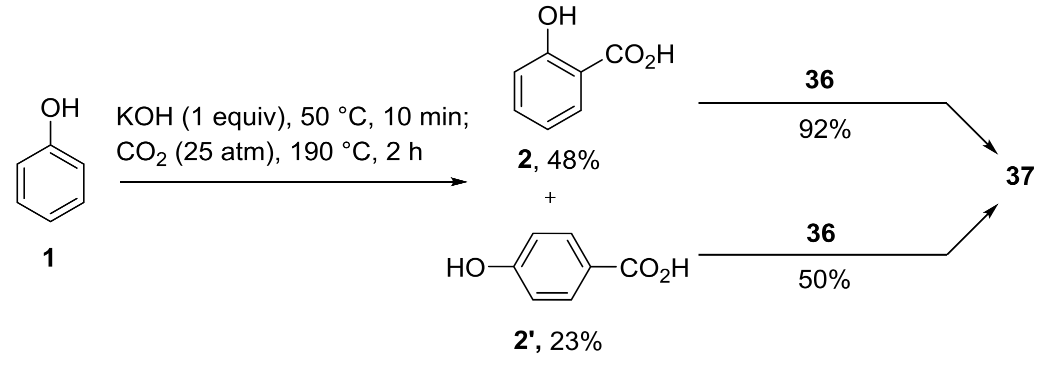
As the one-pot *meta*-arylation of phenols afforded moderate yields in most cases, we decided to investigate the side products which were generated in the reaction (**Scheme 3.30**). Small amounts of the acetylated *meta*-arylphenol **91** were detected, as well as traces of acetylated *meta*-diarylphenol **92** was determined by GCMS analysis. The iodoarene coupling partner reacted with acetic acid to form phenylacetic acid **93** as a main by-product was found. Moreover, carboxylated phenol products at both *ortho*- and *para*-positions (**2** and **2'**) were observed.



Yields are of isolated material, while yields in parenthesis were determined by ^1H NMR using a internal standard.

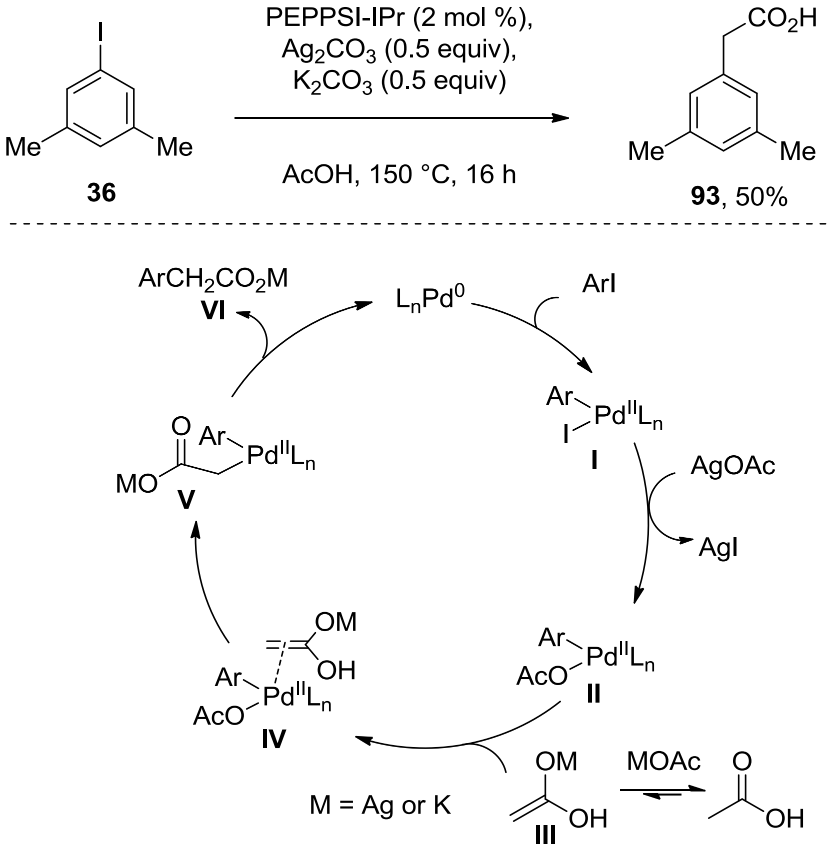
Scheme 3.30 Side products in one-pot *meta*-arylation of phenol

A mixture of salicylic acid (**2**) and 4-hydroxybenzoic acid (**2'**) in a 48:23 ratio was found when we analysed the reaction after the carboxylation step. Then, we submitted **2** and **2'** to the tandem arylation/ protodecarboxylation conditions respectively, and interestingly, both hydroxybenzoic acids **2** and **2'** afforded the *meta*-arylated phenol product **37**. Traces of **92** were observed in the tandem arylation/protodecarboxylation reaction of **2'** but not in the reaction of **2** (**Scheme 3.31**).



Scheme 3.31 Mechanistic study

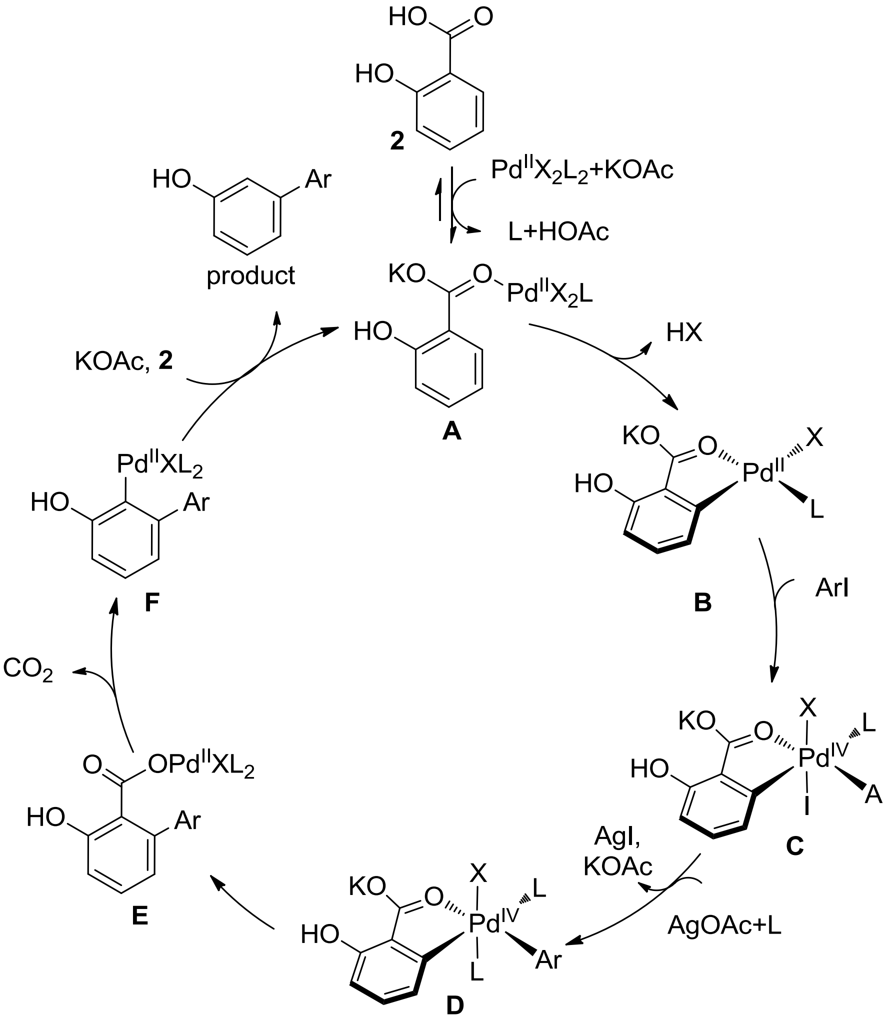
The iodoarene **36** was also submitted to the tandem arylation/protodecarboxylation conditions in the absence of salicylic acid (**2**), interestingly, 50% of arylacetic acid **93** was obtained (**Scheme 3.32**). A plausible catalytic cycle involves the oxidative addition of Pd(0) with iodoarene to form species **I**, followed by the ligand exchange with AgOAc to form species **II**, then species **II** reacts with the α-depronated AcOH **III**, leading to species **V** *via* a Heck-type cross coupling. Finally, the reductive elimination of species **V** produces the metal phenyl acetate **VI** which is transformed to phenyl acetic acid **93** *in situ*, and simultaneously regenerates the Pd(0) catalyst (**Scheme 3.32**).[114]



Scheme 3.32 Proposed catalytic cycle for α-arylation of acetic acid

3.3.6 Proposed catalytic cycle

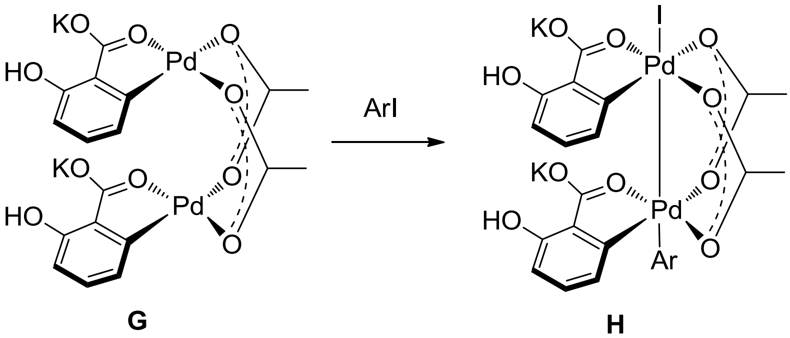
A plausible catalytic cycle for the formation of *meta*-arylated phenol from the salicylic acid intermediate was proposed in **Scheme 3.33**. Initially, Pd(II) κ^1-coordinates to the carboxyl group on salicylic acid **2** in the presence of KOAc to form complex **A**, which then undergoes *ortho* C–H activation to form palladacycle **B**. The oxidative addition of palladacycle **B** with iodoarene generates Pd(IV) complex **C**, followed by ligand exchange to give Pd(IV) species **D**. Then the reductive elimination of species **D** produces species **E**, which subsequently undergoes decarboxylation to give Pd-aryl species **F**. Salicylic acid (**2)** mediated protometallation of Pd-aryl species **F** gives the desired *meta*-arylphenol product and regenerates **A**.



Scheme 3.33 Plausible catalytic cycle for the tandem arylation/protodecarboxylation of salicylic acid

An alternative hypothesis is that the mechanism proceeds *via* the formation of a dimeric palladacycle **G**, rather than the monomeric species **B**, which is then transformed into a

Pd(III)−Pd(III) bimetallic species **H** through an oxidative addition of the aryl iodide. The Pd(III)−Pd(III) bimetallic species **H** would undergo iodide abstraction, reductive elimination and decarboxylation to afford *meta*-arylated phenol (**Scheme 3.34**).



G **H**

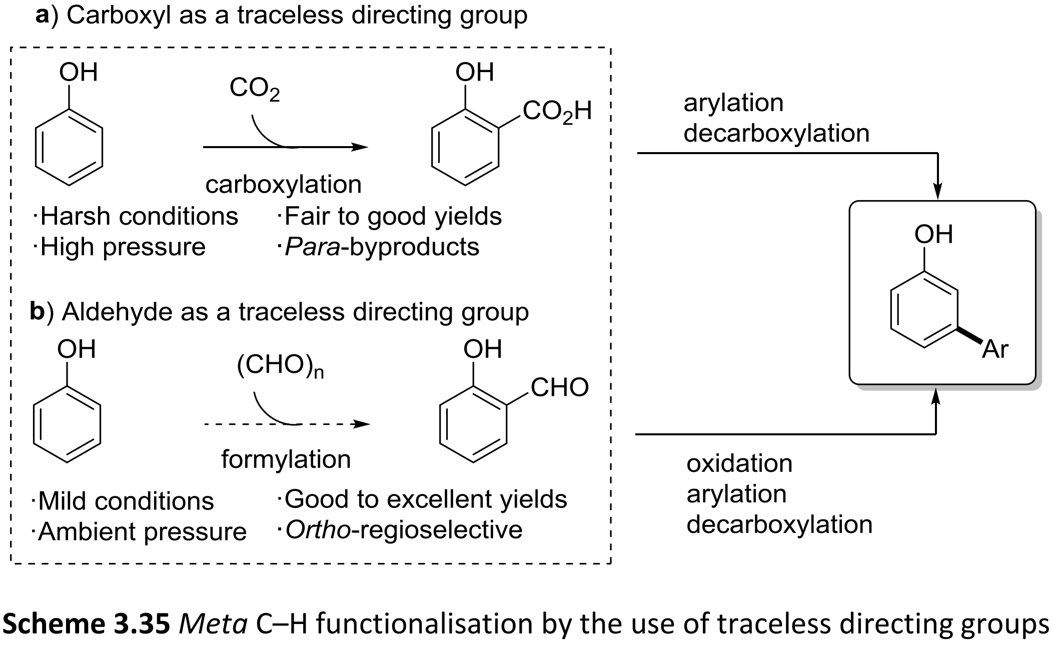
Scheme 3.34 Plausible catalytic cycle *via* Pd(II)/Pd(III)

3.4 A tandem oxidation/arylation/protodecarboxylation reaction of salicylaldehydes: expanded access to *meta*-arylphenols

3.4.1 Objectives

The method of a one-pot *meta*-arylation provides a powerful tool for the synthesis of *meta*-arylphenol derivatives from cheap phenols in a single synthetic operational step. However, the requirement of high CO_2 pressure (25 atm) and high temperature (190 °C) during the carboxylation instalment is a limitation of the methodology (**Scheme 3.35**, **a**).

Consequently, we aimed to discover a functionality that is easily introduced and removed, as well as an ability of beling a directing group directed *ortho* C–H functionalisation. It is well-known that aldehyde groups can be easily and efficiently introduced into phenol derivatives under mild conditions.[75] Therefore, we were interested to explore whether the aldehyde functionality could facilitate *ortho*-functionalisation and be subsequently cleaved (**Scheme 3.35**, **b**).



Scheme 3.35 *Meta* C–H functionalisation by the use of traceless directing groups

3.4.2 Optimisation

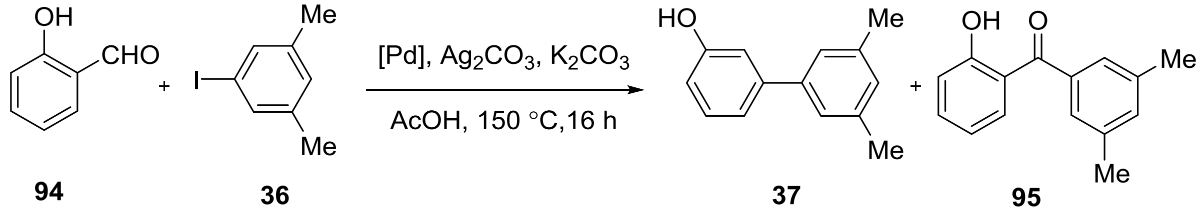
Initially, we took salicylaldehyde **94** and reacted it with 1-iodo-3,5-dimethylbenzene **36** in the presence of 2 mol % of $Pd(OAc)_2$, 0.5 equivalents of Ag_2CO_3 in AcOH, heated at 150 °C for 16 h. Gratifyingly, 17% of desired *meta*-arylphenol product **37** was obtained and 15% of side product **95** was obtained by the coupling between salicylaldehyde and iodoarene *via* cleavage of the aldehyde C–H bond (**Table 3.4**, entry 1).[115] It is to be noticed that in all cases, the by-product **95** was observed. Importantly, none of the arylated salicylaldehyde was observed, suggesting that the aldehyde can be easily cleaved after C–H arylation *in situ*, which meets our requirement for the idea of aldehyde being a removable directing group.

Increasing the amount of Ag_2CO_3 to 1.0 equivalent improved the yield to 27% (**Table 3.4**, entry 2), while, the yield reduced to 18% when the amount of Ag_2CO_3 was increased to 2.0 equivalents (**Table 3.4**, entry 3). The screening of the Pd sources suggested that PEPPSI-IPr was more efficient than $Pd(OAc)_2$ in delivering the product, affording 35% of *meta*-arylated product (**Table 3.4**, entry 4).

Due to the similar conditions with the tandem arylation/protocarboxylation reaction, we thought that the reaction may proceed *via* oxidation of salicylaldehyde to salicylic acid which facilitates a tandem arylation/protodecarboxylation process to afford *meta*-arylphenols. Strong oxidants such as *para*-benzoquinone and *m*-CPBA were then used in the reaction to facilitate oxidation of the aldehyde group to a carboxylic acid. Unfortunately, no desired product was obtained (**Table 3.4**, entries 5 and 6).

Similarly to the tandem arylation/decarboxylation of salicylic acids, the addition of K_2CO_3 was crucial in improving the yields of the reactions (**Table 3.4**, entries 7 and 8). This is possibly due to the favoured κ^1-coordination between Pd(II) and the carboxyl group, which forms from the oxidation of aldehyde group, in the presence of the K-salt.[88,103] Finally, 72% of the product **37** was achieved by increasing the amount of Pd catalyst to 5 mol %. (**Table 3.4**, entry 9).

Table 3.4 Optimisation of *meta*-arylation from salicylaldehyde

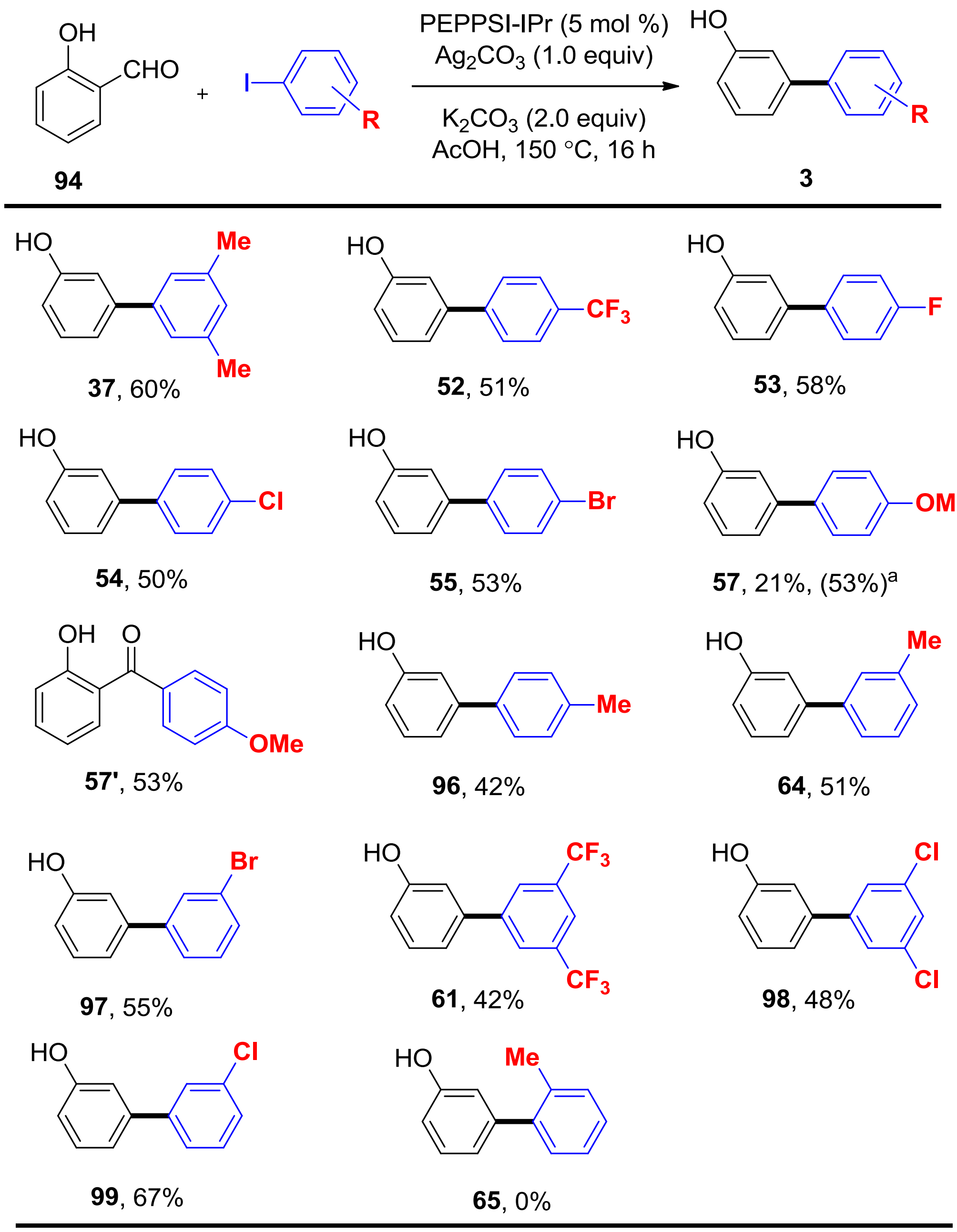


Entry[a]	Pd (mol %)	Ag_2CO_3 (equiv)	K_2CO_3 (equiv)	Yield of **37** (%)	Yield of **95** (%)
1	$Pd(OAc)_2$ (2)	0.5	0	17	15
2	$Pd(OAc)_2$ (2)	1.0	0	27	20
3	$Pd(OAc)_2$ (2)	1.5	0	18	23
4	PEPPSI-IPr (2)	1.0	0	35	30
5[b]	PEPPSI-IPr (2)	1.0	2.0	0	0
6[c]	PEPPSI-IPr (2)	1.0	2.0	0	0
7	PEPPSI-IPr (2)	1.0	0.5	54	18
8	PEPPSI-IPr (2)	1.0	2.0	60	21
9	PEPPSI-IPr (5)	1.0	2.0	72	24

[a] Reactions were carried out using 0.25 mmol of **94** and 0.75 mmol of **36**. Yields were determined by ^{1}H NMR analysis using an internal standard. [b] 1.0 equiv of *p*-benzoquinone was added. [c] 1.0 equiv of *m*-CPBA was added.

3.4.3 Scope on substrates

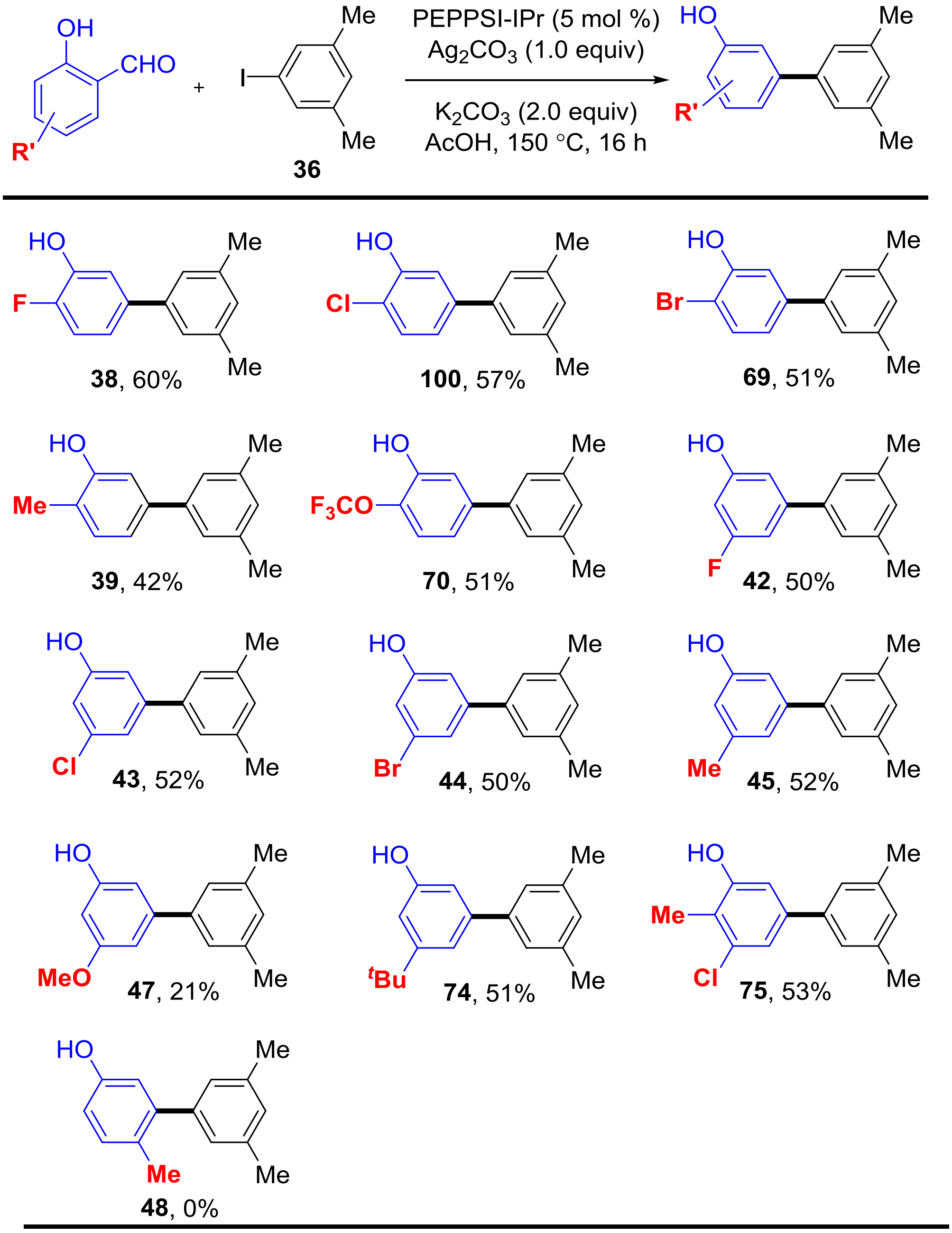
To explore the generality of this new method, we examined a variety of subsitituted aryl iodides (**Scheme 3.36**). We were pleased to find that many substituents, such as -Me, -F, -Br, -Cl, -CF_3, were tolerated at the *meta*- and *para*-positions of the iodoarenes without any further modification. In general, all the yields obtained were moderate due to the unpreventable side reaction of aldehyde C–H activation. In particular, when *para*-iodoanisole was submitted to this catalytic system, only 21% of the desired product was obtained, and instead, the side product of 2-hydroxyphenyl)(4-methoxyphenyl)methanone *via* cleavage of the aldehyde C–H bond was observed as a main product in 53% (**Scheme 3.36**, **57**). Finally, an *ortho*-substituted iodoarene was examined and found to be not compatible, possible due to the steric hindrance proximal to the activated C–H (**Scheme 3.36**, **65**).



3.0 equiv of iodoarenes respect to **94** were used. [a] Yield of (2-hydroxyphenyl)(4-methoxyphenyl)methanone (**57'**) instead of biaryls **57**.

Scheme 3.36 Scope of the domino oxidation/arylation/protodecarboxylation process on substituted iodoarenes

We also tested a variety of substituted salicylaldehyde derivatives to further demonstrate the generality of this new method (**Scheme 3.37**). We were pleased to find that both electron-donating (**Scheme 3.37**, **39**, **45**, **47**, **70**, **74**) and electron-withdrawing group (**Scheme 3.37**, **38**, **42**, **43**, **69**, **100**) are tolerated at the C3 and C4 position of the salicylaldehyde derivatives. However, due to the unpreventable side reaction of aldehyde C–H activation, all of the yields are moderate. The strong electron-donating -OMe group is not tolerated well for salicylaldehyde derivatives. In this case, 3-methoxyphenol was obtained after the reaction probably due to the ‘formal’ decarbonylation of the starting material (**Scheme 3.37**, **47**). Similarly to the *ortho*-substituted iodoarenes, the substituents at the C5 position of the salicylaldehyde derivatives are not tolerated due to the steric hindrance proximal to the activated C–H bond (**Scheme 3.37**, **48**).



3.0 equiv of **36** respect to salicylaldehyde derivatives were used.

Scheme 3.37 Scope of the domino oxidation/arylation/protodecarboxylation process on salicylaldehydes

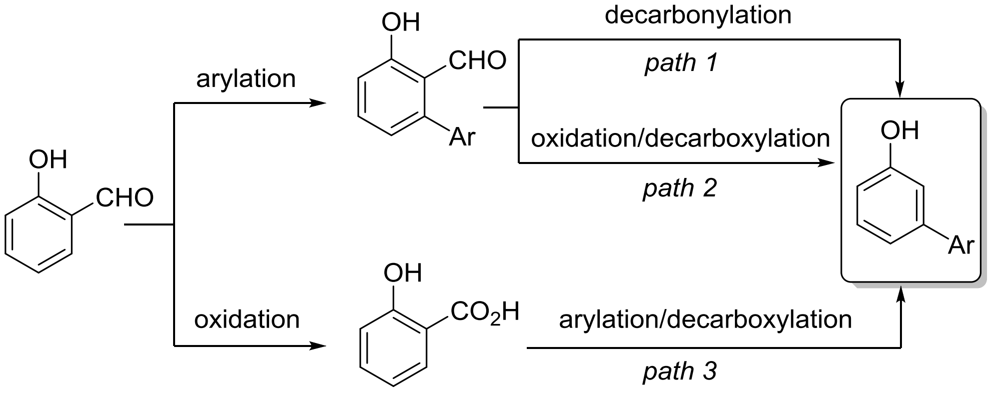
3.4.4 Preliminary mechanistic study

A preliminary mechanistic study has been undertaken to understand in more depth how the *meta*-arylphenols are formed from salicylaldehydes. It has been shown before that benzaldehydes and its derivatives can undergo *ortho*-arylation[116] and decarbonylation[117] under Pd catalysis. Additionally, it is well-known that aldehydes can be easily oxidised into the corresponding carboxylic acids in the presence of Tollens' reagent. In our case, we postulated that Ag_2CO_3 could oxidise salicylaldehyde to salicylic acid. Based upon these assumptions, three possible pathways have been proposed (**Scheme 3.38**):

1) The transformation involves *ortho*-arylation of salicylaldehyde, followed by a Pd-catalysed decarbonylation, giving the *meta*-arylphenol (**Scheme 3.38**, *Path 1*).

2) The transformation involves Pd-catalysed *ortho*-arylation of salicylaldehyde, followed by oxidation of the *ortho*-arylated salicylaldehyde intermediate to the corresponding benzoic acid, which then undergoes protodecarboxylation to generate *meta*-arylated phenol (**Scheme 3.38**, *Path 2*).

3) Salicylaldehyde is oxidised to salicylic acid which then arylates and protodecarboxylates to afford *meta*-arylphenol (**Scheme 3.38**, *Path 3*).

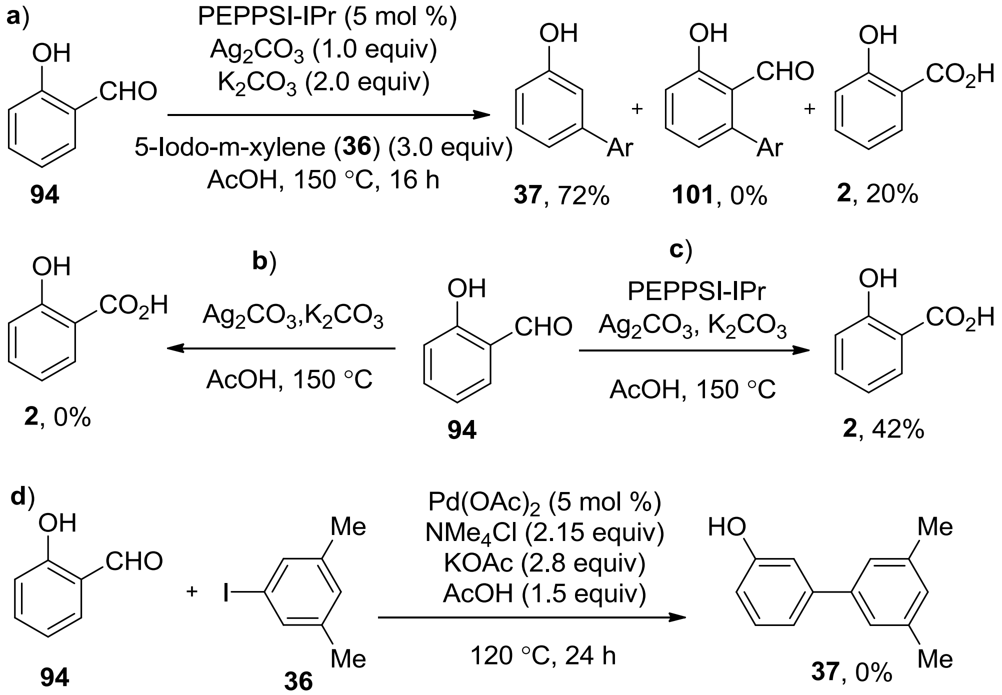


♣ *Path 1. tandem arylation/decarbonylation*
♣ *Path 2. tandem arylation/oxidation/decarboxylation*
♣ *Path 3. tandem oxidation/arylation/decarboxylation*

Scheme 3.38 Possible reaction pathways

Analysis of the crude reaction mixture revealed that 72% of *meta*-arylated phenol (**37**) and 20% of salicylic acid (**2**) were formed after reaction, but no *ortho*-arylated salicylaldehyde intermediate (**101**) was obtained (**Scheme 3.39**, **a**). This indicated that the third pathway may be in operation. To investigate the mechanism further, salicylaldehyde was submitted to the catalytic cycle in the absence of the iodoarene **37**, and 42% of salicylic acid was observed (**Scheme 3.39**, **c**). Interestingly, oxidation of the salicylaldehyde (**94**) to the corresponding acid **2** did not occur without the addition of Pd catalyst (**Scheme 3.39**, **b**). Finally, replacing Ag_2CO_3 for NMe_4OAc as an iodide abstractor[118] did not provide the *meta*-arylated product **37** (**Scheme 3.39**, **d**). This suggested that the oxidation of salicylaldehyde proceeds *via* a Wacker oxidation process.[119]

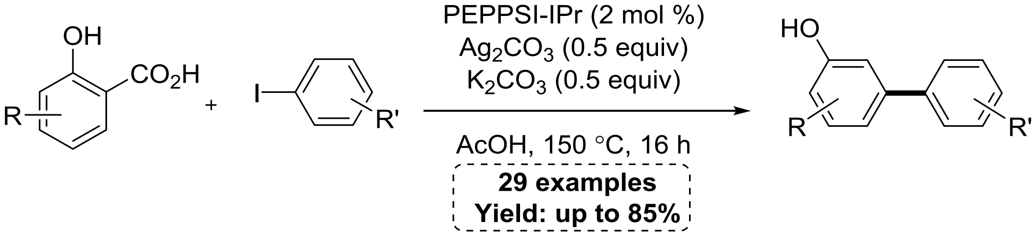
Based on the above experiments, we suggested that this transformation of salicylaldehydes to *meta*-arylphenols proceeds *via* a tandem oxidation/arylation/proto-decarboxylation process.



Scheme 3.39 Investigation of the reactions

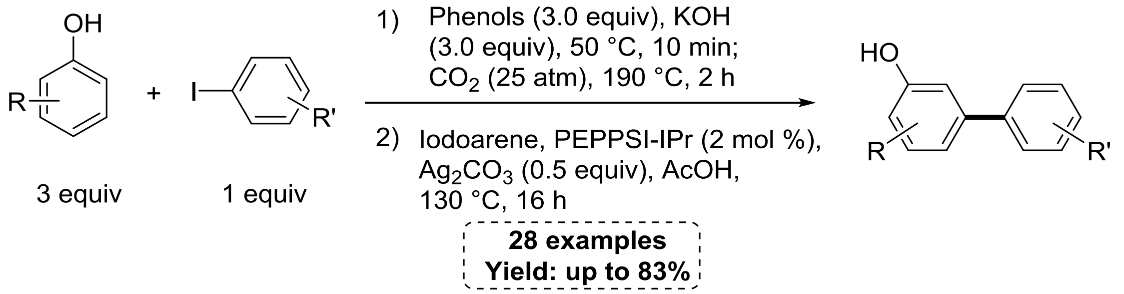
3.5 Conclusions

To summarise, we have reported that salicylic acid derivatives can undergo a tandem arylation/protodecarboxylation process, affording *meta*-arylphenols (**Scheme 3.40**). A broad range of substituents on both salicylic acids and iodoarenes were tested and found to be well tolerated.



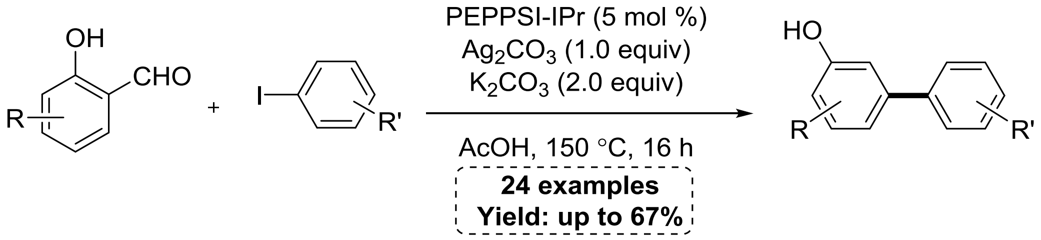
Scheme 3.40 Tandem arylation/protodecarboxylation of salicylic acids

Considering that phenols are more widely available and much cheaper compared to salicylic acid derivatives, we aimed to develop a method for *meta*-arylation of phenols. In Chapter 2, we described a method for carboxylation of phenols at ambient CO_2 pressure in the presence of 2,4,6-trimethylphenol (**15**) and NaH. However, 2,4,6-trimethylphenol (**15**) proved to inhibit the tandem arylation/protodecarboxylation process. After serval explorations, we successfully developed a one-pot *meta*-arylation of phenols process through a Kolbe-Schmitt carboxylation followed by a tandem arylation/ protodecarboxylation of salicylic acid intermediates (**Scheme 3.41**). This methodology provides an efficient synthesis of a broad of *meta*-arylation of phenol derivatives from the wide availability of cheap phenol starting materials. Application of this methodology was explored by showing the efficient synthesis of the ϒ-secretase inhibitor **89** and transformation of *meta*-arylphenols products to a variety of 1,3-biaryls adducts.



Scheme 3.41 One-pot *meta*-arylation of phenols

An alternative to access *meta*-arylphenol derivatives was presented by the use of aldehyde as a traceless directing group (**Scheme 3.42**). This methodology allows access to *meta*-arylphenol derivatives from salicylaldehydes *via* a tandem oxidation/arylation/ protodecarboxylation process. Importantly, as an aldehyde group is easily introduced and removed after C–H functionalisation, it can be used as a convenient removable directing group to control site selectivity towards C–H functionalisation methodologies.

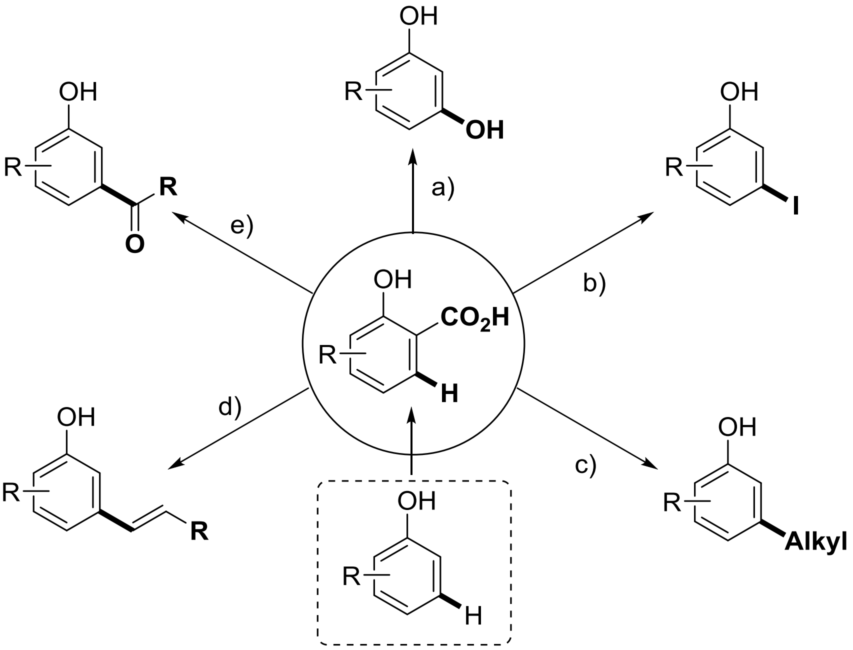


Scheme 3.42 Tandem oxidation/arylation/protodecarboxylation of salicylaldehydes

3.6 Future work

Encouraged by the success of the one-pot process for *meta*-arylation of phenols, we would like to develop a unified methodology which would allow the introduction of various functional groups at the *meta*-position of phenols. (**Scheme 3.43**). These unified methodologies would be very useful in organic synthesis providing a variety of *meta*-substituted phenols.

Our investigation is going to start with *ortho*-functionalisation/protodecarboxylation of salicylic acids for the delivery of *meta*-substituted phenols. Hopefully, after finding the optimal conditions for the functionalisation of salicylic acids, our efforts will be focused towards *meta*-functionalisation of phenols in a one-pot process. We believe that the carboxyl directed hydroxylation, iodination, alkylation, olefination and acylation is worth investigating as these processes have not been described for phenols.



Scheme 3.43 *Meta*-functionalisation of phenols

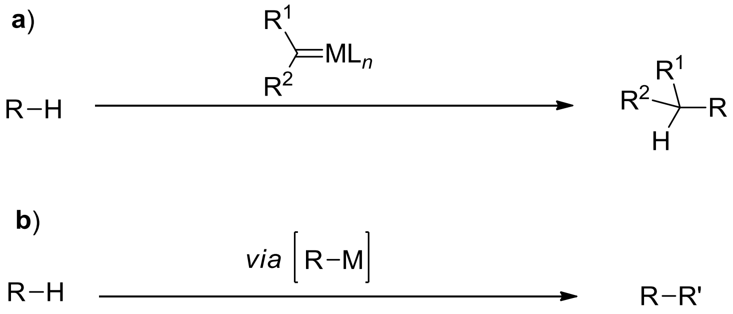
Chapter 4

Chapter 4 Enantioselective C–H arylation of arenes chromium tricarbonyl complexes[ii]

4.1 Introduction

As described in the first chapter, transition metal catalysed direct C–H functionalisation is of great importance in synthetic chemistry as it allows simple and efficient access to myriad molecules from abundant hydrocarbon compounds. However, due to the ubiquitous nature of C–H bonds, it is difficult to distinguish the reactivity among the plentiful C–H bonds in a molecule. As a result, it is a challenge to achieve a high level of selective C–H functionalisation. In the third chapter, we presented a methodology for the regioselective arylation of phenols through the use of a transient carboxyl directing group. This overcomes the 'natural' reactivity of phenol, allowing arylation at the *meta*-position. In this section, we turned our attention towards transition metal-catalysed enantioselective C–H functionalisation.

Very generally, there are two fundamental approaches for enantioselective C–H functionalisation. One strategy utilises the insertion of metal-bound complexes, such as carbenes and nitrenes (**scheme 4.1**, **a**), into a C–H bond. Another strategy involves C–H activation, achieving enantioselective C–H functionalisation *via* a metal-carbon species (**Scheme 4.1**, **b**).



Scheme 4.1 Strategies for C–H functionalisation

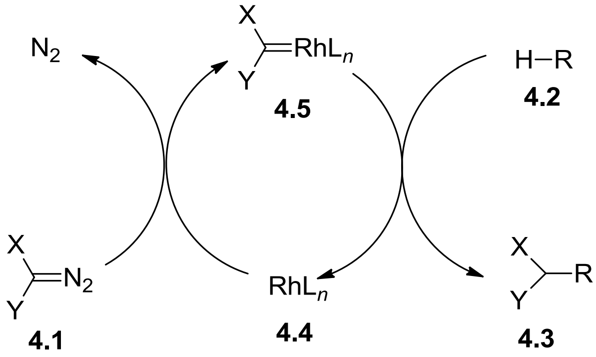
[ii] This work was carried out in collaboration with Katrina Krämer, the contributions where included will be highlighted in the text.

In this introduction, enantioselective C–H functionalisation reactions involving transient metal-carbon species will be discussed, with particular focus towards Pd-catalysed enantioselective C–H functionalisation. C–H bond insertion by metal carbenoids and related species will only be very briefly discussed.

4.1.1 Enantioselective C–H functionalisation involves metal carbenoids and nitrenoids

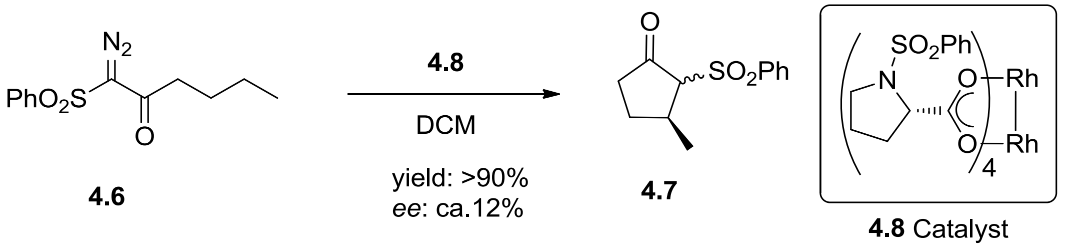
Metal carbenoids

Rhodium carbenes are the most studied metal carbenes for insertion of C–H bonds in an enantioselective manner.[120] Generally, this type of reaction uses a high energy diazo compound **4.1** to react with Rh catalyst **4.4** to generate reactive metal carbenoids **4.5**, with a driving force of forming N_2, followed by the insertion of the metal carbene species **4.5** into C–H bond **4.2** to form the product **4.3** and regenerate the catalyst **4.4** (**Scheme 4.2**).



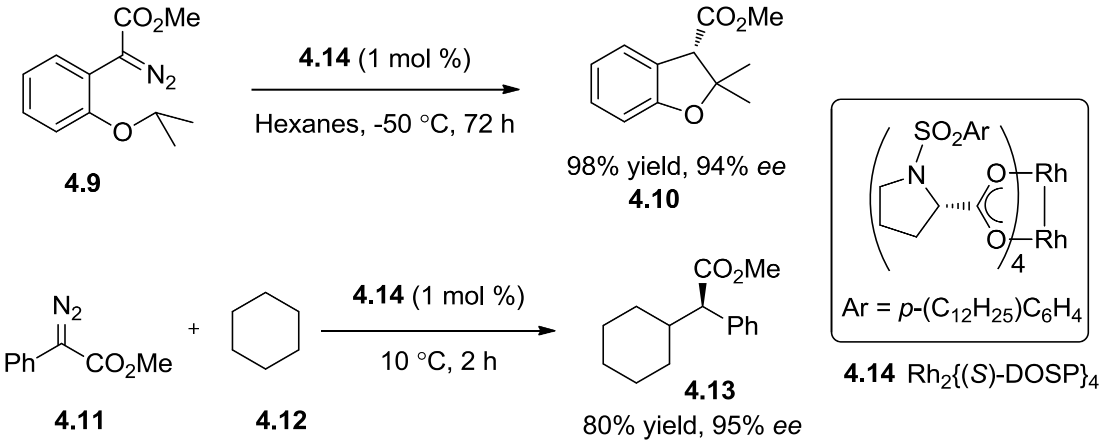
Scheme 4.2 Metal carbenoids insertion of C–H bond

Early work was reported by McKervey and co-workers who used a chiral Rh(II) prolinate catalyst **4.8** with α-diazo-β-ketosulfone **4.6**, affording the cyclised product **4.7** in >90% yield but with only ca.12% *ee* (**Scheme 4.3**).[121]



Scheme 4.3 McKervey's work on Rh carbene insertion into a C(sp^3)–H bond

This field has been extensively expanded upon,[122] with Davies' development of Rh_2\{(*R/S*)-DOSP\}$_4$ being one of the most important advances. The Rh_2\{(*R/S*)-DOSP\}$_4$ catalyst proved to be highly effective for both intra- and intermolecular insertions, with excellent yields and *ee* values (**Scheme 4.4**).[123]

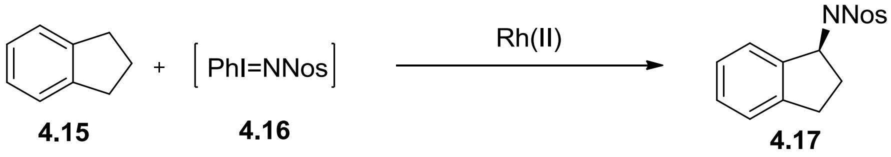


Scheme 4.4 Davies's work on Rh carbene intra- and intermolecular reactions

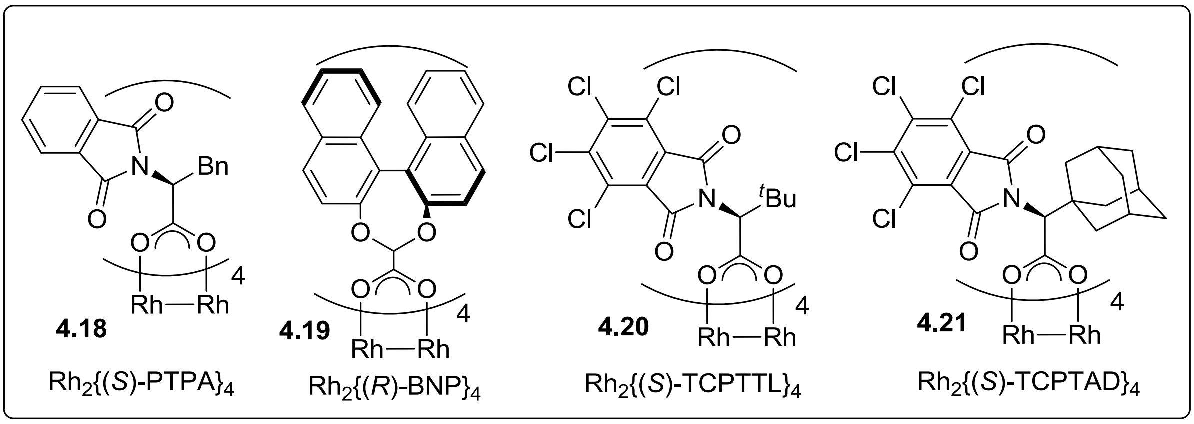
Metal Nitrenes

Instead of forming C–C bonds by the insertion of metal carbenes into C–H bonds, the insertion of metal nitrenes into C–H bonds affords the formation of C–N bonds. The C–H amination with [$Rh_2(OAc)_4$] and other transition metal complexes was reported as early as the 1980s,[124] however, the development of its corresponding enantioselective processes has not been achieved until relatively recently. Many catalysts, such as Ikegami's Rh_2\{(*S*)-PTPA\}$_4$ (**4.18**),[125] Pirrung's Rh_2\{(*R*)-BNP\}$_4$ (**4.19**),[126] Hashimoto's Rh_2\{(*S*)-TCPTTL\}$_4$ (**4.20**),[127] and

Davies's Rh$_2${(*S*)-TCPTAD}$_4$ (**4.21**),[128] have been developed for the enantioselective amination through Rh nitrenes insertion. Among these catalysts, Rh$_2${(*S*)-TCPTAD}$_4$ was found to be the most efficient for intermolecular C–H amination both in terms of yield and *ee* value (**Scheme 4.5**).



Entry	Rh(II)	Yield (%)	ee (%)
1	Rh$_2${(*S*)-PTPA}$_4$ (**4.18**)	77	7
2	Rh$_2${(*R*)-BNP}$_4$ (**4.19**)	71	31
3	Rh$_2${(*S*)-TCPTTL}$_4$ (**4.20**)	51	73
4	Rh$_2${(*S*)-TCPTAD}$_4$ (**4.21**)	95	94

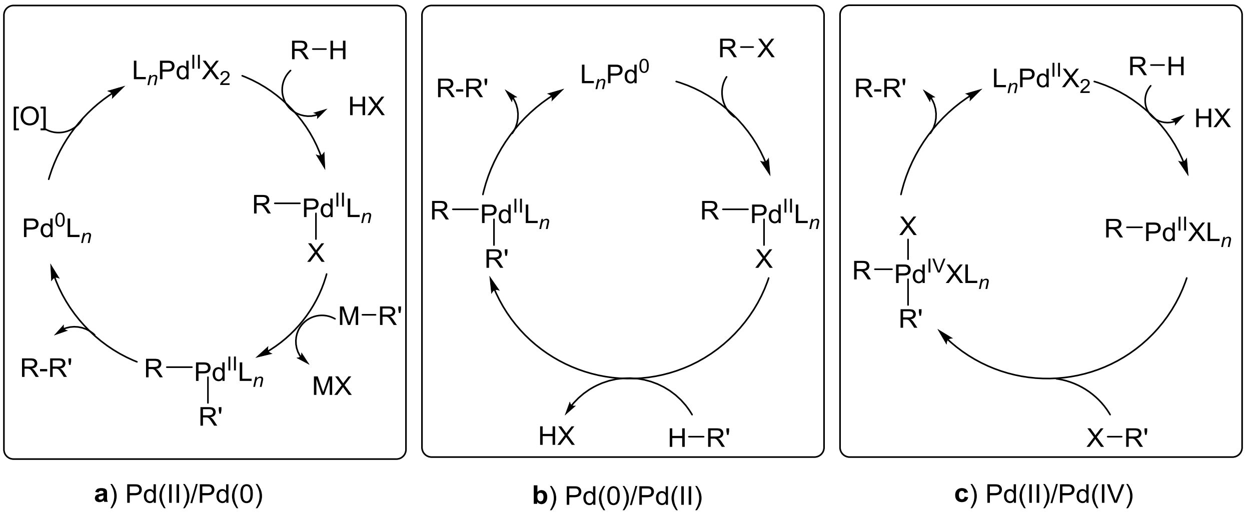


Scheme 4.5 Asymmetric C–H amination by the insertion of Rh(II) nitrenes

4.1.2 Enantioselective C–H functionalisation *via* C–H activation

Though tremendous efforts have been made on the area of catalytic C–H activation, the development of the corresponding enantioselective C–H activation reactions still remains a challenge in part due to the lack of suitable chiral ligands that can promote the cleavage of C–H bond and be compatible with other steps in the catalytic cycle. The following text will focus on Pd-catalysed enantioselective C–H activation.

Generally, there are three mechanistic scenarios described for Pd-catalysed enantioselective C–H activation (**Scheme 4.6**): **a**) Enantioselective C–H activation involving a Pd(II)/Pd(0) catalytic cycle. In this approach, C–H activation takes place in the presence of a Pd(II) catalyst, which transmetallates with an organometallic reagent to form RR'$Pd^{II}L_n$, followed by reductive elimination to give the product R-R' and Pd^0L_n species. The Pd(II) species will be regenerated in the presence of an oxidant to complete the catalytic cycle; **b**) Enantioselective C–H activation involving a Pd(0)/Pd(II) catalytic cycle. In this strategy, a Pd(0) species undergoes oxidative addition to form a R-$Pd^{II}XL_n$ species that cleaves the C–H bond of the coupling partner H-R', followed by the reductive elimination of RR'$Pd^{II}L_n$ to generate the product R-R', and simultaneously regenerate the Pd(0) species; **c**) Enantioselective C–H activation involving a Pd(II)/Pd(IV) catalytic cycle. In this process, after the formation of R-PdX(II)L_n *via* C–H activation, an oxidative addition to produce Pd(IV) species ocurrs, which followed by reductive elimination, forms the product R-R' with concomitant regeneration of catalyst.

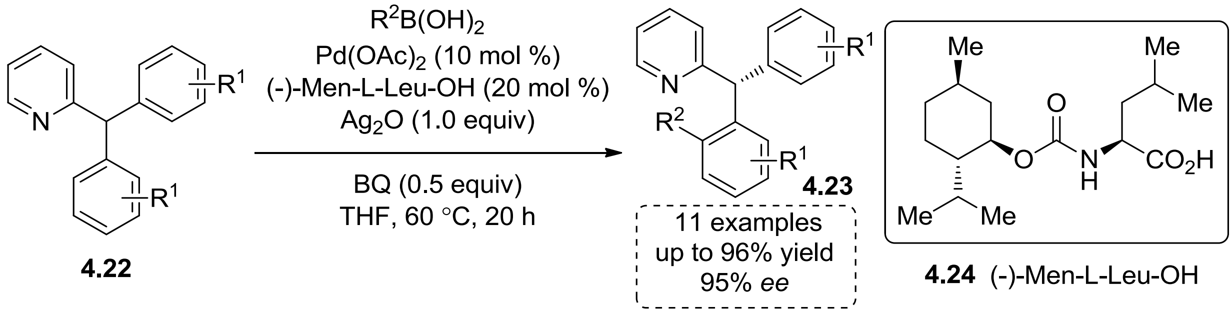


a) Pd(II)/Pd(0) **b**) Pd(0)/Pd(II) **c**) Pd(II)/Pd(IV)

Scheme 4.6 Possible Pd catalytic cycle for enantioselective C–H functionalisation

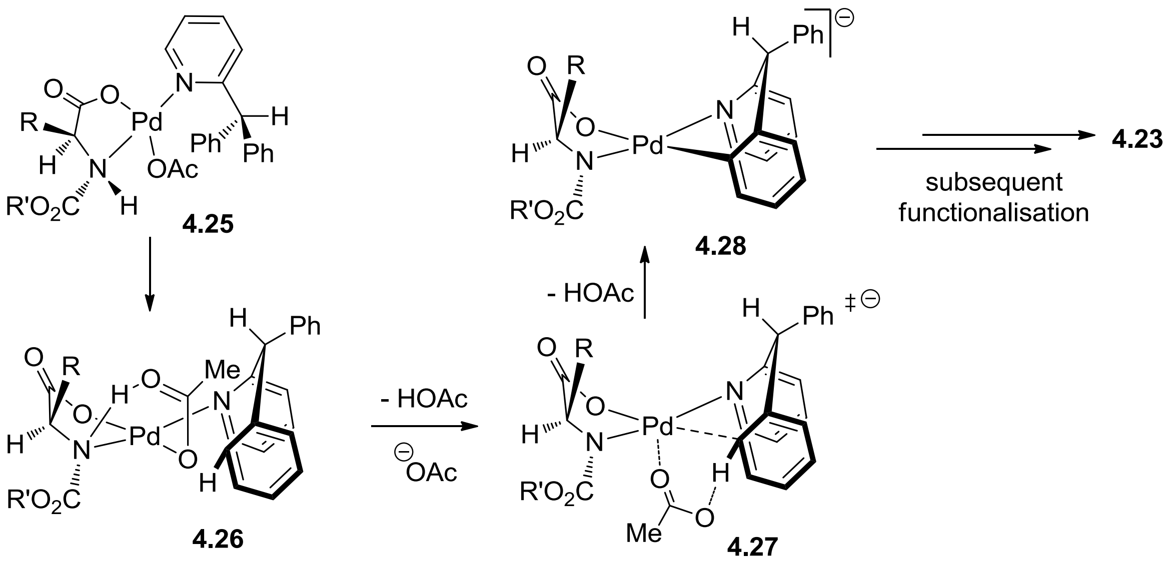
Enantioselective C–H functionalisation *via* Pd(II)/Pd(0) catalysis

A breakthrough in this area was achieved by Yu and co-workers who used an *N*-protected chiral amino acid **4.24** as a suitable ligand in the Pd(II)-catalysed enantioselective C–H functionalisation of pro-chiral 2-benzhydrylpyridine derivatives **4.22** with boronic acids (**Scheme 4.7**).[129] The authors suggested that the *N*-protected chiral amino acid **4.24** ligand coordinates to the Pd centre in an *N,O*-bidentate manner, so a large group at the α-carbon can improve the stereo-control. (-)-Men-L-Leu-OH (**4.24**) was found to be an optimal ligand for this catalytic cycle, with up to 96% yield and 95% *ee* being obtained. The same strategy was applied to the substrates containing carboxylate groups in place of the 2-pyridyl group, showing Boc-L-Ile-OH could enable enantioselective C–H olefination of sodium diphenylcarboxylates with styrene derivatives.[130]



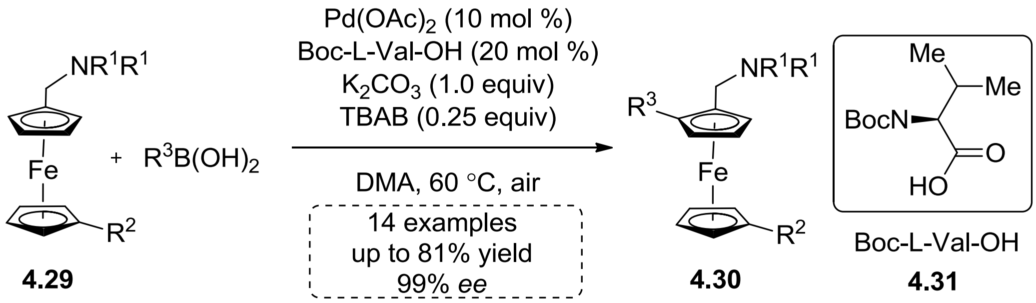
Scheme 4.7 Pd(II)-catalysed asymmetric C–H functionalisation of 2-benzhydrylpyridines

A theoretical study was carried by Musaev, Yu and co-workers to understand this transformation, lending weight to the hypothesis that the *N,O*-bidentate coordination of the ligand to Pd was crucial for high enantioselectivity.[131] Relevant mechanistic steps are shown in **Scheme 4.8**. Cleavage of N–H bond in the ligand occurs by the coordinated acetate, eliminating AcOH. Acetate-assisted metalation of the arene occurs to give palladacycle **4.28**, again with elimination of AcOH. Subsequent functionalisation of this intermediate (**4.28**) *via* transmetallation with the organoboronic acid and reductive elimination affords the desired product **4.23**.



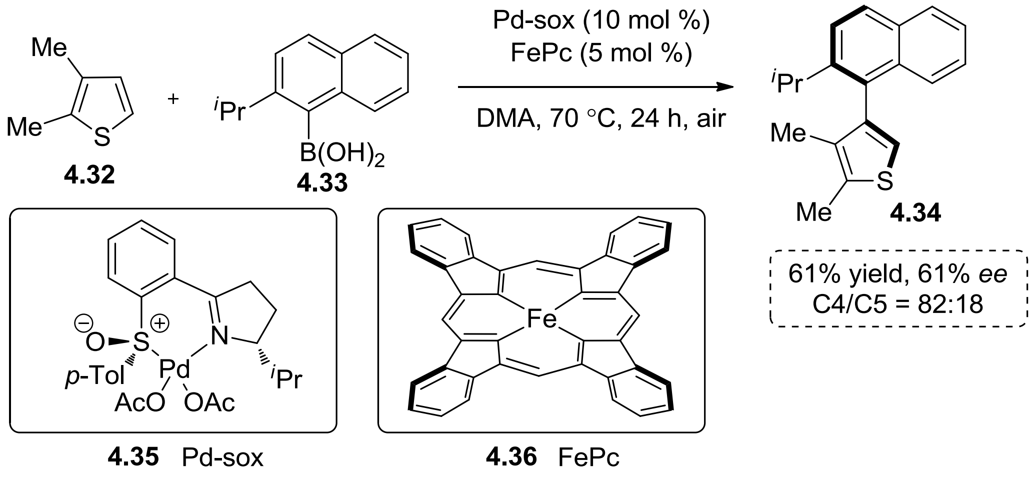
Scheme 4.8 Crucial steps in enantioselective functionalisation of 2-benzhydrylpyridine

N-protected chiral amino acid ligands were also applied to the construction of planar-chiral ferrocene derivatives. Work on asymmetric arylation of *N,N*-dialkylaminomethylferrocenes (**4.29**) was reported by Gu, You and co-workers. Boc-L-Val-OH (**4.31**) was found to be the optimal ligand for this process, leading to excellent enantioselectivity (**Scheme 4.9**).[132] Later on, Cui, Wu and co-workers reported a similar method for enantioselective olefination of ferrocene derivatives by the use of Boc-L-Phe-OH as a chiral ligand.[133]



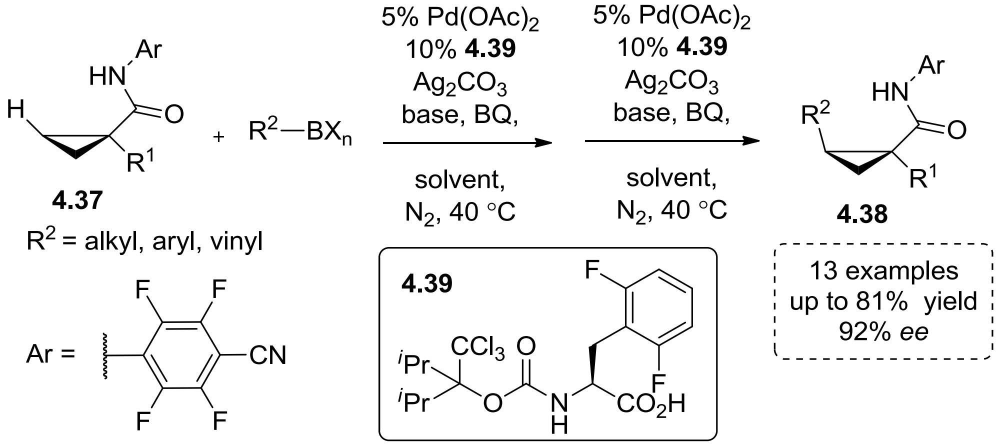
Scheme 4.9 Pd-catalysed asymmetric arylation of *N,N*-dialkylaminomethylferrocenes

Yamaguchi, Itami and co-workers developed a method for preparing axial chiral biaryl molecules using cooperation of Fe and Pd catalysis. The use of Pd(II)-sulfoxide-oxazoline **4.35** and Fe-phthalocyanine **4.36** co-catalysts allowed enantioselective C–H arylation of thiophenes **4.32** with arylboronic acids **4.33**, although moderate yields and *ee*s were obtained.[134]



Scheme 4.10 The synthesis of axial chiral biaryl molecules

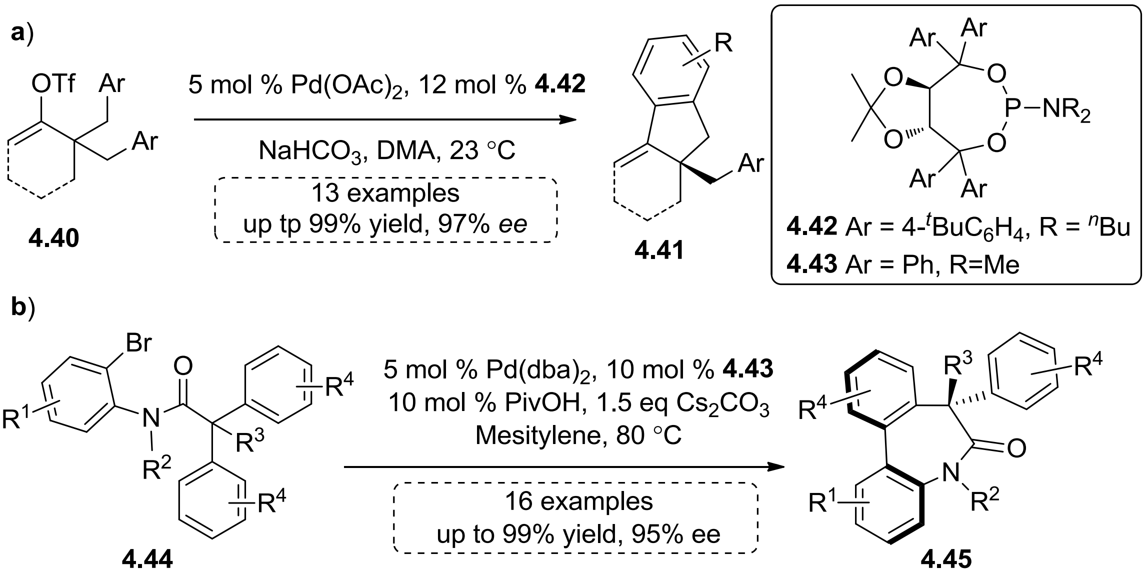
An example of enantioselective C(sp^3)–H bond was reported by Yu's group.[135] After an intensive screening of amino acids, the ligand containing an *N*-Boc group and 2,6-difluorobenzyl substituent at the α-carbon (**4.39**) enabled enantioselective alkylation, arylation and vinylation of 1,1-disubstituted cyclopropanes (**4.37**) incorporating an acidic *N*-arylamide as a weak coordinating directing group.



Scheme 4.11 Enantioselective C–H functionalisation of 1,1-disubstituted cyclopropanes

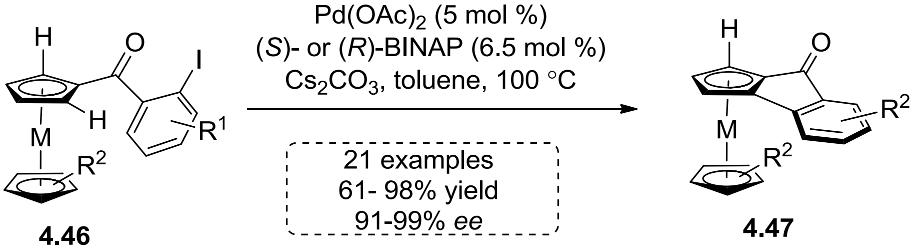
Enantioselective C–H functionalisation *via* Pd(0)/Pd(II) catalysis

Enantioselective C–H functionalisations *via* a Pd(0)/Pd(II) catalytic cycle has also received considerable attention over the past decade. Early work in this area was reported by Alkicker and Cramer who synthesised chiral indane derivatives **4.41** using a Pd catalyst ligated by a specifically designed taddol-based phosphoramidite ligand **4.42** (**Scheme 4.12**, **a**).[136] Later on, the same group extended this method to the enantioselective synthesis of dibenzazepinone derivatives **4.45** by the use of Pd(dba)$_2$ catalyst and the simplest taddol-based phosphoramidite **4.43** as a suitable chiral ligand (**Scheme 4.12**, **b**).[137]



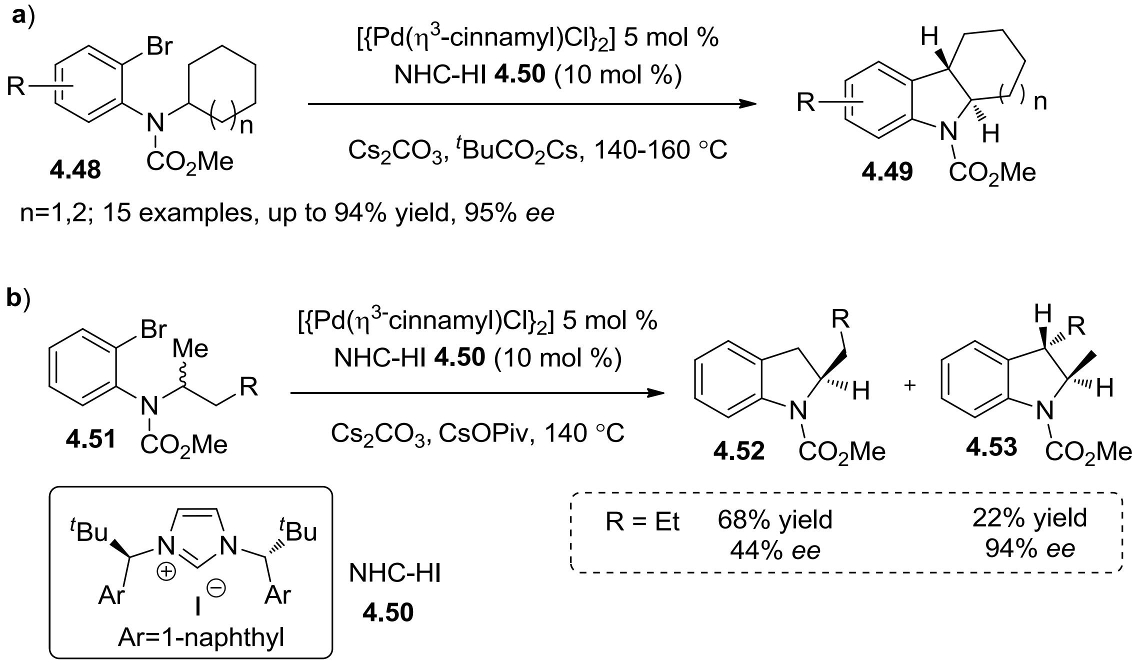
Scheme 4.12 Pd(0)-catalysed enantioselective C–H functionalisation

Kang, Gu and co-workers reported a highly enantioselective Pd(0)-catalysed direct C–H intramolecular arylation of ferrocene and ruthenocene derivatives with aryl iodides by the use of an enantioenriched BINAP ligand (**Scheme 4.13**).[138] At the same time, Gu, You and co-workers reported a method for the enantioselective intramolecular arylation of ferrocene with aryl bromides under very similar conditions. A planar chiral ferrocene phosphine ligand was synthesised from the planar chiral ferrocene product in this case, showing the power of this method in organic synthesis applications.[139]



Scheme 4.13 Pd(0)-catalysed enantioselective C–H intramolecular arylation of metallocenes

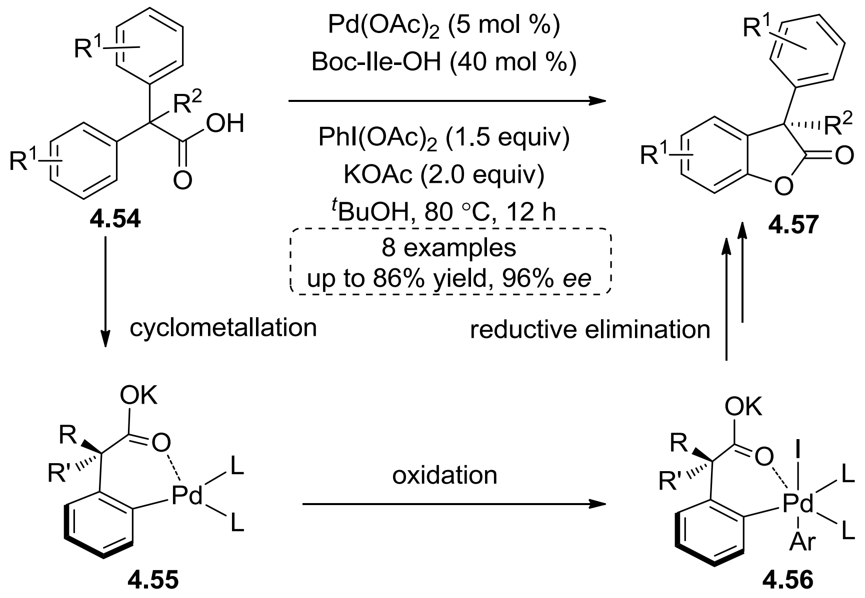
Pd(0)-catalysed enantioselective C(sp^3)–H bond functionalisation reactions have been explored in more depth than the corresponding Pd(II)-catalysed reactions. A selected example reported by Kündig's group is shown in **Scheme 4.14**. The methodology allows easy access to enantioenriched indoline derivatives, a motif commonly found in drugs and natural products.[140] Fused indolines **4.49** bearing trans [3.4.0]- or [3.5.0]-bicyclic backbones could be synthesised *via* intramolecular enantioselective C(sp^3)–H bond arylation of *N*-cycloalkyl substituted carbamates (**4.48**, PG = CO_2Me) catalysed by a Pd complex (either preformed or generated *in situ*) ligated by a bulky chiral NHC ligand **4.50** (**Scheme 4.14**, **a**).[141] This ligand **4.50** also allows the enantioselective C(sp^3)–H arylation of *N*-alkyl substituted carbamates (**4.51**, PG = CO_2Me). The authors showed that regiodivergent C(sp^3)–H bond functionalisations occur both at the terminal methyl and methylene group, leading to 2-substituted indolines **4.52** in higher yields but moderate level of *ee*'s, whereas 2,3-disubstituted indolines **4.53** were the minor products but with excellent *ee*'s (**Scheme 4.14**, **b**).[142] Efforts on this area have also been made by Kagan's[143] and Cramer's[144] groups.



Scheme 4.14 The synthesis of enantioenriched indoline derivatives

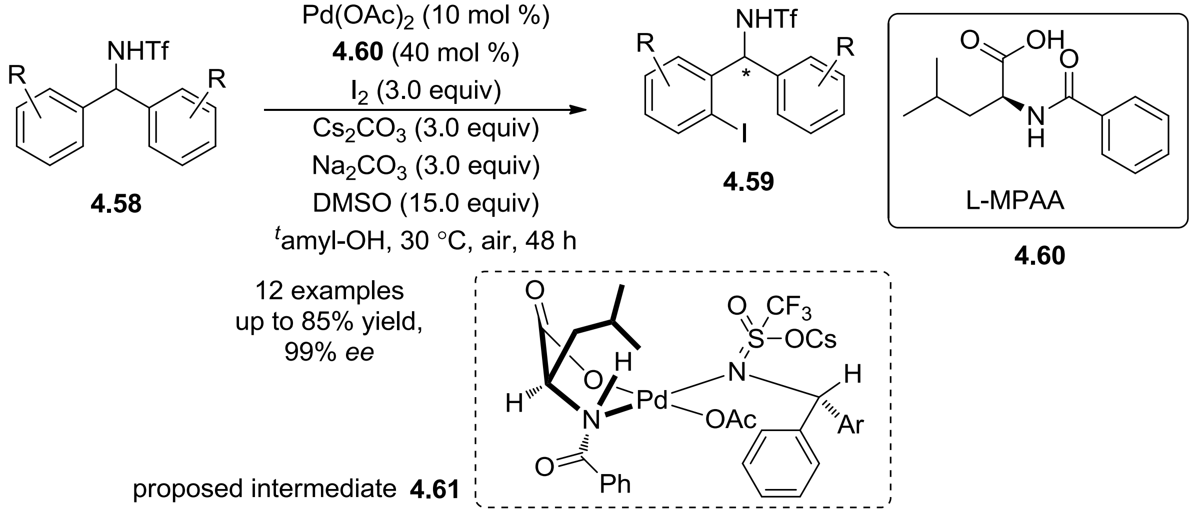
Enantioselective C–H functionalisation *via* Pd(II)/Pd(IV) catalytic cycle

Enantioselective C–H activation involving a Pd(II)/Pd(IV) catalytic cycle has not been explored until recently. In 2013, Yu, Wang and co-workers reported a method for the synthesis of chiral benzofuranones by enantioselective C–H activation of phenylacetic acids **4.54** with Pd(II) species *via* an intramolecular C–O bond formation.[145] The catalytic cycle involves the reductive elimination facilitated by the oxidation of the Pd(II) metallacycle **4.56** to a transient Pd(IV) intermediate **4.55** with a strong iodonium oxidant (**Scheme 4.15**).



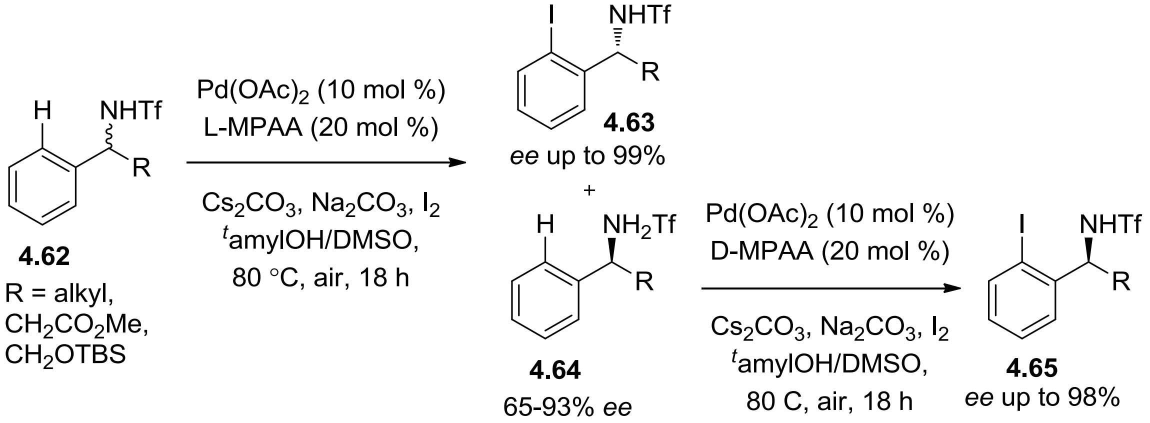
Scheme 4.15 The synthesis of chiral benzofuranones

An enantioselective C–H iodination of a substrate containing trifluoromethanesulfonamide **4.58** as a directing group using an *N*-benzoyl-protected amino acid **4.60** has been developed by Yu's group (**Scheme 4.16**).[146] The author proposed an intermediate (**4.60**) containing Cs triflamide directing group coordinated with Pd(II) as a neutral σ-donor, and bidentate coordination with the chiral ligand. However, it is not clear whether a Pd(IV) intermediate is involved in the catalytic cycle.



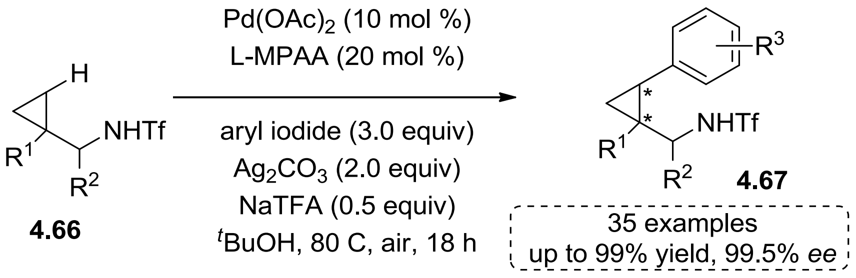
Scheme 4.16 L-MPAA enables enantioselective iodination

Based upon the work above, Yu's group also developed a kinetic resolution *via* Pd-catalysed enantioselective C(sp^2)–H iodination of benzylic amines **4.62**. In this process, one of the enantiomers (racemic benzylic amines) undergoes C(sp^2)–H bond activation faster than the other, thus affording enantioenriched products **4.63**. The remaining enantiomers of the starting material **4.64** could be converted to the opposite configuration of enantioenriched iodinated products **4.65** by the use of the chiral ligand with the opposite configuration (**Scheme 4.17**). The exceedingly high relative rate ratio ((k_{fast}/k_{slow}) is as high as 244 when a fluoro group is substituted at the 3-position of the β-phenyl, and high levels of enantioselectivity between 94% and 99% *ee*s was obtained in all cases.[147] However, whether a Pd(IV) intermediate is involved in the catalytic cycle was not mentioned by the authors.



Scheme 4.17 Enantioselective iodination of benzylic amines *via* kinetic resolution

More recently, Yu's group reported the first example of enantioselective arylation of C(sp^3)–H bond *via* a Pd(II)/Pd(IV) catalytic cycle (**Scheme 4.18**).[148] The method allows the synthesis of chiral *cis*-aryl-cyclopropylmethylamine **4.67** using Pd(II)/MPAA catalysts in excellent yields and *ee*s. Although the Pd(IV) intermediate has not been isolated in support of Pd(II)/Pd(IV) catalytic cycle, the authors suggested that the Pd(II)/Pd(IV) catalytic cycle has been demonstrated for the reaction of the Pd(II) palladacycle with aryl iodides by Daugulis.[149] Moreover, a Pd(II)/Pd(0) catalytic cycle has never been conceived or experimentally supported for C–H arylation of a substrate containing a directing group with aryl iodides. A Pd(II)/Pd(III) catalytic cycle is also unlikely due to the bidentate coordination between catalyst and MPAA ligand, inhibiting the dimerization *via* the bridging carboxylate.[150]



Scheme 4.18 Pd(II)-catalysed enantioselective arylation of cyclopropylmethylamine

4.1.3 Conclusions

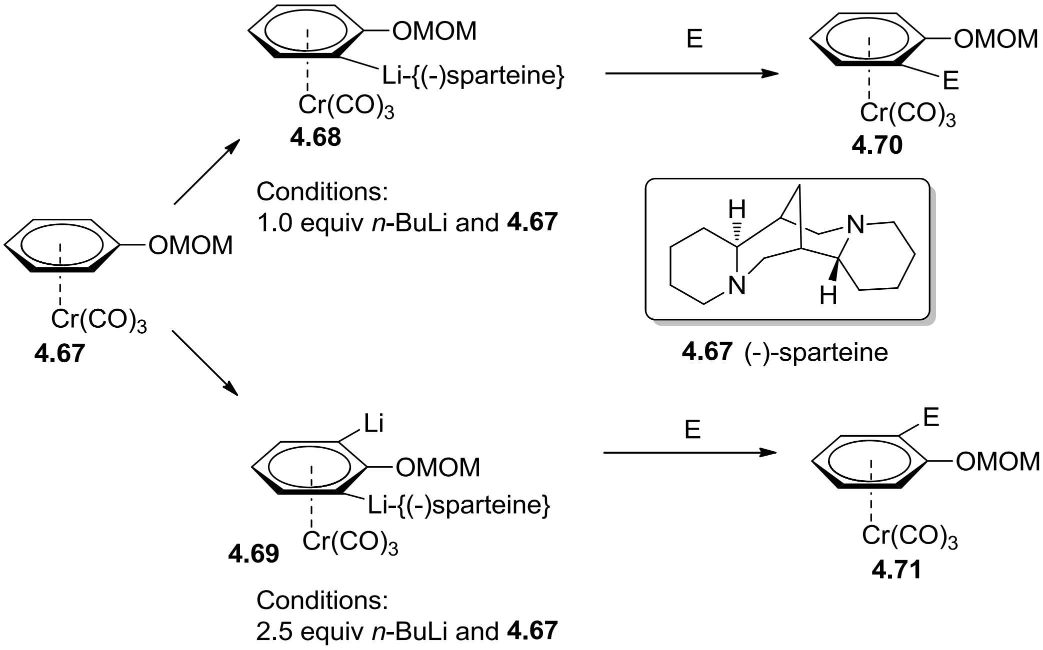
Direct C–H functionalisation has received considerate attention as a promising tool for organic synthesis. The insertions of carbenes and nitrenes into C–H bond in a pro-chiral substrate have been achieved in synthetically useful enantioselectivity. The development of direct enantioselective C–H functionalisation *via* C–H activation, on the other hand, still remains a big challenge. State of the art Pd-catalysed enantioselective C–H activation is presented in this section. The Pd(0)/Pd(II), Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalytic cycles have all been involved as possible mechanisms for enantioselective C–H activation. Both C(sp^2)–H and C(sp^3)–H bonds have been shown to be reactive in an enantioselective fashion under certain conditions. Despite these successful explorations, further efforts on new catalyst and ligand design are required to improve the reactivity and selectivity. Another significant limitation is the substrate scope as most methodologies for enantioselective C–H functionalisation only occur at specialised positions such as those close in proximity to a directing group, and allylic positions. Thus, it is highly desirable to improve the practicality and versatility of enantioselective C–H functionalisation by expanding the substrate scope.

4.2 Objectives of the project

Planar chiral compounds, such as chiral ferrocene derivatives, are of great interest in the research areas of asymmetric catalysis, materials and biomedical research.[151] Nice methodologies for the construction of planar chiral ferrocene derivatives *via* direct C–H functionalisation have been reported by Gu's, You's, and Kang's group as described above.

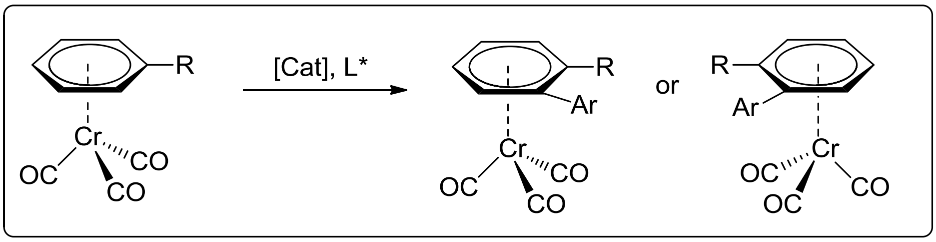
η^6-Arene chromium tricarbonyl complexes have been found to be interesting compounds in organic synthesis for many reasons. Several transformations which can not be carried out with simple arenes but become feasible with the metal complexation of the arene.[152] The easy preparation and purification of these compounds, as well as the unambiguous detection by NMR, make the arene chromium complexes practical in synthetic chemistry.

Planar chiral chromium complexes, on the other hand, have been extensively used as stoichiometric auxiliaries for asymmetric synthesis.[153] Ligands based on planar-chiral η^6-arene chromium scaffolds have also found widespread application in asymmetric synthesis.[154] However, to synthesise the planar chiral η^6-arene chromium complexes, the most common strategy is to use a chiral Li base to enantioselectivity deprotonate a pro-chiral substrate (or use an achiral Li base to enantioselectivity deprotonate a chiral substrate), followed by an electrophilic addition.[35] One impressive example of this strategy is the use of (-)-sparteine, which enables the synthesis of both enantiomers of the planar-chiral chromium complex by altering the amount of base used in the reaction (**Scheme 4.19**). When 1 equivalent of (-)-sparteine and *n*-BuLi are used, the planar-chiral complex (**4.70**) was obtained after an electrophilic quench, such as $(CH_2O)_n$, leading to 58% yield and 92% *ee*. On the other hand, when 2.5 equivalents of (-)-sparteine and *n*-BuLi are used, complex (**4.71**) was obtained after an electrophilic quench, obtaining 30% yield and 95% *ee* when $(CH_2O)_n$ was used as an electrophile.[155]



Scheme 4.19 The synthesis of the planar chiral η^6-arene chromium complexes

The catalytic direct enantioselective C–H functionalisation of η^6-arene chromium complexes, which provides an efficient alternative to planar chiral chromium complexes, has never been achieved before. In this part, ***we aimed to develop a methodology for the synthesis of planar chiral arene chromium tricarbonyl complexes by direct C–H arylation (Scheme 4.20).***

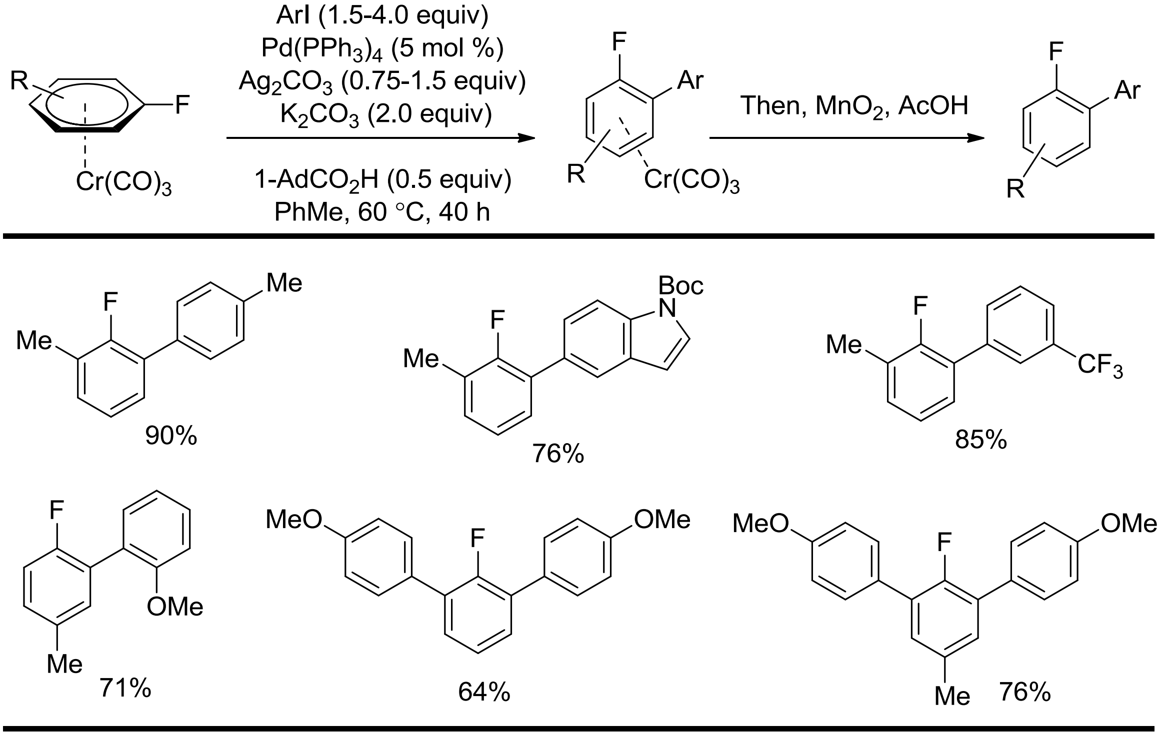


Scheme 4.20 Enantioselective C–H arylation of η^6-arene chromium tricarbonyl complexes

4.3 Pd-catalysed enantioselective C–H arylation of monofluoroarene chromium tricarbonyl complexes

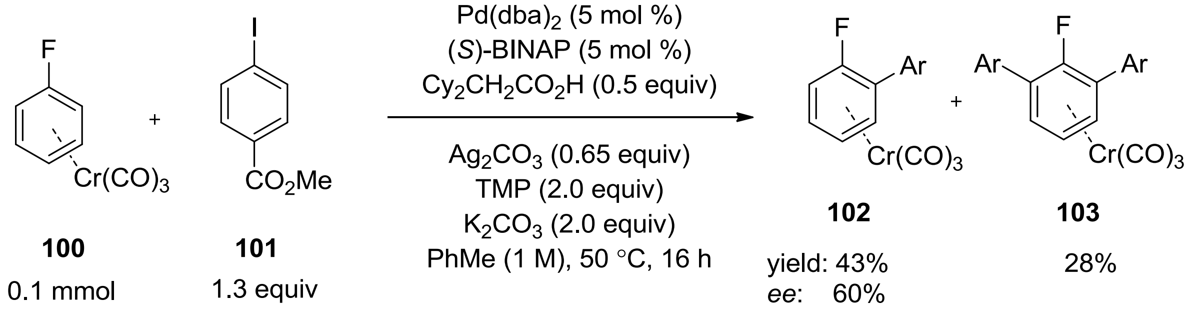
4.3.1 Previous results

Our group has demonstrated that π-complexation to a $Cr(CO)_3$ unit can significantly enhance reactivity of otherwise unreactive monofluoroarenes in Pd-catalysed direct C–H arylation with iodoarenes (**Scheme 4.21**). [156] Although it is well-known that the chromium complexation increases the acidity of protons on the complexed arene, our computational work indicated that the out-of-plane bending of the reacting C–H bond in the transition state was the major contributor to increasing the reactivity of chromium-complexed arenes in a CMD-type C–H activation mechanism. To extend this methodology to electron-rich arenes, our group has also shown that $Cr(CO)_3$-complexation could enhance the reactivity of anisole derivatives, allowing *ortho*-arylation of alkoxyarenes.[157]



Scheme 4.21 Cr-enhanced the reactivity of monofluorobenzene derivatives

Based upon this, Katrina Krämer found that it is possible to achieve an enantioselective C–H arylation of monofluoroarene chromium complexes by the use of a chiral phosphine ligand. Importantly, the use of different carboxylic acids makes a big difference in terms of both reactivity and selectivity. With an extensive screening of carboxylic acids together with phosphine ligands, Katrina Krämer successfully achieved 42% yield of desired monoarylation product with 60% *ee* by the use of 5 mol % of $Pd(dba)_2$, 5 mol % of (*S*) or (*R*)-BINAP, 0.5 equivalents of dicyclohexylacetic acid, 2.0 equivalents of TMP (2,2,6,6-tetramethylpiperidine), 2.0 equivalents of K_2CO_3 and 0.65 equivalents of Ag_2CO_3 in PhMe, heated at 50 °C for overnight (**Scheme 4.22**). $Pd(dba)_2$ is a good replacement for $Pd(PPh_3)_4$. The weak coordination between Pd and dba (dibenzylideneacetone) makes it possible for a chiral ligand to coordinate with Pd. More interestingly, the use of TMP (2,2,6,6-tetramethylpiperidine) crucially increased the reactivity, suggesting a silver-TMP complex was formed to enhance the reactivity.

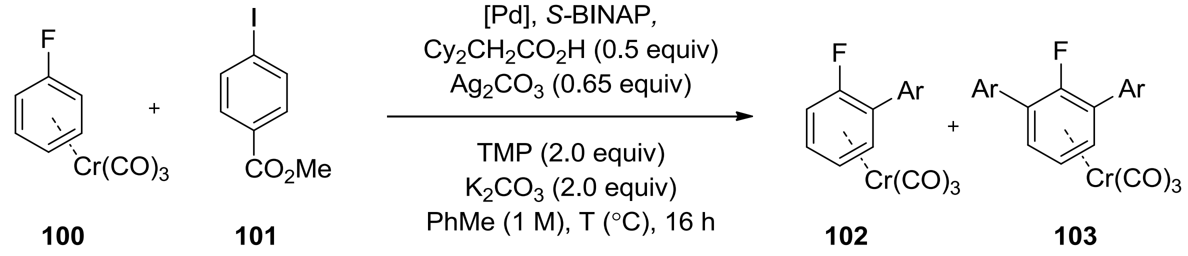


Scheme 4.22 Best results obtained by Katrina Krämer

4.3.2 General statements

After this time, an initial screen of the catalyst and temperature found that the same yield and *ee* was observed at a lower temperature (**Table 4.1**, entry 2), and with lower loading of catalyst and ligand (**Table 4.1**, entry 3). $Pd_2(dba)_3$·CHCl3 was found to be compatible as well (**Table 4.1**, entry 4). A detailed optimisation regarding the catalyst and temperature will be presented later. I have reported these results here to establish that small changes in the nature of the catalyst ($Pd(dba)_2$ vs $Pd_2(dba)_3{\cdot}CHCl_3$), the catalyst loading (5 mol % vs 3 mol %) and reaction temperature have very little effect on the yield and enantioselectivity. This will be important as slightly different conditions are sometimes used when screening phosphine ligands and carboxylic acids in the reaction. However, we presume that any difference in yield or enantioselectivity is the effect of the phosphine ligand or acid addition, and not the small changes between the standard conditions.

Table 4.1 Standard conditions



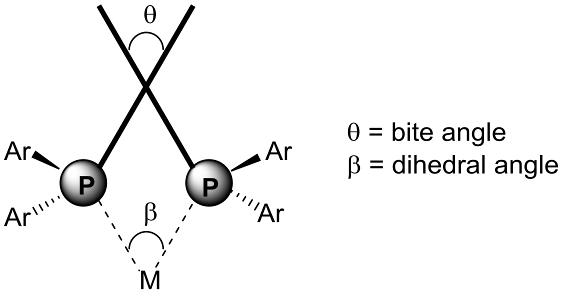
entries	[Pd] (mol %)	*S*-BINAP (mol %)	T (°C)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	$Pd(dba)_2$ (5)	5	50	43	*60*	28
2	$Pd(dba)_2$ (5)	5	40	42	*60*	31
3	$Pd(dba)_2$ (3)	3	40	43	*62*	17
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (1.5)	3	40	47	*60*	30

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^1H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.3 Screening of phosphine ligands

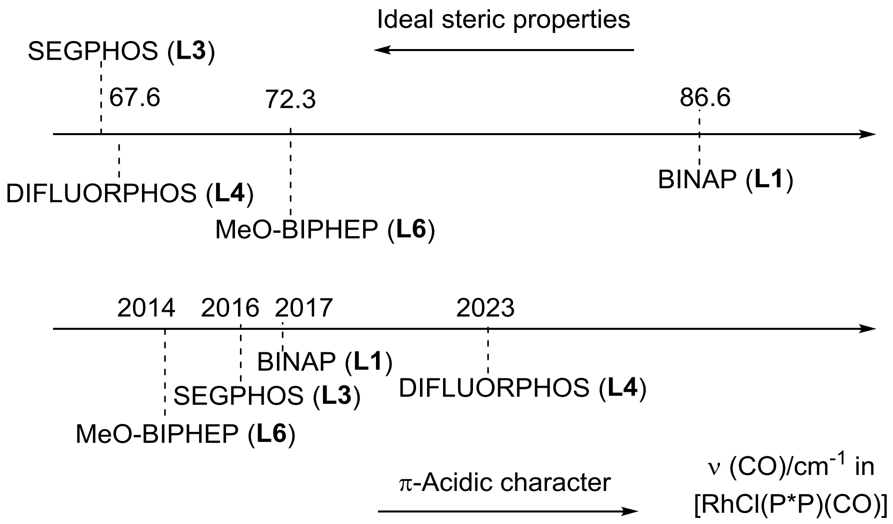
Having determined dicyclohexylacetic acid provides both best reactivity and selectivity among the carboxylic acid derivatives examined by Katrina Krämer, we carried on the screening of chiral phosphine ligands (**Table 4.2**). In order to allow for comparisons to be made, the results presented in the **Table 4.2** are based on both Katrina Krämer's and my work.

As good selectivity was observed when *S*- or *R*-BINAP was used, a large number of bidentate ligands containing biaryl atropisomeric backbones were tested. As we know, the most important factors of a chiral ligand are steric and electronic properties. In terms of this type of bidentate ligands containing biaryl atropisomeric backbone, a molecule model is shown in **Scheme 4.23**. The dihedral angle θ is the angle between the biaryl backbone, which is geometrically related to the bite angle β of P-M-P. With concern to sterics only, the smaller bite angle θ is, the higher interaction between the ligand and substrate should be.[158]



Scheme 4.23 Birayl atropisomeroc backone

The electronic properties were estimated by measuring the carbonyl stretching frequency of [RhCl(P*P)(CO)] complexes by IR spectroscopy. The higher the carbonyl stretching frequency is, the higher the π-acidic character and lower electron-donating ability of the ligand.[159] The steric and electronic properties of some typical ligands are shown in **Scheme 4.24**.[160]



Scheme 4.24 The steric and electronic properties of ligands

Based upon the results in **Table 4.2**, a phosphine ligand with a smaller dihedral angle θ still gave good enantioselectivity. For example, the MeO-BIPHEP (**Scheme 4.25**, **L6**) (72.3° vs. 86.6° in BINAP) gave exactly the same results as with BINAP (**Table 4.2**, entry 6). While a ligand with a very small dihedral angle θ gave a slightly lower *ee* compared with BINAP: For example, SEGPHOS (**Scheme 4.25**, **L3**) with a dihedral angle θ of 67.6°, afforded 45% yield and 50% *ee* (**Table 4.2**, entry 3). DifluoroPhos (**Scheme 4.25**, **L4**) which has a similar dihedral angle θ to SEGPHOS, however, only gave 20% *ee* probably due to the poor electron-donating ability (see **Scheme 4.24**: π-acidic character 2023 cm^{-1} vs. 2016 cm^{-1} in SEGPHOS and 2017 cm^{-1} in BINAP) (**Table 4.2**, entry 4).

Different MeO-BIPHEP derivatives were tested (**Scheme 4.25**, **L6**-**10**), and the most bulky ligand **L9** resulted in no reaction (**Table 4.2**, entry 9). The more sterically hindered **L7** gave lower *ee* compared to **L6** (**Table 4.2**, entries 6 and 7). A furyl substituted phosphine **L10** gave a similar yield with **L6** but with significantly decreased *ee* (**Table 4.2**, entry 10). The ligand with dichlorosubstituted at the biaryl backbone of MeO-BIPHEP (**Scheme 4.25**, **L5**) afforded similar yield to **L6** but significantly decreased *ee* (**Table 4.2**, entry 5).

Some other commonly used bidentate ligands containing biaryl atropisomeric backbone (**Scheme 4.25**, **L11-L15**) were also tested, and (*S*)-*H₈*-BINAP performed best with regard to the *ee* (**Table 4.2**, entry 15).

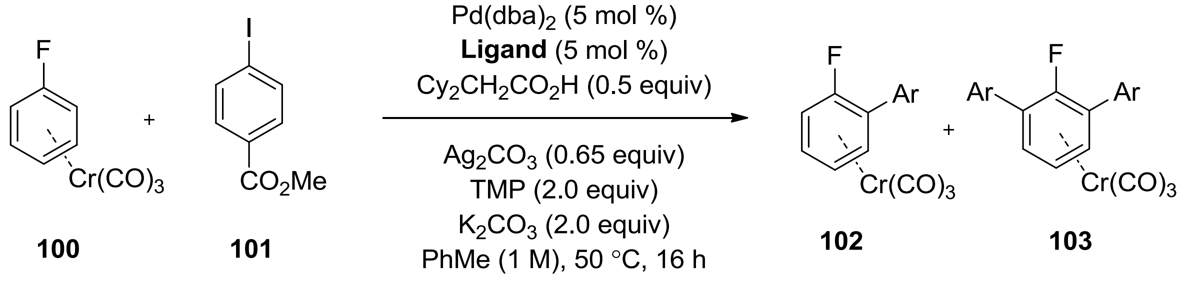
A phenol derivative ligand, (*S*)-BINOL (**Scheme 4.25**, **L17**) was tested, and 40% yield was observed, whereas only 2% *ee* was obtained (**Table 4.2**, entry 17). Finally, a (*S*)-BINAP-$PdCl_2$ complex **L17** was used in the reaction and a slightly lower *ee* was obtained compared to BINAP (**Table 4.2**, entry 17).

Some other bidentate phosphines not based on the axial chirality (**Scheme 4.25**, **L18**-**25**) were tested, but most of them result in low reactivity and selectivity (**Table 4.2**, entries 18-25), except **L20** which afforded 30% yield and 56% *ee* (**Table 4.2**, entry 20).

P*N type bidentate ligands (**Scheme 4.25** and **4-26**, **L26**-**28**) were also tried, and the reaction did not work when employing a ligand containing a primary amine group (**Table 4.2**, entries 26 and 28). And the oxazole containing ligand **L27** gave a low yield and *ee* (**Table 4.2**, entry 27).

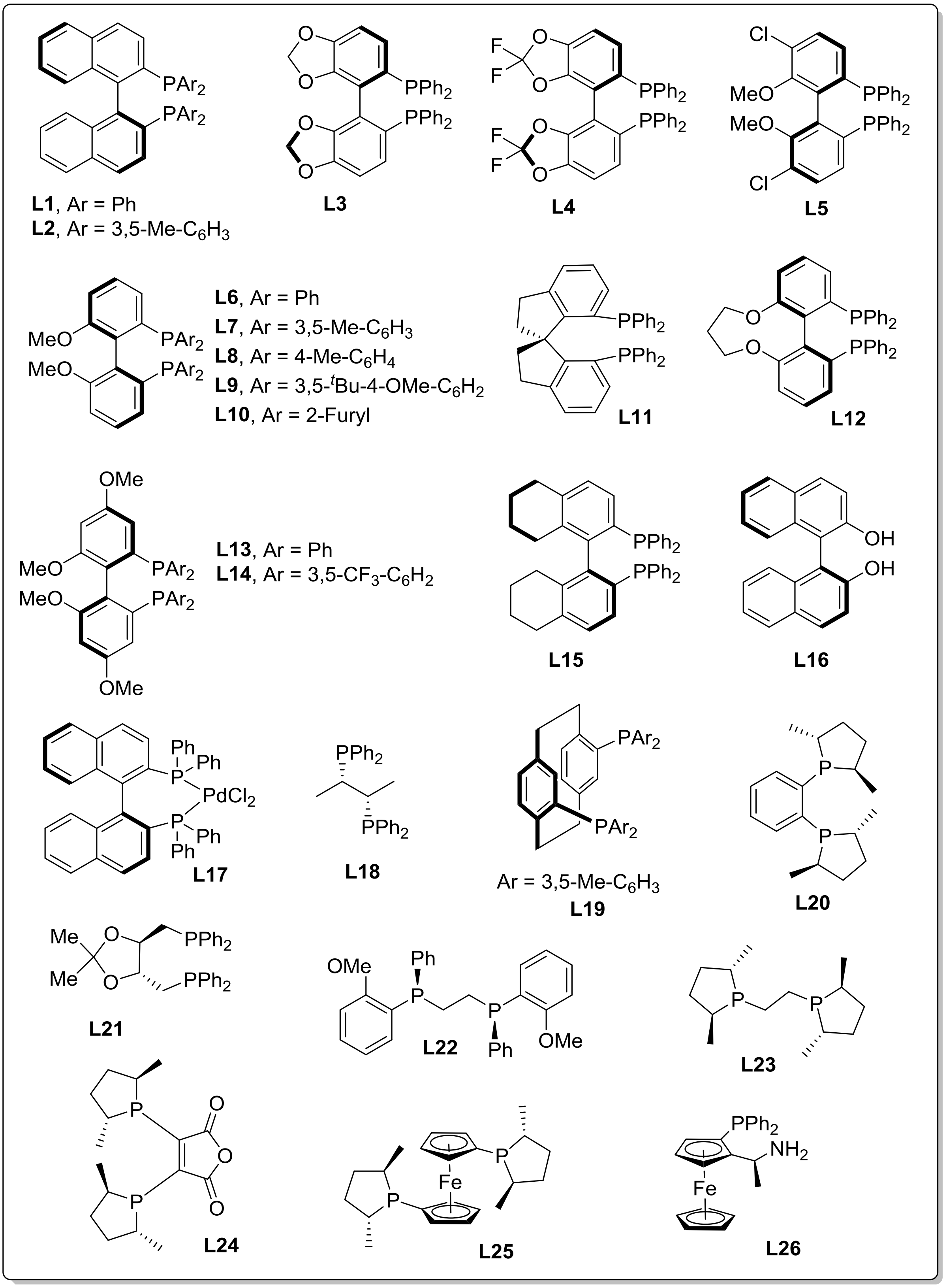
Monodentate ligands containing one phosphine and one etheric oxygen (**Scheme 4.26**, **L29** and **L30**) gave good reactivity but no enantioselectivity. For example, the MOP (**L29**) ligand gave 46% yield, but only 8% *ee* was observed (**Table 4.2**, entry 29). A more bulky MOP derivative **L30** with a naphthalene substituent was made and tried, but similar results were obtained with MOP ligand (**Table 4.2**, entry 30). Phosphoramidite ligand **L31** resulted in no reaction (**Table 4.2**, entry 31).

Table 4.2 Screening of chiral ligands

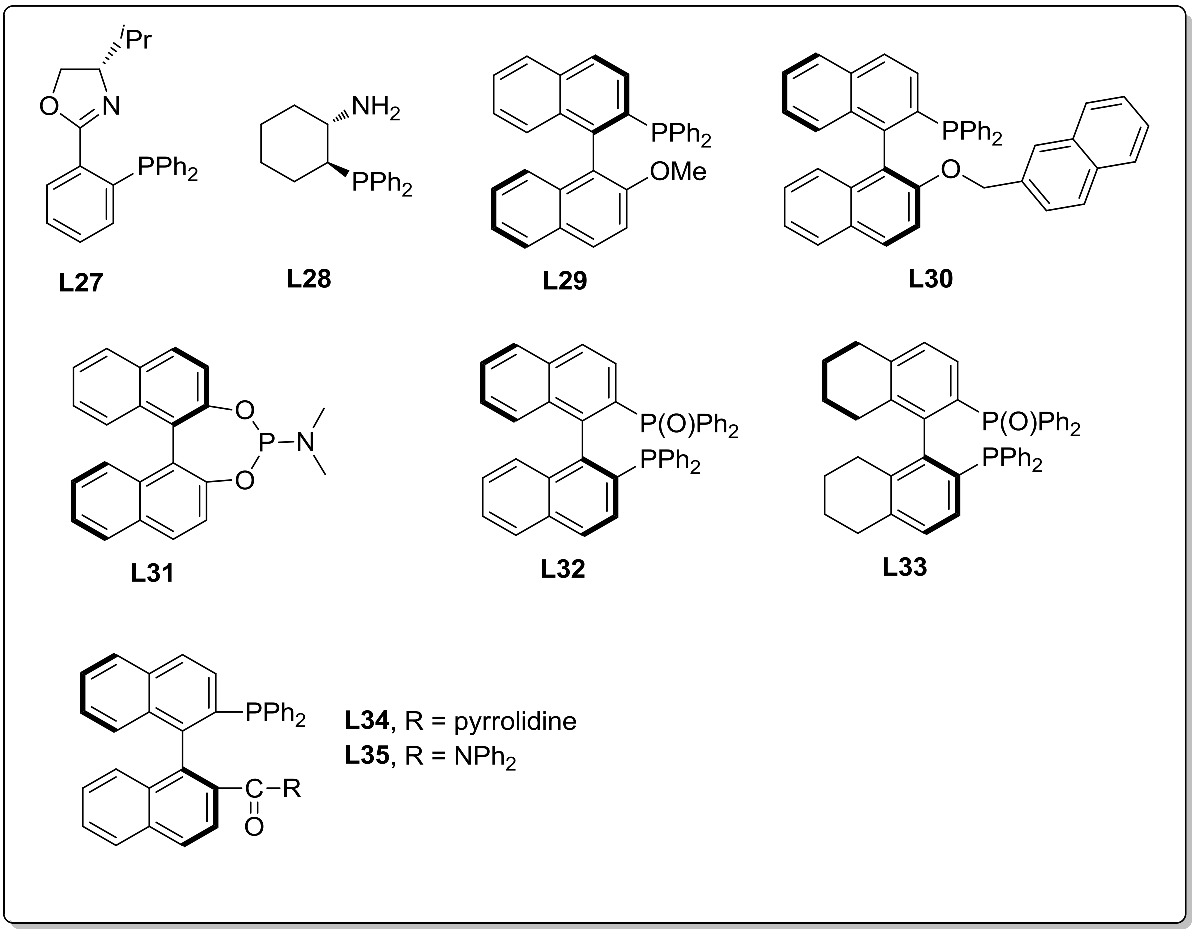


Entries	Ligand	Yield **102**	*ee* **102**	Yield **103**
1	**L1**	42	*64*	31
2	**L2**	40	*36*	26
3	**L3**	45	*50*	28
4	**L4**	45	*20*	17
5	**L5**	42	*43*	35
6[b]	**L6**	43	*64*	27
7[b]	**L7**	47	*38*	30
8[b]	**L8**	50	*54*	20
9[b]	**L9**	0	-	0
10[b]	**L10**	40	*28*	38
11	**L11**	38	*10*	16
12	**L12**	45	*54*	29
13	**L13**	41	*58*	27
14	**L14**	52	*50*	6
15	**L15**	45	*68*	31
16[b,d]	**L16**	40	*2*	12.5
17[b,e]	**L17**	48	*52*	32
18	**L18**	32	*1*	9
19[b]	**L19**	30	*3*	<5
20	**L20**	30	*56*	4
21	**L21**	39	*2*	29
22[c]	**L22**	37	*20*	10
23	**L23**	29	*4*	5
24	**L24**	0	-	0
25	**L25**	39	*18*	23
26	**L26**	0	-	0
27	**L27**	15	*18*	0
28	**L28**	0	-	0
29[a]	**L29**	46	*8*	34
30[b,d]	**L30**	45	*6*	30
31[a]	**L31**	0	-	0

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC. [a] 10 mol % of ligands were used. [b] The reactions were performed at 40 °C. [c] 1.5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 3.3 mol % of phosphine ligands were used. [d] 3 mol % of $Pd(dba)_2$ and 3.3 mol % of ligands were used. [e] Only 5 mol % of **L17** without using $Pd(dba)_2$ was used in the reaction.



Scheme 4.25 library of chiral phosphine ligands (1)

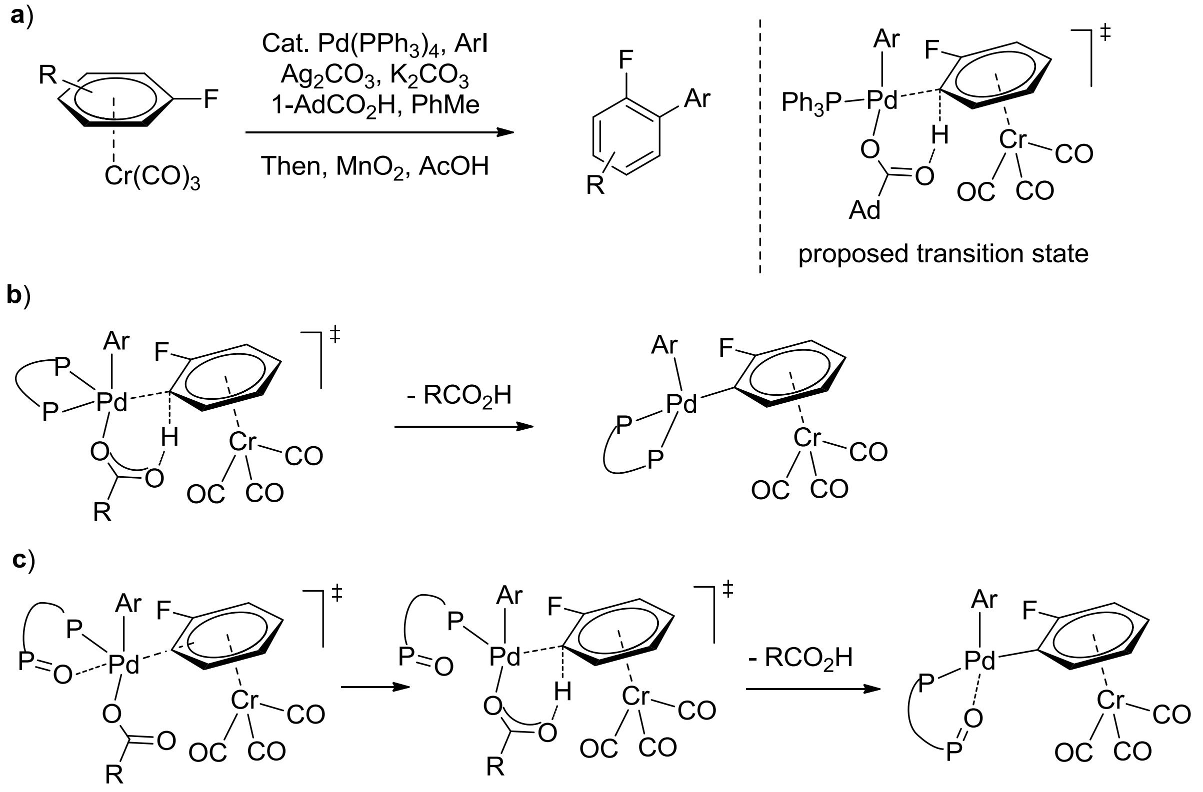


Scheme 4.26 library of chiral phosphine ligands (2)

4.3.4 The exploration of mono-oxidised bidentate phosphine ligands

Based upon the proposed transition state suggested for the Pd-catalysed arylation of monofluoroarenes chromium complex (**Scheme 4.27**, **a**),[37] a transition state was speculated for this Pd-catalysed enantioselective arylation of monofluoroarenes chromium complex ligates with bidentate phosphine (**Scheme 4.27**, **b**).

Considering that a transition state with five bonds to Pd ligated with ligands is hard to achieve for C–H activation and it has never been reported to our knowledge. Thus, we hypothesised that a mono-oxidised BINAP ligand could be a promising alternative to achieve this enantioselective C–H activation. Due to the weakly coordinating ability of the phosphine oxide, the mono-oxidised BINAP could potentially not only act as a bidentate ligand but also as a monodentate phosphine, consequently, making it possible for enantioselective C–H activation to proceed *via* a transition state with four bonds coordination with Pd (**Scheme 4.27**, **c**).

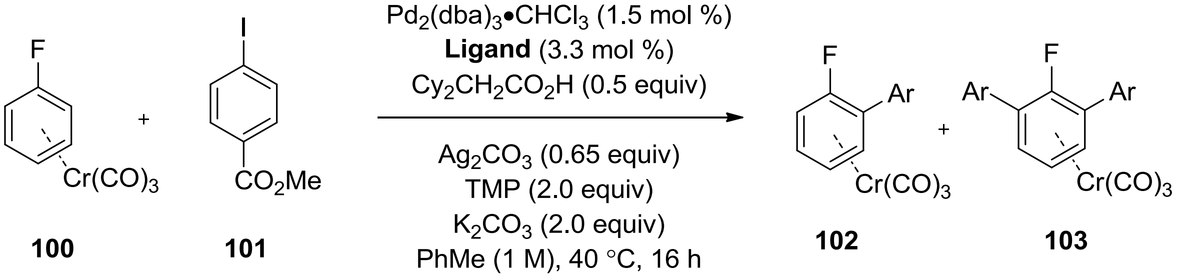


Scheme 4.27 Proposed transition states

Encouragingly, a better *ee* was observed when employing the *S*-BINAP(O) (**Scheme 4.26**, **L32**) ligand compared to *S*-BINAP (**Table 4.3**, entries 1 and 2). The use of *S*-*H₈*-BINAP(O) (**Scheme 4.26**, **L33**) afforded a slightly higher *ee* compared to *S*-BINAP(O) (**Table 4.3**, entry 3).

Finally, given that the carbonyl group could also weakly coordinate to Pd in a similar way to phosphine oxide, phosphine ligands containing a carbonyl group **L34** and **L35** were synthesised and tested in this reaction (**Scheme 4.26**). As it was expected, both **L34** and **L35** gave *ee* as good as *S*-BINAP(O), affording 71% and 72% *ee*s, respectively (**Table 4.3**, entries 4 and 5). Importantly, **L34** and **L35** gave much less undesired bisarylation product **103**.

Table 4.3 Screening of phosphine ligands



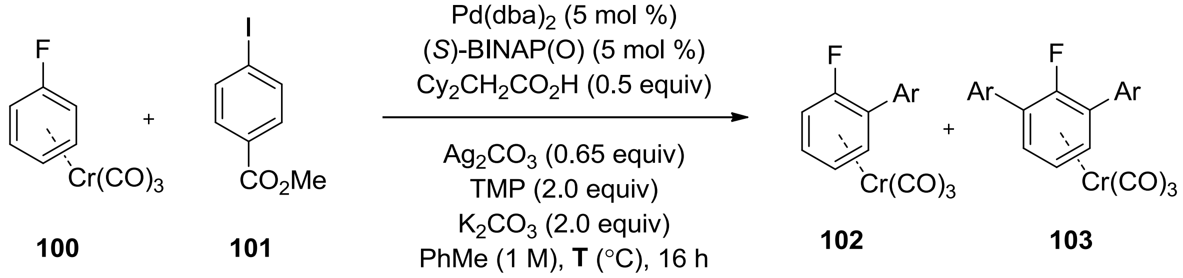
Entries	Ligand	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	**L1**	43	*60*	28
2	**L32**	48	*72*	23
3	**L33**	49	*78*	22
4	**L34**	42	*71*	7.5
5	**L35**	42	*72*	15

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.5 Screening of temperatures

Different temperatures varying from 25 °C to 60 °C were tested, and it was found that the reactions did not make any difference at 40 °C and 50 °C (**Table 4.4**, entries 3 and 4). However, lowering the temperature to 30 °C afforded slightly lower yield and decreased *ee* (**Table 4.4**, entry 2). Leaving the reaction at room temperature (25 °C) decreased both yield and *ee* (**Table 4.4**, entry 1). Increasing the temperature, on the other hand, resulted in a slightly lower yield but a significantly decreased *ee* (**Table 4.4**, entry 5). In this case, a demetallation of the starting material **100** was observed.

Table 4.4 Screening of temperatures



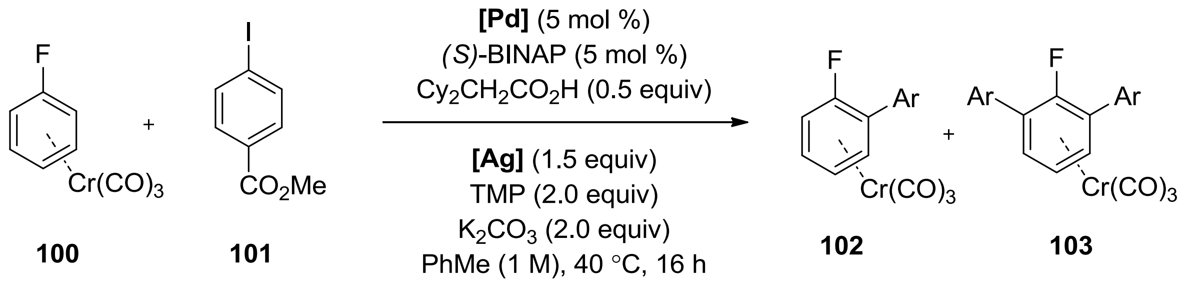
Entry	T (°C)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	25	38	*54*	9
2	30	44	*64*	13
3	40	48	*72*	23
4	50	47	*72*	25
5	60	44	*48*	17

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.6 Screening Pd and Ag sources

Based upon the results in **Table 4.5**, Ag_3PO_4 and AgOPiv quenched the reaction (**Table 4.5**, entries 2 and 3). However, Ag_2O afforded similar results to Ag_2CO_3 (**Table 4.5**, entry 4). In terms of Pd sources, Pd(II) such as $Pd(OAc)_2$ and $Pd(TFA)_2$ gave a slightly lower yield but significantly decreased *ee* (**Table 4.5**, entries 5 and 6). $Pd_2(dba)_3{\cdot}CHCl_3$ which is more stable compared to $Pd(dba)_2$, was found to be compatible for this transformation, affording same results compared to $Pd(dba)_2$ (**Table 4.5**, entry 7).

Table 4.5 Screening of chiral ligands



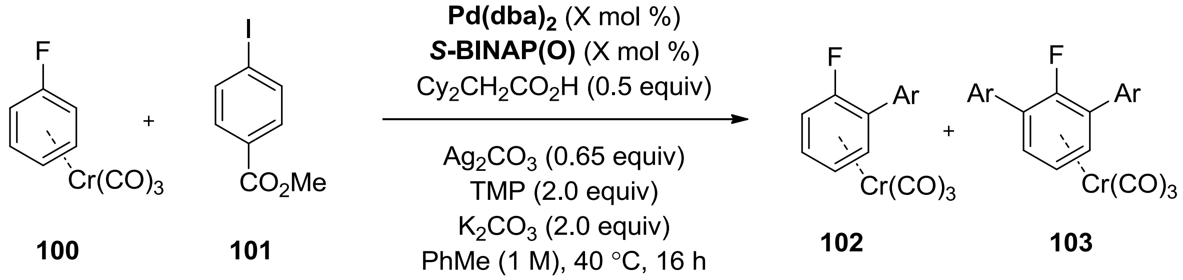
Entry	[Pd] (mol %)	[Ag] (equiv)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	$Pd(dba)_2$ (5)	Ag_2CO_3 (0.75)	43	*60*	28
2	$Pd(dba)_2$ (5)	Ag_3PO_4 (0.5)	0	-	0
3	$Pd(dba)_2$ (5)	AgOPiv (1.5)	0	-	0
4	$Pd(dba)_2$ (5)	Ag_2O (0.75)	45	*62*	33
5	$Pd(OAc)_2$ (5)	Ag_2CO_3 (0.75)	39	*49*	10
6	$Pd(OCOCF_3)_2$ (5)	Ag_2CO_3 (0.75)	41	*25*	13
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)	Ag_2CO_3 (0.75)	47	*60*	30

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^1H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.7 Screening amounts of Pd and Ligands

Different amounts of Pd and phosphine ligand were examined, and it was found that the lower loading of Pd and (*S*)-BINAP(O) caused lower yields to be obtained, whereas only a slightly lower *ee* was observed (**Table 4.6**, entries 1 and 2). However, when increased to 3 mol % of Pd and (*S*)-BINAP(O), the reactions gave similar results to 5 mol % (**Table 4.6**, entries 3-5). The reaction used 1:2 ratio of Pd(dba)$_2$ to (*S*)-BINAP(O) afforded same yield and *ee* of desired product **102** but significantly increased the bisarylation side-product **103** (**Table 4.6**, entry 6).

Table 4.6 Screening amounts of Pd and Ligand (1)

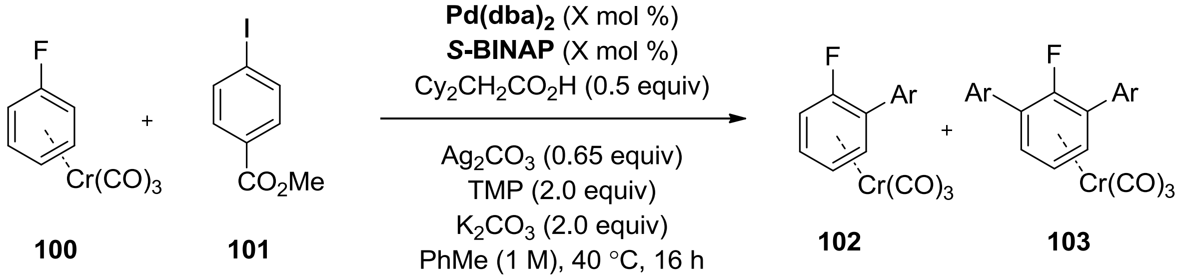


Entry	Pd(dba)$_2$ (mol %)	*S*-BINAP(O) (mol %)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	1.0	1.0	29	*66*	0
2	2.0	2.0	35	*61*	8
3	3.0	3.0	49	*71*	24
4	4.0	4.0	50	*73*	35
5	5.0	5.0	50	*70*	27
6	2.5	5.0	47	72	41

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

Unlike (*S*)-BINAP(O), a significantly decreased yield and *ee* was obtained when only 1 mol % of Pd(dba)$_2$ and (*S*)-BINAP were used in the reaction (**Table 4.7**, entry 1). Increasing amounts of Pd(dba)$_2$ and (*S*)-BINAP to 2.5 mol % gave an improved 47% yield and 63% *ee* (**Table 4.7**, entry 2), similar results were obtained when using 5 mol % of Pd(dba)$_2$ and (*S*)-BINAP (**Table 4.7**, entry 3). Interestingly, when the reaction used a 1:2 ratio of Pd(dba)$_2$ to (*S*)-BINAP, an essentially racemic product **102** was obtained (**Table 4.7**, entry 4).

Table 4.7 Screening amounts of Pd and Ligand (2)



Entry	Pd(dba)$_2$ (mol %)	*S*-BINAP (mol %)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	1.0	1.0	25	*31*	0
2	2.5	2.5	47	*63*	19
3	5.0	5.0	42	*64*	31
4	5.0	10.0	46	*4*	13

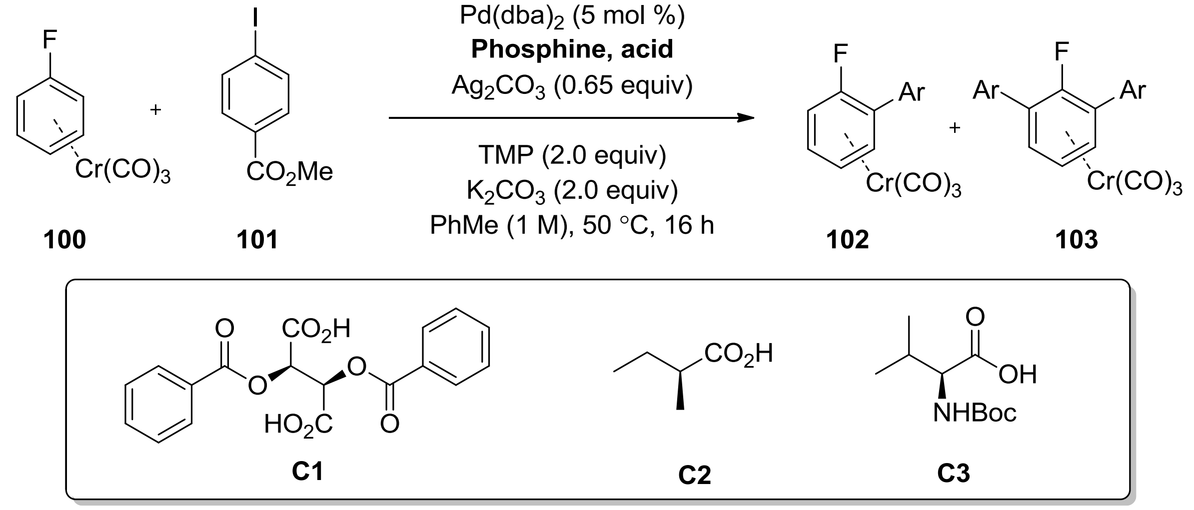
0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.8 Screening carboxylic acids

Chiral carboxylic acids

Based upon the proposed transition state described in **Scheme 4.27**, both phosphine ligand and the carboxylate could be the chirality-inducing components in this transformation. Thus, some selected chiral carboxylic acids were tested. It is easy to create matched/mismatched cases when using two chiral components of which both are ligated in close proximity to catalyst centre. In the case of **C1**, a low 7% *ee* was obtained when **C1** was used in conjunction with *R*-BINAP (**Table 4.8**, entry 1). However, the *ee* increased to 14% when the opposite configuration ligand, *S*-BINAP was employed (**Table 4.8**, entry 2). A chiral carboxylic acid **C1** as a single chirality-inducing component by the use of *rac*-BINAP or simple PPh_3 were also tested, affording 34% and 22% *ee*, respectively (**Table 4.8**, entries 3 and 4). To avoid this 'mismatched' combination, the chiral carboxylic acids **C2** and **C3** were tested in conjunction with both *S*- and *R*-BINAP, both affording enantioselectivity to some extent (**Table 4.8**, entries 5-9), suggesting that chiral carboxylic acid could be the chirality-inducing component in this transformation. Further efforts on the screening of chiral carboxylic acids are required to find the optimum one.

Table 4.8 Screening of chiral carboxylic acids



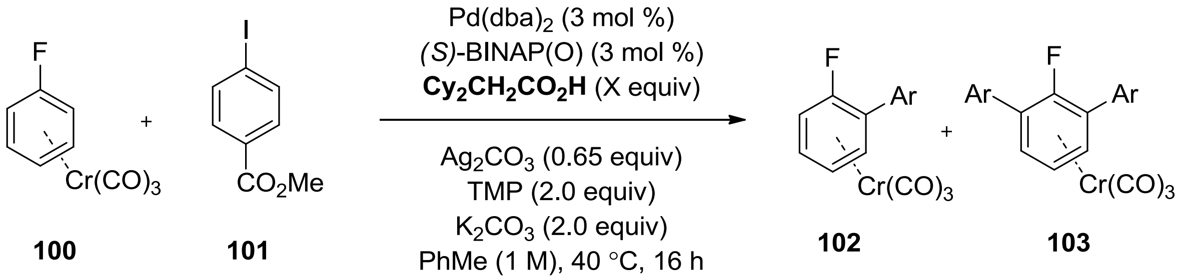
entries	Phosphine (mol %)	Acid (equiv)	Yield **102**	*ee* **102**	Yield **103**
1[a]	*R*-BINAP (3)	**C1** (0.25)	42	*34*	7
2[a]	*S*-BINAP (3)	**C1** (0.25)	39	*20*	14
3[a]	*Rac*-BINAP (3)	**C1** (0.25)	20	*34*	4.5
4[a]	PPh_3 (3)	**C1** (0.25)	41	*22*	28
5	*S*-BINAP (5)	**C2** (0.5)	41	*30*	12
6	*R*-BINAP (5)	**C2** (0.5)	36	*30*	36
7[b]	*Rac*-BINAP (3)	**C3** (0.5)	21	*16*	5
8[b]	*S*-BINAP (3)	**C3** (0.5)	18	*14*	0
9[b]	*R*-BINAP (3)	**C3** (0.5)	21	*16*	0

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^1H NMR using an internal standard, *ee*s were determined by HPLC. [a] 1.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ was used instead of 5 mol % of $Pd(dba)_2$. [b] 3 mol % of $Pd(dba)_2$ was used.

Amount of carboxylic acids

The effect of the amounts of dicyclohexylacetic acids was tested, and it was found that it made no difference with regard both reactivity and selectivity when the amounts of dicyclohexylacetic acids ranged from 0.10 equivalents to 0.75 equivalents were used (**Table 4.9**, entries 1-4). Both yield and *ee* decreased slightly when further decreasing the amount of dicyclohexylacetic acid (**Table 4.9**, entry 5). Interestingly, there was still 38% of desired product obtained when no carboxylic acid was used, whereas no enantioselectivity was observed (**Table 4.9**, entry 6), suggesting that a carboxylic acid plays a crucial role to achieve enantioselective C–H functionalisation, probably due to the interaction between the chiral ligand and the carboxylic acid, inducing carboxylic acid assists enantioselective C–H activation.

Table 4.9 Screening the amounts of carboxylic acids



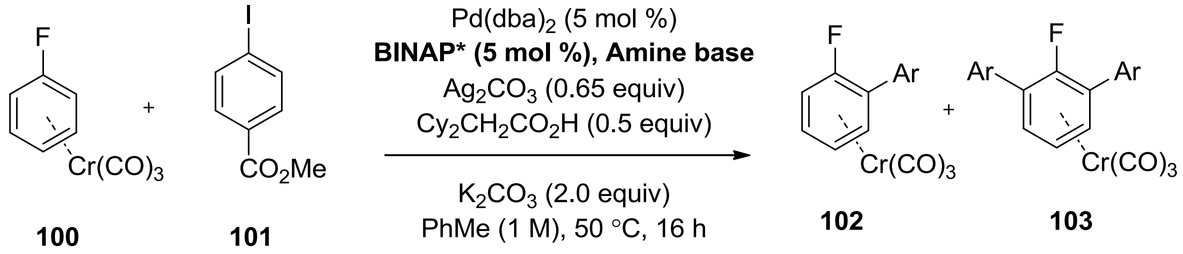
Entry	$Cy_2CH_2CO_2H$ (equiv)	Yield **102** (%)	*ee* **102** (%)	Yield **103** (%)
1	0.750	50	*71*	27
2	0.500	49	*71*	24
3	0.250	49	*73*	29
4	0.100	49	*69*	29
5	0.066	43	*63*	39
6	0.000	38	*2*	11

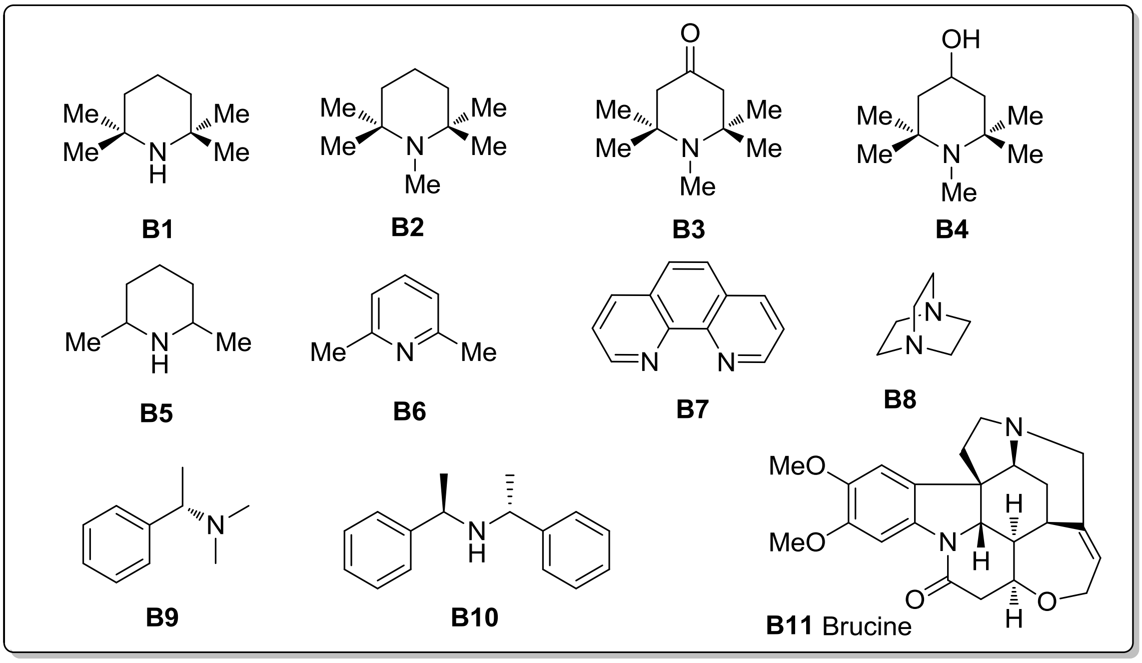
0.1 mmol of 100 and 1.3 equiv of 101 were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

4.3.9 Screening of amine bases

It has been mentioned that TMP (2,2,6,6-tetramethylpiperidine) plays a crucial role to increase the reactivity. Differening amounts of TMP were firstly tested and it was found that the optimum amount was 2.0 equivalents (**Table 4.10**, entry 1-3). The reaction without adding TMP resulted in no reactivity (**Table 4.10**, entry 4). Screening of piperidine derivatives (**B2**-**5**) was then undertaken, and none of the amine additives gave good results (**Table 4.10**, entries 5-8), nor did the 2,6-dimethylpyridine **B6**, 1,10-phenanthroline **B7** and 1,4-DABCO **B8** (**Table 4.10**, entries 9-11). A selection of chiral amine bases (**B9**-**11**) was tested. Similarly to the screening of chiral carboxylic acids, to avoid a 'mismatched' combination, all the chiral amine bases were tested in conjunction with both *S*- and *R*-BINAP. However, only brucine **B11** gave a compatible yield to TMP, but maximum 17% *ee* was obtained (**Table 4.10**, entry 16).

Table 4.10 Screening of amine bases





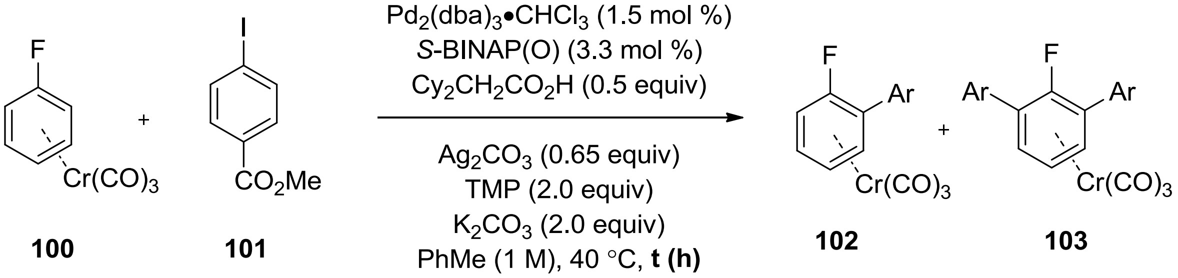
Entry	Phosphine (mol %)	Amine (equiv)	Yield **102**	*ee* **102**	Yield **103**
1	*R*-BINAP	**B1** (2.0)	42	*64*	31
2	*R*-BINAP	**B1** (1.0)	14	*22*	0
3	*R*-BINAP	**B1** (3.0)	41	*56*	14
4	*S*-BINAP	**-**	0	-	0
5	*R*-BINAP	**B2** (2.0)	7	-	0
6	*R*-BINAP	**B3** (2.0)	28	*18*	4
7	*R*-BINAP	**B4** (2.0)	23	*6*	0
8	*R*-BINAP	**B5** (2.0)	18	*2*	0
9	*R*-BINAP	**B6** (2.0)	5	-	0
10	*R*-BINAP	**B7** (2.0)	29	*26*	0
11	*R*-BINAP	**B8** (2.0)	24	*4*	0
12[a]	*S*-BINAP	**B9** (2.0)	15	*12*	-
13[a]	*R*-BINAP	**B9** (2.0)	18	*6*	-
14[a]	*S*-BINAP	**B10** (2.0)	11	*19*	0
15[a]	*R*-BINAP	**B10** (2.0)	12	*8*	0
16[a]	*S*-BINAP	**B11** (2.0)	42	*17*	7
17[a]	*R*-BINAP	**B11** (2.0)	35	*5*	-

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC. [a] The reactions were performed at 40 °C.

4.3.10 Prolonged reaction

A time profile for this reaction was shown in **Table 4.11**, the major enantiomer was assigned as ***S*-102**. From **Figure 4.1**, the amounts of ***S*-102** increased dramatically at the beginning of the reaction and the rate of production decreased over time. The yield of ***R*-102**, however, increased during the first couple of hours and then slowly decreased. The amounts of bisarylated product **103**, on the other hand, keep rising during the whole reaction time. Interestingly, the *ee* of **102** increased at a same rate to the increase in amounts of bisarylation product **103** throughout the reaction time.

Table 4.11 Time profile



Entry	t (h)	Yield **102**	ee **102**	Yield **103**	Yield ***S*-102**	Yield ***R*-102**
1	0.5	5	*48*	0	3.7	1.3
2	1.0	11	*50*	0.5	8.25	2.75
3	2.0	23	*48*	2	17.02	5.98
4	3.0	30	*50*	4.5	22.5	7.5
5	4.0	36	*52*	7.5	27.36	8.64
6	5.0	39	*54*	9.5	30.03	8.97
7	7.0	41	*58*	11.5	32.39	8.61
8	16.0	45	*70*	24	38.25	6.75

0.1 mmol of **100** and 1.3 equiv of **101** were used in the reactions, yields were determined by ^{1}H NMR using an internal standard, *ee*s were determined by HPLC.

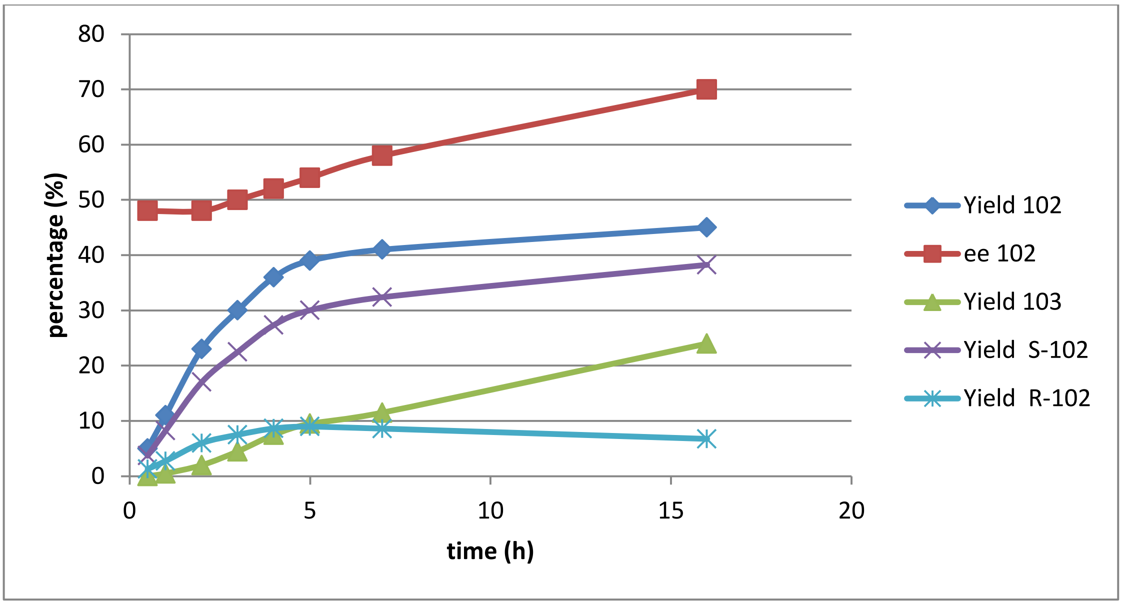
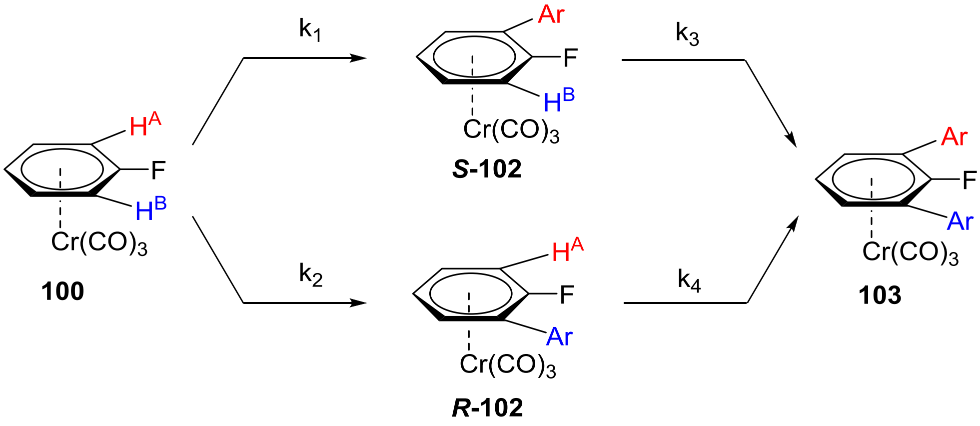


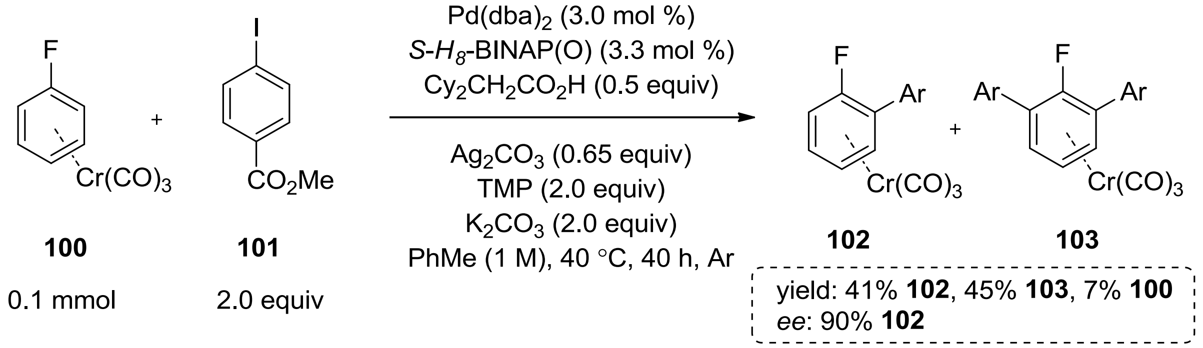
Figure 4.1 Reaction time profile

An *in situ* kinetic resolution has been proposed to explain why the *ee* values keep increasing over time. Based upon the results in **Table 4.11**, a ratio 74:26 of ***S*-102:*S*103** was obtained at the beginning of the reaction, which means our catalytic system is moderately selective for the activation of the C–H^A bond ($k_1 > k_2$). Similarly, as the C–H^A bond is more reactive than the C–H^B bond, the C–H^B bond in ***S*-102** is less reactive than the C–H^A bond in ***R*-102**, consequently, the reaction from ***R*-102** to **103** must be faster than the reaction from ***S*-102** to **103** ($k_3 > k_4$). Thus the formation of **103** would consume ***R*-102** more than ***S*-102**, which leads to an increasing excess of ***S*-102** to ***R*-102** (**Scheme 4.28**).



Scheme 4.28 *In situ* kinetic resolution proposal

Based upon these, it was thought that a higher *ee* would be obtained when leaving the reaction for a longer time. The best ligand, *S-H$_8$*-BINAP(O) (**L33**), was chosen to test this assumption. To compensate for the consumption of the iodoarene *via* bisarylation, 2.0 equivalents of methyl-4-iodo-benzoate **101** were used. As we predicted, the prolonged reaction under argon protection gave a similar yield of **102**, and higher yield of bisarylation product **103**, while the *ee* increases from 78% to 90% (**Scheme 4.29**).



100 0.1 mmol

101 2.0 equiv

102

103

yield: 41% **102**, 45% **103**, 7% **100**
ee: 90% **102**

Scheme 4.29 Prolonged reaction

4.4 Conclusions and future work

The construction of planar chiral complexes *via* an asymmetric C–H arylation on pro-chiral arene chromium substrates under very mild conditions has been explored. The *ee* value has been reached to 90% by extensive optimisation. However, only a moderate yield, 41% of desired planar chiral compound was obtained, concomitant with 45% of undesired achiral bisarylation product which can not be avoided under the current conditions. An investigation of the development of *ee*s over time showed that the formation of achiral bisarylation product increases the *ee* of the remaining planar-chiral monoarylated product.

Future work could focus on improving the yield of the desired monoarylation product. However, the point to reduce the bisarylation product is still to improve the selectivity of the catalytic system. The phosphine ligands containing carbonyl group (**L34** and **L35**) have shown their potential in this enantioselective transformation, affording the same yield and *ee* of the monoarylation product but significantly decreaseing the undesired bisarylation product. Thus further efforts on designing and synthesising a set of this type of ligand by changing the substituents on the carbonyl group could be desirable.

The carboxylic acid, on the other hand, is crucial to achieve enantioselective C–H functionalisation. A test of chiral carboxylic acid showed that the chiral carboxylic acid could also be the chirality-inducing component in this transformation. Thus, the development of chiral carboxylic acids, such as *N*-protected amino acids, as the ligands would also be explored in the future.

Chapter 5

Chapter 5 Experimental

5.1 General experimental information

All chemicals were purchased from commercial sources (Sigma Aldrich, Acros, Alfa Aesar, Strem, Fluorochem) and used without further purification unless otherwise stated. Anhydrous THF, PhMe, DCM, and Et_2O were obtained from a Grubbs type solvent purification system. Analytical thin-layer chromatography was performed on pre-coated Merk silica gel F_{254} plates and visualized under a UV light. Melting points were obtained using a Bibby Stuart Scientific apparatus and are uncorrected. IR spectra were recorded using a Bruker Tensor 37 FTIR machine and are quoted in cm^{-1}. ^1H NMR spectra, recorded at 400 MHz, are referenced to the residual solvent peak at 7.26 ppm ($CDCl_3$) and 2.05 ppm (acetone-d_6). ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the residual solvent peak at 77.0 ppm ($CDCl_3$) and 29.8 ppm (acetone-d_6). HRMS were performed at the EPSRC National Mass Spectrometry Service Centre, Swansea. HPLC analysis was carried out on an Agilent1100 machine using Chiralcel IB or IC columns with a mixture of hexane and isopropanol as the eluent and a flow rate of 0.8 ml/min. Specific rotation was detected by Rudolph Research Analytical polarimeter. Calculated for specific rotation = 100a/lc {a = observed angle of rotation, l = length of cell in dm, c = weight of sample (gram) in 100 mL of solution}. Polarimeter cell part number: 14J-8.5-100-6.0-S/DT, length of cell is 1 dm.

5.2 Experimental procedures for the synthesis of salicylic acids - Chapter 2

5.2.1 General procedures

General procedure 1. **Carboxylation of phenols at atmospheric pressure**

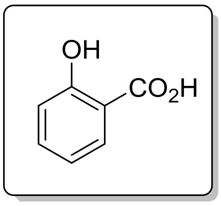
In glovebox, to a vial containing phenol substrate (0.25 mmol) and 2,4,6-trimethylphenol (34 mg, 0.25 mmol, 1.0 equiv) was added NaH (60% dispersion in mineral oil, 40 mg, 2.0 mmol, 4.0 equiv), heating the mixture at 100 °C for 5 minutes. Then, the mixture was cooled down to room temperature and purged with CO_2, and reacted under a balloon filled with CO_2 at 185 °C for 2 h. After this time, the reaction mixture was cooled to room temperature, quenched with 10 mL of H_2O and acidified to the pH ~4 with concentrated HCl, and then extracted with EtOAc (3 x 10 mL). The organic layers were dried over anhydrous $MgSO_4$, evaporated to dryness and purified by column chromatography (*n*-hexanes:EtOAc) to afford salicylic acids.

General procedure 2. **Carboxylation of phenols at 5 atm**

In glovebox, to a vial containing phenol substrate (0.5 mmol) and 2,4,6-trimethylphenol (68 mg, 0.25 mmol, 1.0 equiv) was added NaH (60% dispersion in mineral oil, 80 mg, 2.0 mmol, 4.0 equiv), heating the mixture at 100 °C for 5 minutes. Then, the mixture was cooled down to room temperature and purged with CO_2, and reacted in the autoclave under 5 atm of CO_2 at 185 °C for 2 h. After this time, the reaction mixture was cooled to room temperature, quenched with 10 mL of H_2O and acidified to the pH ~4 with concentrated HCl, and then extracted with EtOAc (3 x 10 mL). The organic layers were dried over anhydrous $MgSO_4$, evaporated to dryness and purified by column chromatography (*n*-hexanes:EtOAc) to afford salicylic acids.

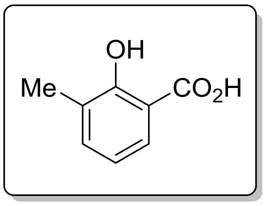
5.2.2 Characterisations of salicylic acid derivatives

Salicylic acid (2)



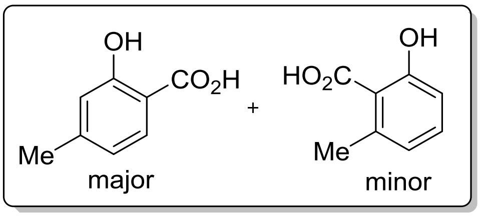
Following general procedure 1 with phenol (23.5 mg. 0.25 mmol) to obtain **2** as a white solid (22.0 mg, 64%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.37 (bs, 1H), 7.91-7.89 (m, 1H), 7.56-7.52 (m, 1H), 6.97-6.93 (m, 2H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.8, 163.2, 137.0, 131.4, 120.2, 118.3, 113.3 ppm. These data are consistent with those previously reported.[161]

2-Hydroxy-3-methylbenzoic acid (6)



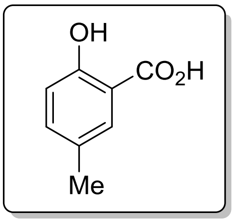
Following general procedure 1 with *o*-cresol (27.0 mg, 0.25 mmol) to obtain **6** as a white solid (29.1 mg, 77%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.91 (bs, 1H), 11.38 (bs, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 6.84 (app. t, *J* = 7.6 Hz, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 173.3, 161.5, 137.6, 128.9, 127.2, 119.5, 112.5, 15.7 ppm. These data are consistent with those previously reported.[41]

2-Hydroxy-4-methylbenzoic acid (17)



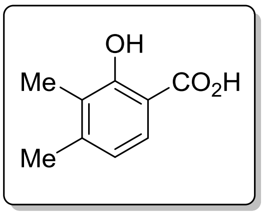
Following general procedure 1 with *m*-cresol (27.0 mg, 0.25 mmol) to obtain **17** (major:minor = 85:15) as white solid as a white solid (33.3 mg, 88%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.76 (d, *J* = 8.1 Hz, 1H) (major), 7.32 (dd, *J* = 8.2, 7.6 Hz, 0.13H) (minor), 6.79-6.75 (m, 2.26H) (major + minor), 2.58 (s, 0.35H) (minor), 2.33 (s, 3H) (major) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) Major:δ 172.7, 163.1, 148.0, 131.1, 121.1, 118.2, 110.5, 21.7 ppm. Minor: δ 174.1, 164.2, 142.5, 135.1, 123.4, 116.1, 113.1, 23.9 ppm. These data are consistent with those previously reported.[161, 162]

2-Hydroxy-4-methylbenzoic acid (18)



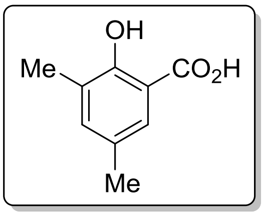
Following general procedure 1 with *p*-cresol (27.0 mg, 0.25 mmol) to obtain **18** as a white solid (27.6 mg, 73%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.69 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 2.28 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 171.8, 160.1, 136.8, 130.0, 128.2, 117.0, 111.8, 19.4 ppm. These data are consistent with those previously reported.[161]

2-hydroxy-3,4-dimethylbenzoic acid (19)



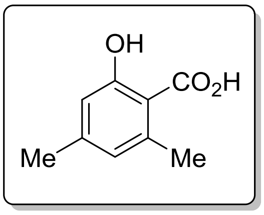
Following general procedure 1 with 2,3-dimethyphenol (30.5 mg, 0.25 mmol) to obtain **19** as a white solid (37.3 mg, 90%). mp: 192-193 °C. IR: 2914.7, 1640.8, 1620.4, 1456.1, 1245.3, 1090.0, 774.6, 686.2, 619.7 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.77 (bs, 1H), 11.44 (bs, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 173.4, 161.2, 146.2, 128.1, 125.2, 121.5, 110.3, 20.7, 11.3 ppm. HRMS: calcd for $C_9H_{10}O_3$, 166.0624 (M); found, 166.0625.

2-Hydroxy-3,5-dimethylbenzoic acid (20)



Following general procedure 1 with 2,4-dimethyphenol (30.5 mg, 0.25 mmol) to obtain **20** as a white solid (31.6 mg, 76%). mp: 181-182 °C. IR: 2920.1, 1655.5, 1452.4, 1290.7, 1221.7, 794.8, 546.1 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.81 (bs, 1H), 11.16 (s, 1H), 7.53 (s, 1H), 7.23 (s, 1H), 2.24 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 173.3, 159.7, 138.7, 128.5, 128.5, 127.0, 112.2, 20.5, 15.7 ppm. HRMS: calcd for $C_9H_{10}O_3$, 166.0624 (M); found, 166.0624.

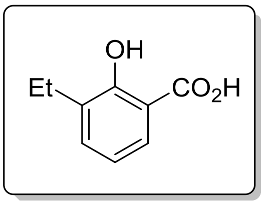
2-Hydroxy-4,6-dimethylbenzoic acid (21)



Following general procedure 1 with 3,5-dimethyphenol (30.5 mg, 0.25 mmol) to obtain **21** as a white solid (15.2 mg, 37%). mp: 166-167 °C.

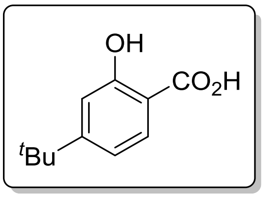
IR: 2923.5, 1641.3, 1619.7, 1543.8, 1257.4, 1200.0, 916.7, 840.7, 793.0, 763.1, 611.8, 574.1 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.96 (bs, 1H), 11.68 (s, 1H), 6.62 (s, 1H), 6.61 (s, 1H), 2.55 (s, 3H), 2.26 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 174.3, 164.8, 146.4, 142.6, 124.9, 116.5, 110.4, 24.1, 21.6 ppm. HRMS: calcd for $C_9H_{11}O_3$, 167.0708 (M+H$^+$); found, 167.0702.

2-Hydroxy-3-ethylbenzoic acid (22)



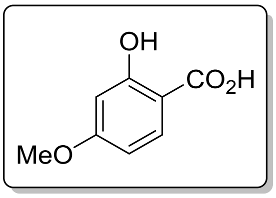
Following general procedure 1 with 2-ethylphenol (30.5 mg, 0.25 mmol) to obtain **22** as a white solid (31.6 mg, 76%). mp: 112-113 °C. IR: 2936.6, 1659.7, 1610.9, 1297.1, 1242.5, 1162.7, 884.6, 759.8, 698.9 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.49 (bs, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 6.87 (app. t, *J* = 7.6 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 173.4, 161.2, 136.1, 133.2, 129.0, 119.7, 112.7, 23.5, 14.4 ppm. HRMS: calcd for $C_9H_{10}O_3$, 166.0624 (M); found, 166.0619.

4-(*tert*-Butyl)-2-hydroxybenzoic acid (23)



Following general procedure 1 with 3-*tert*-butylphenol (37.6 mg, 0.25 mmol) to obtain **23** as a white solid (42.7 mg, 88%). mp: 139-140 °C. IR: 2960.9, 1655.6, 1616.5, 1445.1, 1199.0, 940.8, 787.7, 653.0, 604.1 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.14 (bs, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 1.32 (s, 9H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.7, 163.1, 161.1, 131.0, 117.7, 114.9, 110.7, 35.9, 31.3 ppm. HRMS: calcd for $C_{11}H_{14}O_3$, 194.0937 (M); found, 167.0932.

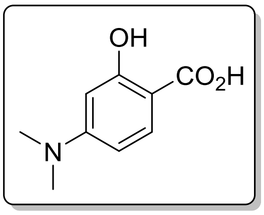
2-Hydroxy-4-methoxybenzoic acid (24)



Following general procedure 1 with 3-methoxyphenol (31.0 mg, 0.25 mmol) to obtain **24** as a white solid (33.5 mg, 80%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.79 (d, *J* = 8.8 Hz, 1H), 6.50 (dd, *J* = 8.8 Hz, *J* =

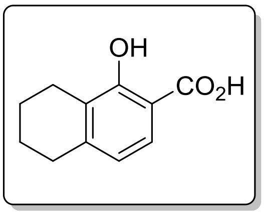
2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.6, 167.0, 165.4, 132.7, 108.1, 106.1, 101.6, 56.1 ppm. These data are consistent with those previously reported.[161]

4-(Dimethylamino)-2-hydroxybenzoic acid (25)



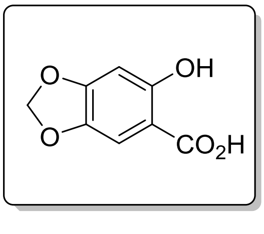
Following general procedure 1 with 3-(dimethylamino)phenol (34.3 mg, 0.25 mmol) to obtain **25** as a pink solid (28.0 mg, 62%). mp: 134-135 °C. IR: 2917.8, 2567.8, 1644.2, 1563.8, 1445.0, 1310.9, 1178.8, 894.8, 763.8, 687.4 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.22 (bs, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 6.31 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 6.09 (d, *J* = 2.4 Hz, 1H), 3.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.8, 164.8, 156.9, 132.2, 104.9, 101.0, 98.3, 40.0 ppm. HRMS: calcd for $C_9H_{12}O_3N$, 182.0812 (M+H$^+$); found, 182.0812.

1-Hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (26)



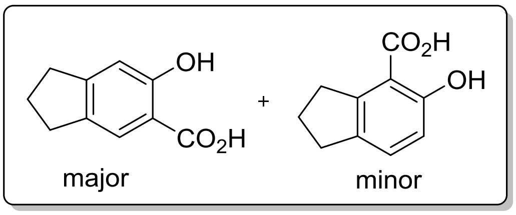
Following general procedure 1 with 5,6,7,8-tetrahydro-1-naphthol (37.1 mg, 0.25 mmol) to obtain **26** as a white solid (43.7 mg, 91%). mp: 164-165 °C. IR: 2933.7, 2858.8, 1654.8, 1620.1, 1454.3, 1252.7, 888.9, 770.8 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.73 (bs, 1H), 11.43 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 2.76-2.74 (m, 2H), 2.65-2.62 (m, 2H), 1.77-1.75 (m, 4H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 173.2, 161.3, 146.5, 127.4, 126.1, 120.6, 109.5, 30.6, 23.2, 23.1, 23.1 ppm. HRMS: calcd for $C_{11}H_{12}O_3$, 192.0781 (M); found, 192.0779.

6-hydroxybenzo[d][1,3]dioxole-5-carboxylic acid (27)



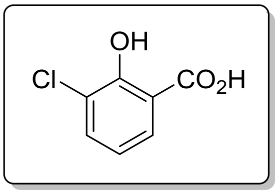
Following general procedure 1 with sesamol (34.5 mg, 0.25 mmol) to obtain **27** as a white solid (34.0 mg, 75%). mp: 208-209 °C. IR: 2928.1, 1638.9, 1614.0, 1440.4, 1195.6, 1125.1, 1037.1, 931.5, 855.3, 693.1 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 11.42 (bs, 1H), 7.20 (s, 1H), 6.46 (s, 1H), 6.05 (s, 2H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.7, 161.7, 155.2, 141.7, 107.8, 104.5, 103.1, 98.8 ppm. HRMS: calcd for $C_8H_6O_5$, 182.0210 (M); found, 182.0208.

6-Hydroxy-2,3-dihydro-1H-indene-5-carboxylic acid (28)



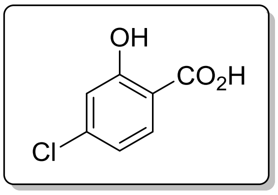
Following general procedure 1 with 5-indanol (33.5 mg, 0.25 mmol) to obtain **28** (major:minor = 79:21) as a white solid (41.0 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 0.26H) (minor), 10.39 (s, 1H) (major), 7.73 (s, 1H) (major), 7.35 (d, *J* = 8.3 Hz, 0.27H) (minor), 6.87 (s, 1H) (major), 6.82 (d, *J* = 8.3 Hz, 0.26H) (minor), 3.27 (t, *J* = 7.5 Hz, 0.57H) (minor), 2.93-2.84 (m, 4.57H) (major + minor), 2.13-2.05 (m, 2.53H) (major + minor) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) major + minor: δ 176.3, 175.6, 161.9, 161.6, 155.5, 148.2, 136.2, 135.7, 132.3, 125.7, 115.8, 113.4, 109.1, 108.9, 35.7, 33.7, 32.1, 31.7, 25.8, 25.2 ppm. These data are consistent with those previously reported.[41]

3-Chloro-2-hydroxybenzoic acid (29)



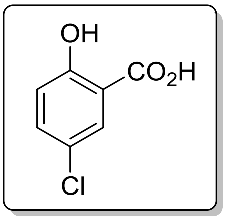
Following general procedure 2 with 2-chlorophenol (64.3 mg, 0.50 mmol) to obtain **29** as a white solid (47.3 mg, 55%). ^{1}H NMR (500 MHz, acetone-d6): δ ppm 7.88 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, acetone-d6): δ 172.6, 158.8, 136.8, 130.1, 122.5, 120.4, 115.0 ppm. These data are consistent with those previously reported.[41]

4-Chloro-2-hydroxybenzoic acid (30)



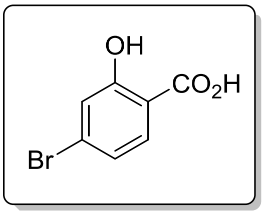
Following general procedure 2 with 3-chlorophenol (64.3 mg, 0.50 mmol) to obtain **30** as a white solid (58.3 mg, 68%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.90 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.98 (dd, *J* = 8.5, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 172.2, 163.8, 141.8, 132.8, 120.6, 118.1, 112.4 ppm. These data are consistent with those previously reported.[161]

5-chloro-2-hydroxybenzoic acid (31)

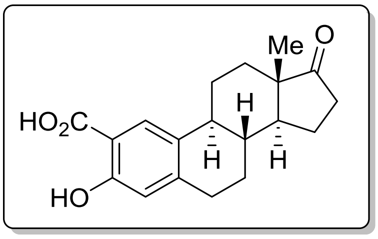


Following general procedure 2 with 4-chlorophenol (64.3 mg, 0.50 mmol) to obtain **31** as a white solid (49.3 mg, 57%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.72 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 171.6, 161.7, 136.5, 130.3, 124.1, 120.1, 114.5 ppm. These data are consistent with those previously reported.[161]

4-Bromo-2-hydroxybenzoic acid (32)



Following general procedure 2 with 3-bromophenol (86.5 mg, 0.50 mmol) to obtain **32** as a white solid (72.7 mg, 67%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.73 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 172.20, 163.52, 132.71, 130.19, 123.45, 121.11, 112.58 ppm. These data are consistent with those previously reported.[163]



Follow general procedure 2 with estrone (135.2 mg, 0.50 mmol) to obtain **34** as a white solid (49.8 mg, 51%). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 10.80 (s, 1H), 7.81 (s, 1H), 6.68 (s, 1H), 2.94-2.90 (m, 2H), 2.48-2.39 (m, 2H), 2.29-2.20 (m, 1H), 2.13-2.07 (m, 2H), 1.90-1.86 (m, 1H), 1.710-1.40 (m, 7H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, acetone-d$_6$) δ 219.3, 172.7, 160.8, 147.1, 132.3, 127.8, 117.5, 110.8, 51.1, 48.4, 44.5, 39.0, 36.1, 32.5, 30.3, 26.9, 26.6, 22.1, 14.1 ppm. These data are consistent with those previously reported.[41]

5.3 Experimental procedures for the synthesis of *m*-arylphenols

5.3.1 Tandem arylation/decarboxylation of salicylic acids - Chapter 3.2

General Procedure 3 To a vial containing salicylic acid derivative (0.50 mmol), PEPPSI-IPr catalyst (6.8 mg, 0.010 mmol), Ag_2CO_3 (69.0 mg, 0.25 mmol), K_2CO_3 (25.0 mg, 0.18 mmol), and aryl iodide (1.5 mmol, 3.0 equiv) was added AcOH (500 µL). The mixture was stirred at 150 °C for 16 h. After this time, the reaction mixture was cooled down and filtered through a small plug of Celite® with EtOAc (4 × 5 mL). The filtrate was evaporated to dryness and purified by column chromatography using hexanes:EtOAc (gradient from 100:0 to 90:10) as the eluent.

General Procedure 4 To a vial containing salicylic acid derivative (0.50 mmol), PEPPSI-IPr catalyst (2.3 mg, 3.3 µmol), Ag_2CO_3 (11.5 mg, 83 µmol), K_2CO_3 (25.0 mg, 0.18 mmol), and aryl iodide (0.167 mmol) was added AcOH (500 µL). The mixture was stirred at 130 °C for 16 h. After this time, the reaction mixture was cooled down and filtered through a small plug of Celite® with EtOAc (4 × 5 mL). The filtrate was evaporated to dryness and purified by column chromatography using hexanes:EtOAc (gradient from 100:0 to 90:10) as the eluent.

5.3.2 Ag-free arylation of salicylic acids - Chapter 3.2

General Procedure 5 To a mixture of $Pd(OAc)_2$ (5.6 mg, 25 µmol), salicylic acid derivative (0.50 mmol), Me_4NCl (68.5 mg, 0.63 mmol), KOAc (98.0 mg, 1.0 mmol) and 1-iodo-3,5-dimethylbenzene (218 µL, 1.5 mmol) was added AcOH (43 µL, 0.75 mmol). The mixture was was stirred at 120 °C for 24 h. Then, the mixture was cooled down to room temperature, extra Me_4NCl (44.0 mg, 0.4 mmol) and KOAc (39.0 mg, 0.4 mmol) were added into the mixture and heated at 120 °C for extra 16 h. After this time, the reaction mixture was filtered through a plug of Celite® with EtOAc (4 × 5 mL). The filtrate was evaporated to dryness. The crude product was purified by column chromatography.

5.3.3 One-pot *meta*-selective arylation of phenols - Chapter 3.3

General Procedure 6 To a mixture of the phenol substrate (0.50 mmol) and KOH (33.3 mg, 0.50 mmol) was added $PhCH_3$ (1.0 mL), the mixture was stirred at 50 °C for 10 min. After this time, $PhCH_3$ was removed in a stream of argon, the reaction flask was purged with CO_2, followed by stirring in an autoclave under 25 atm of CO_2 at 190 °C for 2 h. The reaction mixture was then cooled down to room temperature, and PEPPSI-IPr (2.3 mg, 3.3 µmol), Ag_2CO_3 (11.5 mg, 83 µmol), the iodoarene (0.167 mmol) and AcOH (400 µL) were added. The resulting slurry was heated at 130 °C for 16 h. After this time, the reaction mixture was filtered through a plug of Celite with EtOAc (3 × 5 mL). The filtrate was evaporated to dryness and purified by column chromatography.

General Procedure 7 To a mixture of the phenol substrate (0.50 mmol) and KOH (33.3 mg, 0.5 mmol) was added $PhCH_3$ (1.0 mL), the mixture was stirred at 50 °C for 10 min. After this time, $PhCH_3$ was removed in a stream of argon, the reaction flask was purged with CO_2, followed by stirring in an autoclave under 25 atm of CO_2 at 190 °C for 2 h. The reaction mixture was then cooled down to room temperature, and $Pd(OAc)_2$ (0.7 mg, 3.3 µmol), Ag_2CO_3 (11.5 mg, 83 µmol), the iodoarene (0.167 mmol) and AcOH (400 uL) were added. The resulting slurry was heated at 130 °C for 16 h. Then, a second addition of $Pd(OAc)_2$ (0.7 mg, 3.3 µmol) was added, heating the mixture at 130 °C for another 24 h. After this time, the reaction mixture was filtered through a plug of Celite with EtOAc (3 × 5 mL). The filtrate was evaporated to dryness and purified by column chromatography.

5.3.4 Tandem oxidation/arylation/decarboxylation of salicylaldehydes - Chapter 3.4

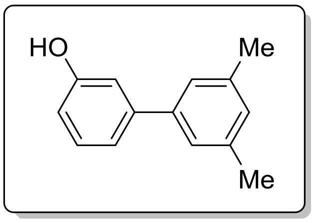
General Procedure 8 To a mixture of PEPPSI-IPr (8.5 mg, 13 µmol), Ag_2CO_3 (69.0 mg, 0.25 mmol), K_2CO_3 (69.0 mg, 0.50 mmol), salicylaldehyde (0.25 mmol) and iodoarene (0.75 mmol) was added AcOH (500 µL). The mixture was stirred at 150 °C for 16 h. After this time, the reaction mixture was cooled down to room temperature and filtered through a plug of

Celite® with EtOAc (4 × 5 mL). The filtrate was evaporated to dryness. The crude product was purified by column chromatography.

General Procedure 9 To a mixture of PEPPSI-IPr (6.8 mg, 10 μmol), Ag_2CO_3 (55.0 mg, 0.20 mmol), K_2CO_3 (55.0 mg, 0.40 mmol), salicylaldehyde (0.20 mmol) and iodoarene (0.60 mmol) was added AcOH (500 μL). The mixture was stirred at 150 °C for 16 h. After this time, the mixture was cooled down to room temperature and filtered through a plug of Celite® with EtOAc (4 × 5 mL). The filtrate was evaporated to dryness. The crude product was purified by column chromatography.

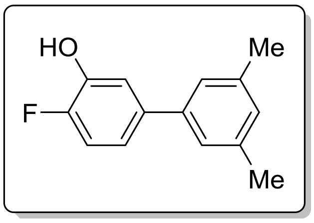
5.3.5 Characterisation of *meta*-arylphenols

3',5'-Dimethyl-[1,1'-biphenyl]-3-ol (37)



Following general procedure 3 to obtain **37** as a light orange oil (80.0 mg, 81%). The reaction following general procedure 5 afforded **37** in 60% yields (59.5 mg). The reaction following general procedure 6 afforded **37** in 65% yields (21.5 mg). The reaction following general procedure 8 afforded **37** in 60% yields (29.7 mg). IR: 3327, 2916, 1582, 1178, 846, 780 cm^{-1}. ^1H NMR (400 MHz, CDCl3) δ 7.29 (t, J = 7.9 Hz, 1H), 7.20 (s, 2H), 7.17-7.15 (m, 1H), 7.07-7.05 (m, 1H), 7.01 (s, 1H), 6.80 (ddd, J = 8.0, 2.6, 0.9 Hz, 1H), 4.76 (s, 1H), 2.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 155.7, 143.3, 140.8, 138.3, 129.9, 129.1, 125.1, 119.9, 114.1, 114.0, 21.4 ppm. HRMS: calcd for $C_{14}H_{15}O$, 199.1123 ($M+H^+$); found, 199.1117.

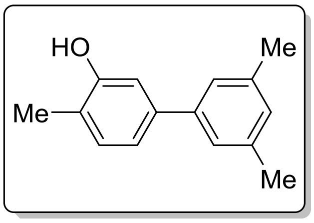
4-Fluoro-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (38)



Following general procedure 3 but with 1.0 mL of AcOH and heated at 160 °C to obtain **38** as a yellow oil (81.1 mg, 75%). The reaction following general procedure 7 afforded **38** in 68% yields (24.6 mg). The reaction following general procedure 8 afforded **38** in 60% yields (32.2 mg). IR: 3372, 2917, 1598, 1262, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ

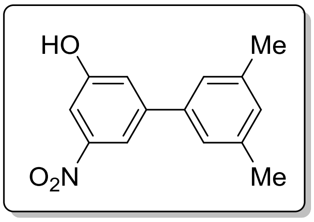
7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.15 (s, 2H), 7.14-7.09 (m, 1H), 7.06-7.04 (m, 1H), 6.99 (s, 1H), 5.17 (s, 1H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (d, *J* = 237.4 Hz), 143.5 (d, *J* = 14.6 Hz), 140.1, 138.7 (d, *J* = 3.6 Hz), 138.3, 129.1, 125.0, 119.5 (d, *J* = 6.4 Hz), 116.0 (d, *J* = 1.8 Hz), 115.5 (d, *J* = 18.3 Hz), 21.4 ppm. HRMS: calcd for $C_{14}H_{14}FO$, 217.1029 (M+H$^+$); found, 217.1021.

3',4,5'-Trimethyl-[1,1'-biphenyl]-3-ol (39)



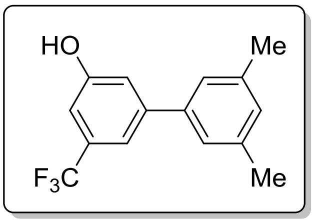
Following general procedure 3 but with 1.0 mL of AcOH and without adding K_2CO_3 to obtain **39** as an orange oil (75.3 mg, 71%). The reaction following general procedure 5 afforded **39** in 56% yields (59.0 mg). The reaction following general procedure 7 afforded **39** in 49% yields (17.3 mg). The reaction following the general procedure 9 afforded **39** in 42% yields (17.9 mg). IR: 3409, 2917, 1578, 1119, 808 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.16 (m, 3H), 7.08 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.01-7.00 (m, 1H), 6.98 (s, 1H), 4.69 (s, 1H), 2.37 (s, 6H), 2.29 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 140.8, 140.8, 138.2, 131.2, 128.8, 124.9, 122.5, 119.6, 113.7, 21.4, 15.4 ppm. HRMS: calcd for $C_{15}H_{17}O$, 213.1279 (M+H$^+$); found, 213.1275.

3',5'-dimethyl-5-nitro-[1,1'-biphenyl]-3-ol (40)



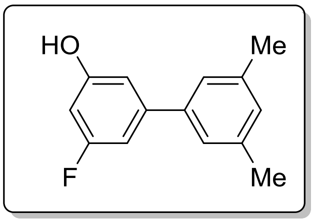
Following general procedure 3 to obtain **40** as a yellow solid (63.2 mg, 52%). mp: 147-148 °C. IR: 3424, 3092, 1591, 1343, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 2.0, 1.6 Hz, 1H), 7.64 (app. t, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.21 (s, 2H), 7.07(s, 1H), 5.36 (s, 1H), 2.40 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 149.5, 144.5, 138.8, 138.4, 130.3, 125.0, 120.3, 114.8, 108.9, 21.4 ppm. HRMS: calcd for $C_{14}H_{13}NO_3$, 243.0895 (M$^+$); found, 243.0890.

3',5'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-ol (41)



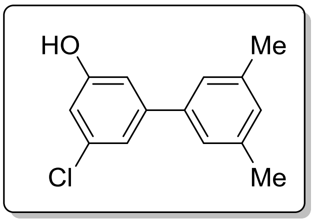
Following general procedure 3 to obtain **41** as a brownish red oil (89.0 mg, 67%). IR: 3350, 2918, 1599, 1120, 699 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.39 (m, 1H), 7.21-7.20 (m, 1H), 7.18 (s, 2H), 7.04 (s, 2H), 5.08 (s, 1H), 2.39 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.0, 144.2, 139.4, 138.6, 132.3 (q, *J* = 32.3 Hz), 129.8, 123.9 (q, *J* = 272.4 Hz), 125.0, 117.4, 116.6 (q, *J* = 3.9 Hz), 110.9 (q, *J* = 3.8 Hz), 21.3 ppm. HRMS: calcd for $C_{15}H_{13}F_3O$, 266.0918 (M$^+$); found, 266.0913.

5-fluoro-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (42)



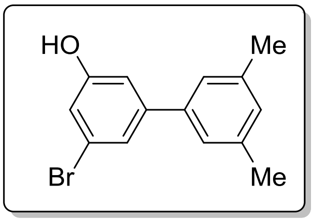
Following general procedure 3 to obtain **42** as a brownish orange solid (73.1 mg, 68%). The reaction following general procedure 8 afforded **42** in 50% yields (27.1 mg). mp: 95-96 °C. IR: 3375, 2917, 1620, 1126, 840cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16-7.15 (m, 2H), 7.02-7.01 (m, 1H), 6.87 (ddd, *J* = 9.8, 2.3, 1.5 Hz, 1H), 6.83-6.82 (m, 1H), 6.54 (dt, *J* = 9.8, 2.3 Hz, 1H), 4.90 (s, 1H), 2.37 (s, 6H) ppm. ^{13}C NMR(101 MHz, CDCl$_3$) δ 163.8 (d, *J* = 244.9 Hz), 156.8 (d, *J* = 12.0 Hz), 144.6 (d, *J* = 9.8 Hz), 139.7 (d, *J* = 2.6 Hz), 138.4, 129.7, 124.9, 109.9 (d, *J* = 2.7 Hz), 106.7 (d, *J* = 22.3 Hz), 101.8 (d, *J* = 24.9 Hz), 21.4 ppm. HRMS: calcd for $C_{14}H_{13}FO$, 216.0959 (M$^+$); found, 216.0945.

5-Chloro-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (43)



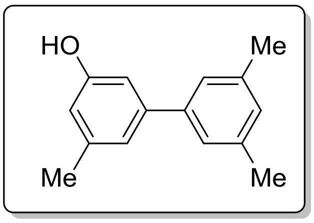
Following general procedure 3 but without adding K_2CO_3 and heated at 160 °C to obtain **43** as a light orange solid (73.3 mg, 63%). The reaction following general procedure 7 afforded **43** in 69% yields (26.7 mg). The reaction following general procedure 8 afforded **43** in 52% yields (30.0 mg). mp: 85-87 °C. IR: 3219, 2916, 1573, 832, 679 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.15-7.14 (m, 3H), 7.02 (s, 1H), 6.93-6.92 (m, 1H), 6.82-6.81 (m, 1H), 4.84 (s, 1H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.3, 144.4, 139.5, 138.4, 135.1, 129.7, 124.9, 120.1, 114.4, 112.6, 21.3 ppm. HRMS: calcd for $C_{14}H_{13}{}^{35}ClO$, 232.0655 (M^+); found, 232.0649.

5-Bromo-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (44)



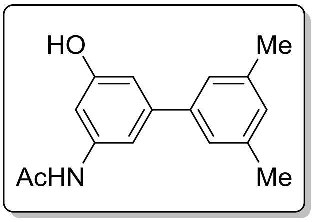
Following general procedure 3 to obtain **44** as a light yellow solid (92.5 mg, 67%). The reaction following general procedure 6 afforded **44** in 60% yields (27.6 mg). The reaction following general procedure 8 afforded **44** in 50% yields (34.6 mg). mp: 93-94 °C. IR: 3206, 2915, 1568, 830, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (app. t, J = 1.6 Hz, 1H), 7.15 (s, 2H), 7.02 (s, 1H), 6.97 (app. p, J = 2.3 Hz, 2H), 4.83 (s, 1H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 144.7, 139.4, 138.4, 129.7, 125.0, 123.0 (CH+C), 117.3, 113.1, 21.4 ppm. HRMS: calcd for $C_{14}H_{14}{}^{79}BrO$, 277.0228 ($M+H^+$); found, 277.0225.

3',5,5'-trimethyl-[1,1'-biphenyl]-3-ol (45)



Following general procedure 3 to obtain **45** as a light orange solid (75.2 mg, 71%). The reaction following general procedure 5 afforded **45** in 70% yields (74.0 mg). The reaction following general procedure 7 afforded **45** in 75% yields (26.5 mg). The reaction following general procedure 8 afforded **45** in 52% yields (27.7 mg). mp: 93-95 °C. IR: 3227, 2916, 1589, 1336, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H), 6.99-6.97 (m, 2H), 6.85-6.84 (m, 1H), 6.63 (s, 1H), 4.66 (s, 1H), 2.37 (s, 6H), 2.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 143.1, 140.9, 139.9, 138.2, 129.0, 125.0, 120.8, 114.8, 111.3, 21.44, 21.37 ppm. HRMS: calcd for $C_{15}H_{17}O$, 213.1279 ($M+H^+$); found, 213.1275.

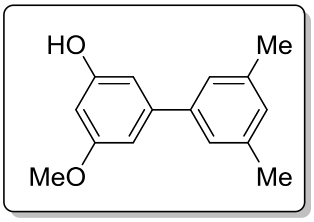
N-(5-hydroxy-3',5'-dimethyl-[1,1'-biphenyl]-3-yl)acetamide (46)



Following general procedure 3 but without adding K_2CO_3 to obtain **46** as a light brown solid (52 mg, 41%). mp: 238-240 °C. IR: 3355, 3098, 1746, 1626, 1656, 1592, 1552, 1268, 695 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 9.09 (s, 1H), 8.35 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 7.17 (s, 2H), 6.98 (s, 1H), 6.80-6.78 (m, 1H), 2.33 (s, 6H), 2.09 (s, 3H). ^{13}C

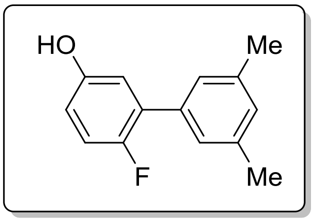
NMR (101 MHz, acetone-d_6) δ 168.9, 158.9, 143.7, 141.9, 141.9, 138.9, 129.8, 125.5, 109.9, 109.7, 106.1, 24.4, 21.4. HRMS: calcd for $C_{16}H_{17}NO_2$, 255.1259 (M^+); found, 255.1254.

5-Methoxy-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (47)



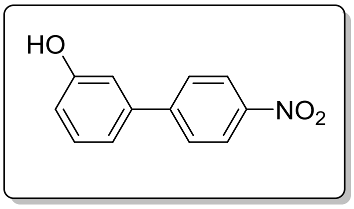
Following general procedure 3 but without adding K_2CO_3 to obtain **47** as a brownish orange oil (25.0 mg, 22%). The reaction following general procedure 6 afforded **47** in 25% yields (9.5 mg). The reaction following general procedure 8 afforded **47** in 21% yields (11.8 mg). IR: 3387, 2917, 1702, 1588, 1147, 834, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 7.00 (s, 1H), 6.71-6.70 (m, 1H), 6.65-6.64 (m, 1H), 6.39 (app. t, *J* = 2.3 Hz, 1H), 4.83 (s, 1H), 3.84 (s, 3H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 156.8, 144.1, 140.8, 138.2, 129.3, 125.0, 106.9, 105.7, 100.3, 55.4, 21.4. HRMS: calcd for $C_{15}H_{17}O_2$, 229.1229 ($M+H^+$); found, 229.1224.

6-fluoro-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (50)



Following general procedure 3 to obtain **50** as an orange solid (58.0 mg, 53%). mp: 53-54 °C. IR: 3352, 2916, 1420, 1204, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H), 7.03-6.98 (m, 2H), 6.89-6.86 (m, 1H), 6.76-6.72 (m, 1H), 4.70 (s, 1H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 (d, *J* = 239.9 Hz), 151.6 (d, *J* = 2.3 Hz), 138.1, 135.6 (d, *J* = 1.4 Hz), 130.3 (d, *J* = 15.5 Hz), 129.7, 126.9 (d, *J* = 2.9 Hz), 117.1 (d, *J* = 3.5 Hz), 116.9 (d, *J* = 25.1 Hz), 115.1 (d, *J* = 8.1 Hz), 21.5 ppm. HRMS: calcd for $C_{14}H_{13}FO$, 216.0950 (M^+); found, 216.0945.

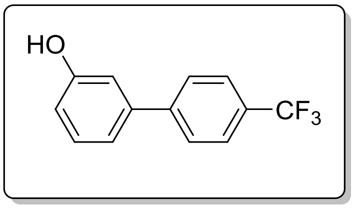
4'-Nitro-[1,1'-biphenyl]-3-ol (51)



Following general procedure 3 to obtain **51** as a yellow solid (64.5 mg, 60%). The reaction following general procedure 6 afforded **51** in 54% yields (19.4 mg). mp: 194-196 °C. IR: 3409, 3091, 1581, 785 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 8.61 (s, 1H), 8.36-8.32 (m, 2H), 7.94-7.91 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.27-7.23 (m, 2H), 6.98

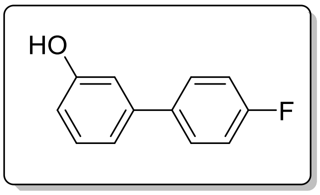
(ddd, *J* = 8.1, 2.4, 0.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 159.0, 148.3, 148.1, 141.0, 131.2, 128.7, 124.8, 119.5, 116.8, 115.0 ppm. HRMS: calcd for $C_{12}H_{10}NO_3$, 216.0661 (M+H$^+$); found, 216.0657.

4'-(trifluoromethyl)-[1,1'-biphenyl]-3-ol (52)



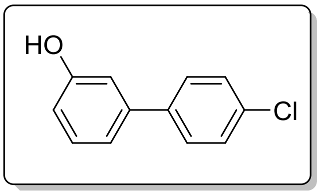
Following general procedure 3 to obtain **52** as a pale yellow solid (79.5 mg, 67%). The reaction following general procedure 8 afforded **52** in 51% yields (30.2 mg). mp: 73-75 °C. IR: 3261, 1573, 1322, 840 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73-7.68 (m, 4H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.21 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.11-7.10 (m, 1H), 6.91 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.91 (s, 1H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.0, 144.2, 141.6, 130.3, 129.6 (q, *J* = 32.5 Hz), 124.3 (q, *J* = 272.0 Hz), 127.4, 125.7 (q, *J* = 3.8 Hz), 119.9, 115.1, 114.3 ppm. HRMS: calcd for $C_{13}H_9F_3O$, 238.0605 (M$^+$); found, 238.0600.

4'-Fluoro-[1,1'-biphenyl]-3-ol (53)



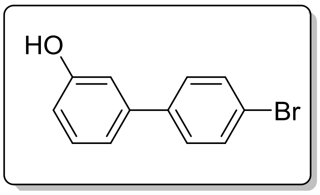
Following general procedure 3 to obtain **53** as an off white solid (64.9 mg, 69%). The reaction following general procedure 6 afforded **53** in 46% yields (14.5 mg). The reaction following general procedure 9 afforded **53** in 58% yields (21.9 mg). mp: 77-79 °C. IR: 3270, 1453, 1189, 832 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56-7.50 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.15-7.09 (m, 3H), 7.02-7.01 (m, 1H), 6.82 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.83 (bs, 1H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 162.6 (d, *J* = 246.6 Hz), 155.9, 142.1, 136.9 (d, *J* = 3.2 Hz), 130.1, 128.7, 128.6, 119.7, 115.6 (d, *J* = 21.4 Hz), 114.1 (d, *J* = 18.4 Hz) ppm. HRMS: calcd for $C_{12}H_{10}FO$, 189.0716 (M+H$^+$); found, 189.0710.

4'-Chloro-[1,1'-biphenyl]-3-ol (54)



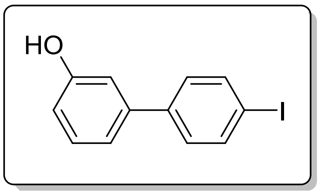
Following general procedure 3 to obtain **54** as a light orange solid (69.5 mg, 68%). The reaction following the general procedure 6 afforded **54** in 65% yields (22.1 mg). The reaction following the general procedure 9 afforded **54** in 50% yields (20.3 mg). mp: 47-48 °C. IR: 3245, 1587, 1197, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.41-7.38 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.13 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.03-7.02 (m, 1H), 6.83 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.85 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 141.8, 139.2, 133.6, 130.1, 128.9, 128.4, 119.6, 114.5, 114.0 ppm. HRMS: calcd for $C_{12}H_{10}{}^{35}ClO$, 205.0420 ($M+H^+$); found, 205.0412.

4'-Bromo-[1,1'-biphenyl]-3-ol (55)



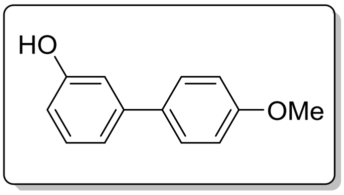
Following general procedure 3 to obtain **55** as a light orange solid (74.7 mg, 60%). The reaction following the general procedure 6 afforded **55** in 61% yields (25.3 mg). The reaction following the general procedure 9 afforded **55** in 53% yields (26.2 mg). mp: 86-88 °C. IR: 3246, 1470, 1197, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.45-7.42 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.13 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.03-7.02 (m, 1H), 6.83 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.79 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 141.9, 139.8, 132.0, 130.3, 128.8, 121.9, 119.7, 114.7, 114.1 ppm. HRMS: calcd for $C_{12}H_9{}^{79}BrO$, 247.9837 (M^+); found, 247.9828.

4'-iodo-[1,1'-biphenyl]-3-ol (56)



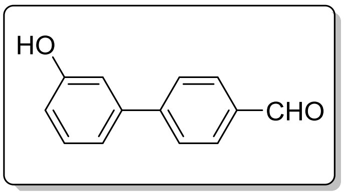
Following general procedure 3 to obtain **56** as an orange solid (59.2 mg, 40%). mp: 123-126 °C. IR: 3335, 1593, 1445, 1388, 1194, 1002, 878, 823, 780, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.33-7.29 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.02-7.01 (m, 1H), 6.83 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.84 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 141.9, 140.2, 137.9, 130.2, 129.0, 119.6, 114.6, 113.8, 93.3 ppm. HRMS: calcd for $C_{12}H_{10}IO$, 296.9776 ($M+H^+$); found, 296.9771.

4'-Methoxy-[1,1'-biphenyl]-3-ol (57)



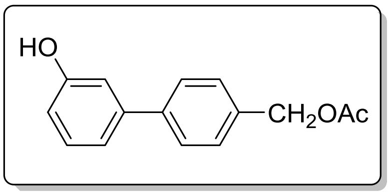
Following general procedure 4 to obtain **57** as an off white solid (27.7 mg, 83%). The reaction following the general procedure 6 afforded **57** in 64% yields (21.0 mg). The reaction following the general procedure 8 afforded **57** in 21% yields (10.6 mg). mp: 115-116 °C. IR: 3419, 2976, 1596, 1205, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.13 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.03-7.02 (m, 1H), 6.99-6.95 (m, 2H), 6.78 (ddd, *J* = 8.0, 2.5, 0.9 Hz, 1H), 4.78 (s, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 155.8, 142.6, 133.3, 129.9, 128.1, 119.4, 114.2, 113.7, 113.6, 55.4 ppm. HRMS: calcd for $C_{13}H_{13}O_2$, 201.0916 (M+H$^+$); found, 201.0910.

3'-Hydroxy-[1,1'-biphenyl]-4-carbaldehyde (58)



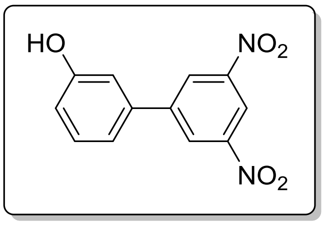
Following general procedure 4 to obtain **58** as a white solid (28.2 mg, 85%). The reaction following general procedure 6 afforded **58** in 50% yields (16.5 mg). mp: 173-175 °C. IR: 3214, 2840, 1669, 1584, 1562, 1303, 1199, 831, 783, 708 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.09 (s, 1H), 8.56 (s, 1H), 8.01-7.99 (m, 2H), 7.86-7.84 (m, 2H), 7.34 (app. t, *J* = 7.7 Hz, 1H), 7.23-7.19 (m, 2H), 6.94-6.91 (m, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 192.5, 158.9, 147.6, 142.0, 136.6, 131.1, 130.9, 128.4, 119.4, 116.4, 115.0 ppm. HRMS: calcd for $C_{13}H_{10}O_2$, 198.0681 (M$^+$); found, 198.0676.

(3'-Hydroxy-[1,1'-biphenyl]-4-yl)methyl acetate (59)



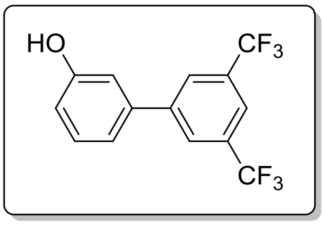
Following general procedure 4 to obtain **59** as an off white solid (32.3 mg, 80%). The reaction following general procedure 6 afforded **59** in 59% yields (23.8 mg). mp: 112-114 °C. IR: 3387, 1716, 1601, 1233, 911, 737 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 2H), 7.43-7.41 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.16-7.14 (m, 1H), 7.07-7.06 (m, 1H), 6.83 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 5.26 (s, 1H), 5.15 (s, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 156.0, 142.4, 140.9, 135.1, 130.0, 128.8, 127.3, 119.7, 114.4, 114.1, 66.1, 21.1 ppm. HRMS: calcd for $C_{15}H_{14}O_3$, 242.0943 (M^+); found, 242.0935.

3',5'-dinitro-[1,1'-biphenyl]-3-ol (60)



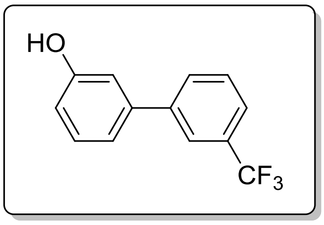
Following general procedure 3 to obtain **60** as a yellow solid (82.1 mg, 63%). mp: 208-210 °C. IR: 3440, 3076, 1522, 1336, 727 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ 8.93 (t, *J* = 2.1 Hz, 1H), 8.84 (d, *J* = 2.1 Hz, 2H), 8.70 (s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.38 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 7.34 (t, *J* = 2.0 Hz, 1H), 7.04 (ddd, *J* = 8.0, 2.4, 1.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 159.2, 150.0, 145.2, 138.9, 131.6, 127.6, 119.4, 117.8, 117.5, 115.0 ppm. HRMS: calcd for $C_{12}H_8N_2O_5$, 260.0433 (M^+); found, 260.0428.

3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-ol (61)



Following general procedure 3 to obtain **61** as a white solid (97.0 mg, 63%). The reaction following general procedure 8 afforded **61** in 42% yields (32.0 mg). mp: 93-94 °C. IR: 3296, 1378, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H), 7.86 (s, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.08 (t, *J* = 2.4 Hz, 1H), 6.92 (ddd, *J* = 8.1, 2.5, 0.8 Hz, 1H), 4.96 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 142.8, 140.0, 132.1 (q, *J* = 33.2 Hz), 130.6, 123.4 (q, *J* = 272.7 Hz), 127.2 (d, *J* = 2.7 Hz), 121.1 (dt, *J* = 7.8, 3.8 Hz), 119.8, 115.8, 114.2. HRMS: calcd for $C_{14}H_8F_6O$, 306.0479 (M^+); found, 306.0474.

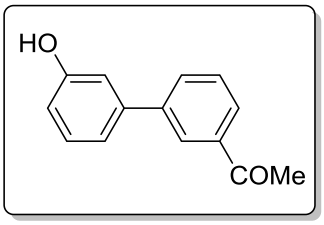
3'-(Trifluoromethyl)-[1,1'-biphenyl]-3-ol (62)



Following general procedure 3 to obtain **62** as an off white solid (80.9 mg, 68%). The reaction following general procedure 6 afforded **62** in 46% yields (18.3 mg). mp: 64-66 °C. IR: 3336, 1332, 1115, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75-7.73 (m, 1H), 7.62-7.53 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.08-7.07 (m, 1H), 6.87 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.85 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 141.5, 131.2 (q, *J* = 32.2 Hz), 130.4, 130.4, 130.3, 129.2, 124.2 (q, *J* = 272.4

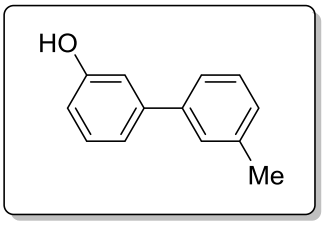
Hz), 124.2 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 3.8 Hz), 119.8, 115.0, 114.2 ppm. HRMS: calcd for $C_{13}H_9F_3O$, 238.0605 (M^+); found, 238.0597.

1-(3'-Hydroxy-[1,1'-biphenyl]-3-yl)ethanone (63)



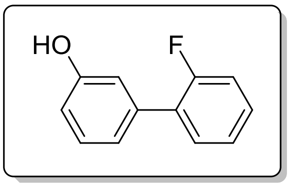
Following general procedure 4 to obtain **63** as a light orange oil (27.3 mg, 77%). The reaction following general procedure 6 afforded **63** in 56% yields (23.4 mg). IR: 3314, 1665, 1195, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (app. t, *J* = 1.6 Hz, 1H), 7.93 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H), 7.77 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.12-7.11 (m, 1H), 6.88 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 5.34 (s, 1H), 2.66 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 156.2, 141.9, 141.3, 137.6, 131.8, 130.2, 129.1, 127.5, 126.9, 119.7, 114.8, 114.2, 26.8 ppm. HRMS: calcd for $C_{14}H_{12}O_2$, 212.0837 (M^+); found, 212.0830.

3'-Methyl-[1,1'-biphenyl]-3-ol (64)



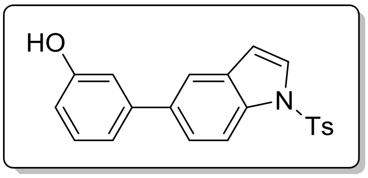
Following general procedure 3 to obtain **64** as an orange oil (50.6 mg, 55%). The reaction following general procedure 6 afforded **64** in 60% yields (18.3 mg). The reaction following the general procedure 8 afforded **64** in 51% yields (23.4 mg). IR: 3315, 2917, 1578, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 4H), 7.18-7.16 (m, 2H), 7.07-7.06 (m, 1H), 6.82 (ddd, *J* = 8.0, 2.6, 0.9 Hz, 1H), 4.84 (s, 1H), 2.42 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 143.2, 140.7, 138.4, 129.9, 128.7, 128.3, 127.9, 124.2, 119.8, 114.1, 114.1, 21.5 ppm. HRMS: calcd for $C_{13}H_{12}O$, 184.0888 (M^+); found, 184.0881.

2'-fluoro-[1,1'-biphenyl]-3-ol (66)



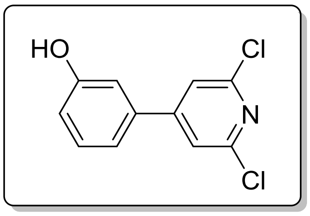
Following general procedure 3 to obtain **66** as a light brown solid (23.0 mg, 24%). mp: 99-101 °C. IR: 3222, 2926, 1571, 1584, 1180, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34-7.29 (m, 2H), 7.22-7.12 (m, 3H), 7.05-7.03 (m, 1H), 6.85 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 4.78 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7(d, *J* = 248.0 Hz), 155.5, 137.4, 130.7 (d, *J* = 3.4 Hz), 129.7, 129.1 (d, *J* = 8.3 Hz), 128.6 (d, *J* = 13.3 Hz), 124.3 (d, *J* = 3.7 Hz), 121.6 (d, *J* = 2.8 Hz), 116.2 (d, *J* = 17.6 Hz), 116.0 (d, *J* = 2.0 Hz), 114.7 ppm. HRMS: calcd for $C_{12}H_9FO$, 188.0637 (M^+); found, 188.0632.

3-(1-Tosyl-1*H*-indol-5-yl)phenol (67)



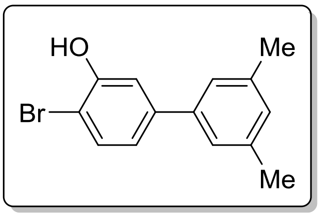
Following general procedure 3 to obtain **67** as a brown solid (54.5 mg, 30%). The reaction following general procedure 6 afforded **67** in 28% yields (16.7 mg). mp: 93-94 °C. IR: 3411, 3140, 1595, 1123, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.81-7.78 (m, 2H), 7.70-7.69 (m, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.51 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.24-7.22 (m, 2H), 7.16-7.14 (m, 1H), 7.07-7.05 (m, 1H), 6.80 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 6.69 (dd, *J* = 3.7, 0.7 Hz, 1H), 4.91 (s, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 145.1, 143.1, 136.3, 135.3, 134.3, 131.3, 130.0, 130.0, 127.0, 126.9, 124.1, 120.0, 119.8, 114.3, 114.0, 113.7, 109.3, 21.6 ppm. HRMS: calcd for $C_{21}H_{17}NO_3S$, 363.0929 (M^+); found, 363.0924.

3-(2,6-Dichloropyridin-4-yl)phenol (68)



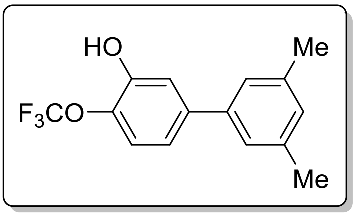
Following general procedure 3 to obtain **68** as a pale yellow solid (84.0 mg, 70%). The reaction following general procedure 6 afforded **68** in 48% yields (19.2 mg). mp: 103-106 °C. IR: 3534, 3267, 1580, 1528, 1170, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.17-7.15 (m, 1H), 7.06-7.05 (m, 1H), 6.95 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H) 5.01 (bs, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 153.7, 151.1, 137.4, 130.7, 120.9, 119.5, 117.3, 114.1 ppm. HRMS: calcd for $C_{11}H_7{}^{35}Cl_2NO$, 238.9905 (M^+); found, 238.9899.

4-Bromo-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (69)



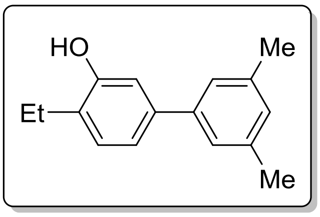
Following general procedure 7 to obtain **69** as a colourless oil (28.5 mg, 62%). The reaction following general procedure 9 afforded **69** in 51% yields (28.4 mg). IR. 3505, 2917, 1567, 1468, 1300, 1178, 1027, 848, 797 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.17 (s, 2H), 7.05-7.01 (m, 2H), 5.52 (s, 1H), 2.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 152.4, 143.0, 139.8, 138.4, 132.0, 129.5, 124.9, 120.7, 114.7, 109.0, 21.4 ppm. HRMS: calcd for $C_{14}H_{14}{}^{79}BrO$, 277.0228 (M+H$^+$); found, 277.0224.

3',5'-Dimethyl-4-(trifluoromethoxy)-[1,1'-biphenyl]-3-ol (70)



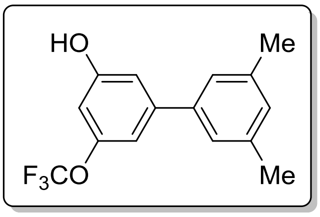
Following general procedure 7 to obtain **70** as colorless oil (39.2 mg, 83%). The reaction following general procedure 8 afforded **70** in 51% yields (35.9 mg). IR: 3195, 2921, 1595, 1204, 1160, 850, 827, 805, 788, 678 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28-7.25 (m, 2H), 7.17 (s, 2H), 7.12 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.01 (s, 1H), 5.54 (s, 1H), 2.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 147.8, 141.8, 139.7, 138.4, 135.7 (d, *J* = 1.5 Hz), 129.5, 125.0, 121.4 (d, *J* = 0.9 Hz), 120.81 (q, *J* = 258.9 Hz), 119.6, 116.0, 21.4 ppm. HRMS: calcd for $C_{15}H_{13}F_3O_2$, 282.0868 (M$^+$); found, 282.0861.

4-Ethyl-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (71)



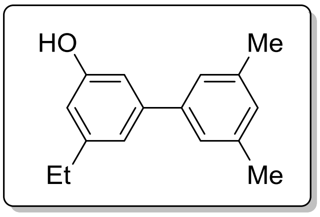
Following general procedure 7 to obtain **71** as an orange oil (17.5 mg, 46%). IR: 3527, 2965, 1401, 1168, 1121, 848, 819 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.19-7.17 (m, 3H), 7.11 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.99-6.98 (m, 2H), 4.68 (s, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 6H), 1.28 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.5, 140.7, 140.6, 138.2, 129.5, 128.8, 128.7, 124.9, 119.7, 113.9, 22.7, 21.4, 14.0 ppm. HRMS: calcd for $C_{16}H_{19}O$, 227.1436 (M+H$^+$); found, 227.1430.

3',5'-Dimethyl-5-(trifluoromethoxy)-[1,1'-biphenyl]-3-ol (72)



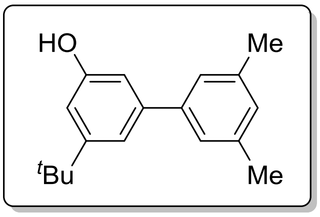
Following general procedure 6 to obtain **72** as a yellow oil (32.5 mg, 69%). IR: 3360, 2922, 1595, 1250, 1213, 1160, 843, 647 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.15 (s, 2H), 7.03 (s, 1H), 7.01 (s, 1H), 6.97-6.96 (m, 1H), 6.69 (s, 1H), 4.97 (bs, 1H), 2.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.6, 150.3, 144.6, 139.5, 138.5, 129.8, 125.0, 120.49 (q, *J* = 257.5 Hz), 112.6, 112.2, 107.0, 21.3 ppm. HRMS: calcd for $C_{15}H_{13}F_3O_2$, 282.0868 (M$^+$); found, 282.0866.

5-Ethyl-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (73)



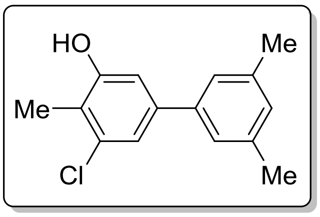
Following general procedure 7 to obtain **73** as an orange solid (25.3 mg, 67%). mp: 64-67 °C. IR: 3259, 2920, 1589, 1345, 845, 695 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (s, 2H), 6.99 (s, 2H), 6.88-6.84 (m, 1H), 6.66 (s, 1H), 4.66 (s, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 6H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.8, 146.46, 143.2, 141.0, 138.2, 129.0, 125.1, 119.6, 113.6, 111.5, 28.9, 21.4, 15.5 ppm. HRMS: calcd for $C_{16}H_{19}O$, 227.1436 (M+H$^+$); found, 227.1432.

5-(*tert*-Butyl)-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (74)



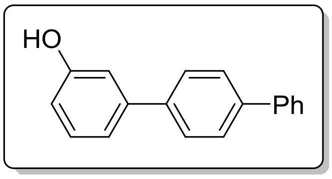
Following general procedure 7 to obtain **74** as an orange oil (32.5 mg, 77%). The reaction following general procedure 8 afforded **74** in 51% yields (32.6 mg). IR: 3272, 2960, 1590, 1179, 847, 702 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.17 (s, 2H), 7.16 (app. t, *J* = 1.6 Hz, 1H), 7.00 (s, 1H), 6.85 (m, 2H), 4.70 (s, 1H), 2.38 (s, 6H), 1.35 (s, 9H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.5, 153.5, 142.9, 141.5, 138.2, 129.0, 125.2, 117.2, 111.4, 111.3, 34.86, 31.4, 21.4 ppm. HRMS: calcd for $C_{18}H_{23}O$, 255.1749 (M+H$^+$); found, 255.1743.

5-Chloro-3',4,5'-trimethyl-[1,1'-biphenyl]-3-ol (75)



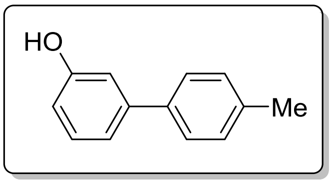
Following general procedure 7 to obtain **75** as a colorless oil (22.5 mg, 55%). The reaction following general procedure 8 afforded **75** in 53% yields (32.7 mg). IR: 3286, 2919, 1568, 1390, 1265, 1144, 1019, 810 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (app. d, *J* = 1.6 Hz, 1H), 7.14 (s, 2H), 7.00 (m, 1H), 6.90 (app. d, *J* = 1.6 Hz, 1 H), 4.88 (s, 1H), 2.37 (s, 6H), 2.33 (s, 3H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.6, 140.7, 139.5, 138.4, 135.6, 129.4, 124.7, 121.3, 120.4, 112.2, 21.4, 12.4 ppm. HRMS: calcd for $C_{15}H_{15}{}^{35}ClO$, 246.0811 (M^+); found, 246.0806.

[1,1':4',1''-terphenyl]-3-ol (76)



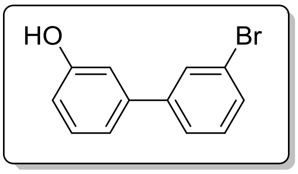
Following general procedure 6 to obtain 75 as a light brown solid (23.0 mg, 56%). mp: 228-229 °C. IR: 3489, 2917, 2849, 1595, 1164, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.62 (m, 6H), 7.48-7.45 (m, 2H), 7.39-7.31 (m, 2H), 7.24-7.21 (m, 1H), 7.12-7.11 (m, 1H), 6.84 (ddd, *J* = 8.0, 2.5, 0.8 Hz, 1H), 4.77 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 142.5, 140.7, 140.4, 139.6, 130.1, 128.8, 129.49, 127.46, 127.4, 127.1, 119.7, 114.3, 114.0 ppm. HRMS: calcd for $C_{18}H_{15}O$, 247.1123 ($M+H^+$); found, 247.1118.

4'-Methyl-[1,1'-biphenyl]-3-ol (96)



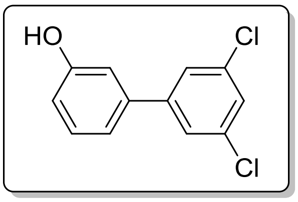
Following general procedure 8 to obtain **96** as a brownish solid (19.3 mg, 42%). IR: 3280.9, 2915.4, 1588.7, 1189.0, 772.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.05 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.80 (ddd, *J* = 8.0, 2.6, 0.9 Hz, 1H), 4.85 (s, 1H), 2.40 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 143.0, 137.9, 137.3, 130.0, 129.5, 127.0, 119.6, 113.9, 21.1 ppm. MS (EI): *m/z* (M^+), 184.0. These data are consistent with those previously reported.[50]

3'-bromo-[1,1'-biphenyl]-3-ol (97)



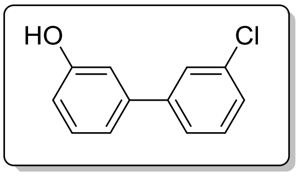
Following general procedure 9 to obtain **97** as a brownish oil (27.4 mg, 55%). IR: 3315.4, 1557.5, 1466.1, 1194.1, 771.9, 687.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.7 Hz, 1H), 7.50-7.47 (m, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.03-7.02 (m, 1H), 6.86-6.83 (m, 1H), 4.81 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 142.9, 141.5, 130.4, 130.3, 130.2, 130.2, 125.7, 122.9, 119.8, 114.8, 114.1 ppm. HRMS: calcd for $C_{12}H_{10}{}^{79}BrO$, 248.9915 ($M+H^+$); found, 248.9910.

3',5'-dichloro-[1,1'-biphenyl]-3-ol (98)



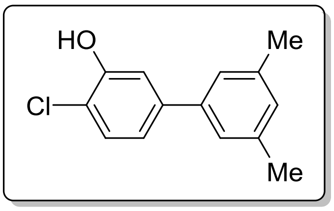
Following general procedure 8 to obtain **98** as an off white solid (28.5 mg, 48%). mp: 88-91 °C. IR: 3228.5, 1556.8, 1402.9, 1203.4, 768.6 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.9 Hz, 2H), 7.34-7.30 (m, 2H), 7.10 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 7.01-7.00 (m, 1H), 6.87 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.90 (s, 1H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 143.7, 140.3, 135.3, 130.3, 127.4, 125.7, 119.7, 115.4, 114.1.ppm. HRMS: calcd for $C_{14}H_9{}^{35}Cl_2O$, 237.9952 (M^+); found, 238.0025.

3'-Chloro-[1,1'-biphenyl]-3-ol (99)



Following general procedure 8 to obtain **99** as a brownish oil (34.5 mg, 67%). IR: 3324.9, 1564.2, 1196.2, 774.0, 688.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.55 (m, 1H), 7.44 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.38-7.30 (m, 3H), 7.14 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 7.04-7.03 (m, 1H), 6.84 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 4.79 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 142.6, 141.6, 134.7, 130.2, 130.0, 127.5, 127.3, 125.3, 119.8, 114.8, 114.1 ppm. HRMS: calcd for $C_{12}H_{10}{}^{35}ClO$, 205.0420 ($M+H^+$); found, 205.0415.

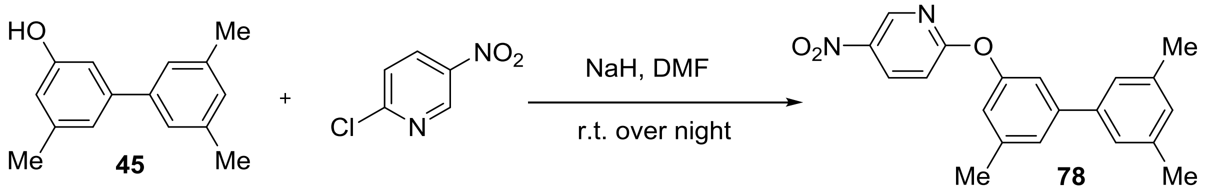
4-Chloro-3',5'-dimethyl-[1,1'-biphenyl]-3-ol (100)



Following general procedure 8 to obtain **100** as a light yellow solid (33.4 mg, 57%). mp: 32-35 °C. IR: 3517.5, 3025.9, 2916.7, 1571.8, 1201.4, 1179.8, 1045.2, 848.7, 807.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.17 (s, 2H), 7.09 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.01 (s, 1H), 5.54 (s, 1H) 2.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 142.1, 139.8, 138.4, 129.4, 129.0, 124.9, 120.2, 118.7, 114.8, 21.4 ppm. MS (EI): m/z (M+), 232.1.

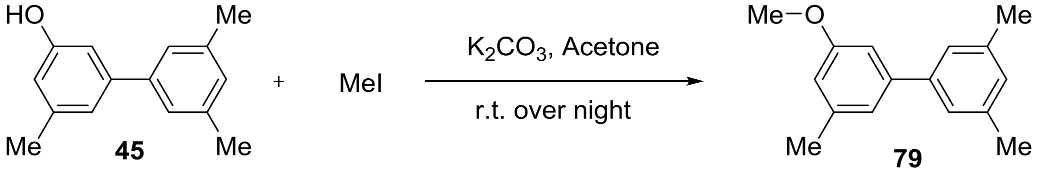
5.3.6 Experimental procedures for the synthesis of *meta*-biaryls - Chapter 3.3.4

Procedure to prepare 2-((3',5'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)-5-nitropyridine (78)[164]



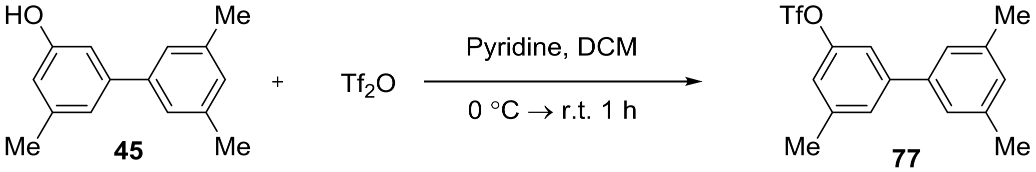
To a solution of **45** (53.1 mg, 0.25 mmol) in DMF (0.5 mL) was slowly added NaH (11 mg, 0.275 mmol, 60% dispersion in mineral oil) at 0 °C. After stirring the mixture for 30 min, 2-chloro-5-nitro-pyridine (40.0 mg, 0.25 mmol) was added into the solution, the mixture was then stirred room temperature for 16 h. After that time, the mixture was filtered through a plug of Celite® with EtOAc (4 × 5 mL), the filtrate was evaporated to dryness, the crude product was purified by column chromatography (Hexanes:EtOAc 85:15) to afford 2-((3',5'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)-5-nitropyridine (**78**) as a pale brownish solid (81.0 mg, 97%). mp: 93-95 °C. IR: 2916, 1569, 1347, 1300, 1259, 842, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 2.8 Hz, 1H), 8.47 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.33 (s, 1H), 7.19 (s, 2H), 7.16 (s, 1H), 7.04 (d, *J* = 9.1 Hz, 1H), 7.00 (s, 1H), 6.94 (s, 1H), 2.45 (s, 3H), 2.37 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 153.1, 145.2, 143.4, 140.4, 140.3, 140.2, 138.4, 134.9, 129.4, 125.7, 125.1, 120.5, 117.3, 111.2, 21.6, 21.4 ppm. HRMS: calcd for $C_{20}H_{19}N_2O_3$, 335.1396 (M+H$^+$); found, 335.1390.

Procedure to prepare 3-methoxy-3',5,5'-trimethyl-1,1'-biphenyl (79)[165]



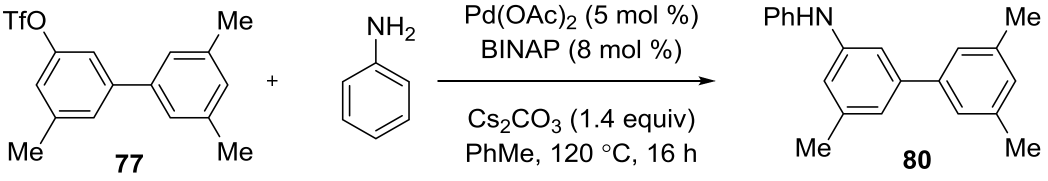
To a solution of **45** (21.2 mg, 0.10 mmol) in acetone (0.5 mL) was added K_2CO_3 (32 mg, 0.23 mmol). After stirring the mixture for 5 min, MeI (14 µL, 0.23 mmol) was added into the solution. The mixture was then stirred at room temperature for 16 h. After this time, the mixture was filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was evaporated to dryness, the crude product was purified by column chromatography (Hexanes) to afford 3-methoxy-3',5,5'-trimethyl-1,1'-biphenyl (**79**) as a colorless oil (21.7 mg, 96%). IR: 2918, 1590, 1461, 1262, 1152, 1064, 836, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 7.00 (s, 2H), 6.93 (s, 1H), 6.72 (s, 1H), 3.86 (s, 3H), 2.40 (s, 3H), 2.39 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 142.9, 141.3, 139.6, 138.2, 129.0, 125.1, 120.7, 113.5, 109.9, 55.3, 21.7, 21.4 ppm. HRMS: calcd for $C_{16}H_{19}O$, 227.1436 (M+H$^+$); found, 227.1430.

Procedure to prepare 3',5,5'-trimethyl-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (77).[166]



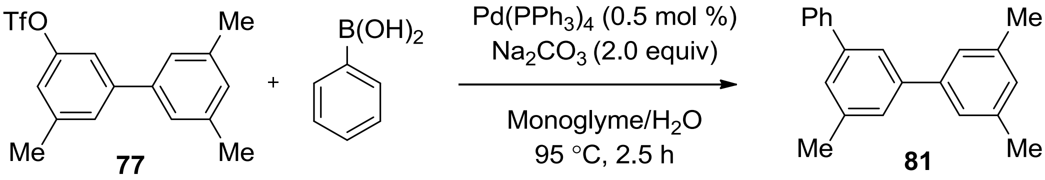
To a solution of **45** (254 mg, 1.2 mmol) and pyridine (195 µL, 2.4 mmol) in anhydrous DCM was dropwise added a solution of trifluoromethanesulfonic anhydride (245 µL, 1.44 mmol) in DCM (0.6 mL) at 0 °C. After complete addition, the mixture was warmed to room temperature and stirred for 1 h. The mixture as then filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was evaporated to dryness, the crude product was purified by column chromatography (Hexanes) to afford 3',5,5'-trimethyl-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (**77**) as a colorless oil (397 mg, 96%). IR: 2924, 1584, 1422, 1206, 1141, 959, 828, 691, 609 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.26 (s, 1H), 7.16 (s, 2H), 7.05 (s, 2H), 2.46 (s, 3H), 2.39 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 143.9, 140.9, 139.3, 138.6, 129.8, 127.9, 125.1, 120.1, 118.8 (d, J = 320.7 Hz), 117.0, 21.5, 21.4 ppm. HRMS: calcd for $C_{16}H_{19}F_3NO_3S$, 362.1038 (M+NH$_4^+$); found, 362.1032.

Procedure to prepare 3',5,5'-trimethyl-*N*-phenyl-[1,1'-biphenyl]-3-amine (80)[167]



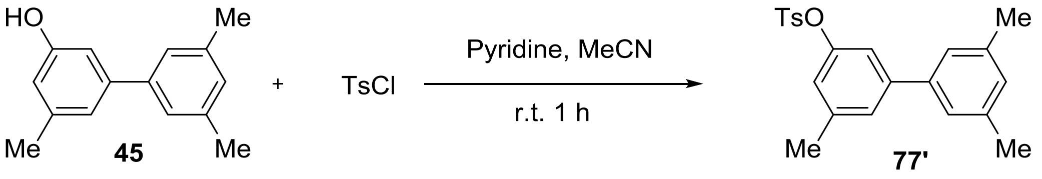
Under argon, to a solution of **45** (34.4 mg, 0.1 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 µmol), BINAP (5.0 mg, 8.0 µmol) and Cs_2CO_3 (45.6 mg, 0.14 mmol) in $PhCH_3$ (1.0 mL) was added aniline (11 µL, 0.12 mmol). The reaction mixture was stirred at 120 °C for 16 h. After this time, the mixture was filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was then evaporated to dryness and the crude product was purified by column chromatography (Hexanes:EtOAc 85:15) to afford 3',5,5'-trimethyl-N-phenyl-[1,1'-biphenyl]-3-amine **(80)** as a brown oil (27.6 mg, 96%). IR: 3394, 2916, 1586, 1494, 1348, 1235, 1030, 837, 741, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.18 (s, 2H), 7.12-7.10 (m, 3H), 6.99-6.98 (m, 2H), 6.96-6.92 (m, 1H), 6.88 (s, 1H), 5.72 (s, 1H), 2.37 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 143.3, 142.7, 141.3, 139.5, 138.2, 129.4, 128.9, 125.1, 121.1, 120.9, 117.9, 117.4, 114.0, 21.6, 21.4 ppm. HRMS: calcd for $C_{21}H_{22}N$, 288.1752 ($M+H^+$); found, 288.1747.

Procedure to prepare 3,5,5'-trimethyl-1,1':3',1''-terphenyl (81)[168]



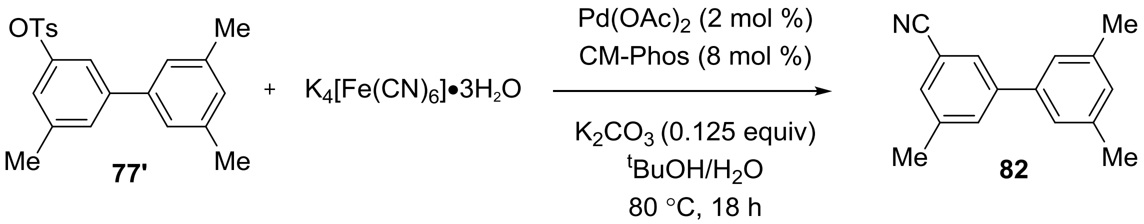
Under argon, To a mixture of $Pd(PPh_3)_4$ (0.6 mg, 0.5 µmol), **77** (34.4 mg, 0.1 mmol) and phenylboronic acid (13.7 mg, 0.112 mmol) in degased monoglyme (1.0 mL) was added a solution of Na_2CO_3 (21.2 mg, 0.2 mmol) in degased H_2O (1.0 mL). The reaction mixture was then stirred at 95 °C for 2.5 h. After this time, the mixture was filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was then evaporated to dryness and the crude product was purified by column chromatography (Hexanes) to afford 3,5,5'-trimethyl-1,1':3',1''-terphenyl **(81)** as a colourless oil (26.3 mg, 97%). IR: 3030, 2917, 1560, 1459, 1032, 844, 761, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.59 (s, 1H), 7.47-7.43 (m, 2H), 7.38-7.33 (m, 3H), 7.26-7.25 (m, 2H), 7.01 (s, 1H), 2.48 (s, 3H), 2.39 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 141.7, 141.5, 141.4, 138.7, 138.3, 129.0, 128.8, 127.3, 127.3, 127.0, 126.9, 125.2, 123.5, 21.6, 21.5 ppm. HRMS: calcd for $C_{21}H_{21}$, 273.1643 ($M+H^+$); found, 273.1638.

Procedure to prepare 3',5,5'-trimethyl-[1,1'-biphenyl]-3-yl 4-methylbenzenesulfonate (77’)



To a solution of **45** (42.4 mg, 0.2 mmol) and *p*-Toluenesulfonyl chloride (41.9 mg, 0.22 mmol) in MeCN (1.0 mL) was slowly added Et_3N (31 µL, 0.22 mmol). The reaction mixture was stirred at room temperature for 1 h. After this time, the mixture was filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was then evaporated to dryness and the crude product was purified by column chromatography (Hexanes) to 3',5,5'-trimethyl-[1,1'-biphenyl]-3-yl 4-methylbenzenesulfonate **(77’)** as a colourless oil (69.5 mg, 95%). IR: 1598, 1358, 1189, 1178, 965, 862, 847, 790, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 7.00 (s, 2H), 6.98 (s, 1H), 6.87 (s, 1H), 6.84 (s, 1H), 2.47 (s, 3H), 2.35 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 145.2, 142.8, 140.0, 139.8, 138.3, 132.7, 129.7, 129.4, 128.7, 126.6, 125.0, 121.6, 118.0, 21.7, 21.4, 21.4 ppm. HRMS: calcd for $C_{22}H_{26}NO_3S$, 384.1633 (M+NH_4^+); found, 384.1628.

Procedure to prepare 3',5,5'-trimethyl-[1,1'-biphenyl]-3-carbonitrile (82)[169]

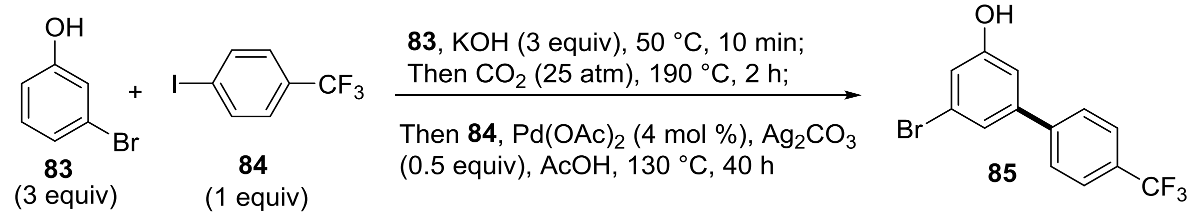


Under argon, to a vial containing a mixture of $Pd(OAc)_2$ (0.45 mg, 2.0 µmol) and CM-Phos (3.2 mg, 8.0 µmol) in degased anhydrous DCM (0.5 mL) was added Et_3N (0.1 µL). After stirring the mixture at 50 °C for 5 min, DCM was removed under vacuum. **77’** (34.4 mg, 0.1 mmol), K_2CO_3 (1.7 mg, 0.0125 mmol) and $K_4[Fe(CN)_6]\cdot H_2O$ (21.1 mg, 0.05 mmol) were then charged successively to the vial, degased ^{t}BuOH (0.25 µL) and degased of H_2O (0.25 µL) were added as solvent. The reaction mixture was stirred at 80 °C for 18 h. After this time, the mixture was filtered through a small plug of silica with EtOAc (4 × 5 mL), the filtrate was then evaporated to dryness and the crude product was purified by column chromatography

(Hexanes:EtOAc 85:15) to afford 3',5,5'-trimethyl-[1,1'-biphenyl]-3-carbonitrile **(82)** as an offwhite solid (21.0 mg, 95%). mp: 68-70 °C. IR: 2919, 2227, 1598, 1453, 1376, 840, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.52 (s, 1H), 7.34 (s, 1H), 7.08 (s, 2H), 6.97 (s, 1H), 2.37 (s, 3H), 2.31 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 139.5, 139.1, 138.7, 132.4, 130.9, 129.9, 128.0, 125.0, 119.1, 112.6, 21.4, 21.3 ppm. HRMS: calcd for $C_{16}H_{16}N$, 222.1283 ($M+H^+$); found, 222.1277.

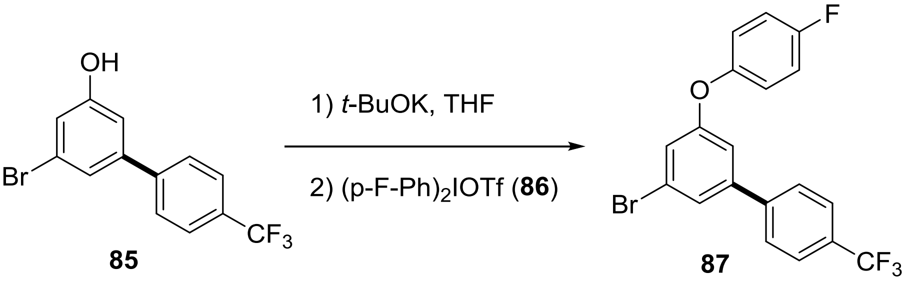
5.3.7 Experimental procedures for the synthesis of ϒ-secretase inhibitor - Chapter 3.3.4

Preparation of 5-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-ol (85)



Following general procedure 7 with 3-bromophenol **83** (260 mg, 1.5 mmol) and 4-iodobenzotrifluoride **84** (74.0 µL, 0.50 mmol) to obtained 5-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-ol (**85**) as a pale yellow solid (102 mg, 64%). mp: 89-91 °C. IR: 3256, 1576, 1328, 1114, 834 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.32 (t, *J* = 1.5 Hz, 1H), 7.06-7.05 (m, 1H), 6.99-6.98 (m, 1H), 4.93 (s, 1H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 156.6, 143.0, 142.8, 130.2 (q, *J* = 32.7 Hz), 127.4, 125.9 (dd, *J* = 7.3, 3.6 Hz), 124.1 (q, *J* = 272.2 Hz), 123.4, 123.1, 118.4, 113.3 ppm. HRMS: calcd for $C_{13}H_{9}{}^{79}BrF_{3}O$, 316.9789 (M+H^{+}); found, 316.9782.

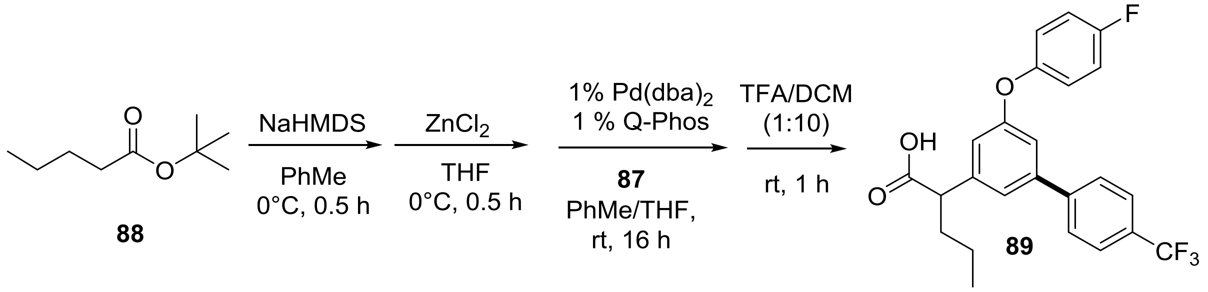
Preparation of 3-bromo-5-(4-fluorophenoxy)-4'-(trifluoromethyl)-1,1'-biphenyl (87)



Under argon, **85** (95.0 mg, 0.30 mmol) was charged into a dry vial, a suspension of *t*-BuOK (38.4 mg, 0.33 mmol) in THF (1.5 mL) was added into the vial at 0 °C and the reaction mixture was stirred at 0 °C for 15 min, bis(4-fluorophenyl)iodonium triflate **86** (168 mg, 0.36 mmol) was then added and the reaction mixture was stirred at 40 °C for 16 h. After this time, the mixture was evaporated to dryness and the crude was purified by flash chromatography (hexanes) to give 3-bromo-5-(4-fluorophenoxy)-4'-(trifluoromethyl)-1,1'-biphenyl (**87**) as a colorless oil (92 mg, 75%). IR: 2935, 2362, 1710, 1503, 1328, 1207, 839 cm^{-1}. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.45 (t, *J* = 1.6 Hz, 1H), 7.13-7.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (d, *J* = 239.5 Hz), 159.2, 151.7, 143.0, 142.6, 130.3 (q, *J* = 32.6 Hz), 127.4, 125.9 (q, *J* = 3.8 Hz), 124.9, 124.1 (q, *J* = 272.1 Hz), 123.5, 121.3 (d, *J* = 8.4 Hz), 120.4, 116.7 (d, *J* = 23.4 Hz), 115.6 ppm. HRMS: calcd for $C_{19}H_{12}{}^{79}BrF_4O$, 411.0002 ($M+H^+$); found, 411.0003.

Preparation of 2-(5-(4-fluorophenoxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)pentanoic acid (89)



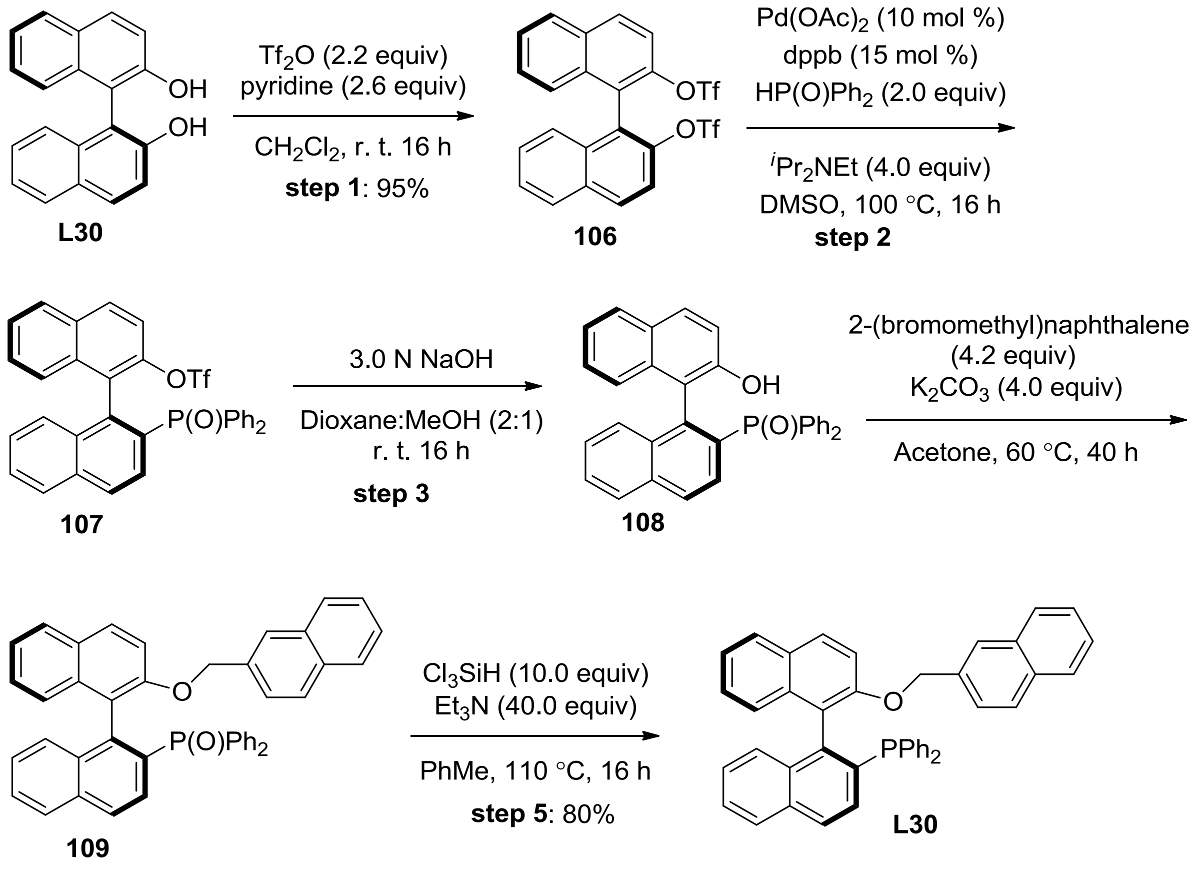
Under argon, NaHMDS (0.6 M in PhMe, 217 µL, 0.13 mmol) was charged into a well-flamed dried vial, *tert*-butyl pentanoate **88** (21.0 µL, 0.11 mol) was then added dropwise into the vial at 0 °C and the resulting mixture was stirred at 0°C for 0.5 h. To this suspension of sodium enolate was then added a solution of $ZnCl_2$ (1.0 M in THF, 260 µL, 0.26 mmol) and the resulting mixture was stirred at 0 °C for 0.5 h. To the suspension of zinc enolate, a solution of **87** (41.1 mg, 0.10 mmol), $Pd(dba)_2$ (0.6 mg, 0.1 µmol) and Q-phos (0.7 mg, 0.1 µmol) in $PhCH_3$ (0.5 mL) was added. The reaction mixture was stirred at room temperature for 16 h. After this time, the solvent of this mixture was evaporated and TFA/DCM (1:10, 1.0 mL) was added, followed by stirring at room temperature for 1 h. After this time, the reaction mixture was filtered through a plug of Celite with EtOAc (3 x 5 mL). The filtrate was evaporated to dryness and purified by chromatography (hexanes to hexanes:EtOAc 50:50) to afford 2-(5-(4-fluorophenoxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)pentanoic acid (**89**) as a light yellow solid (37.0 mg, 86%). mp: 112-115 °C. IR: 1561, 1499, 1323, 1200, 1123, 924, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (bs, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 1H), 7.07-7.02 (m, 6H), 3.62 (t, *J* = 7.7 Hz, 1H), 2.14-2.05 (m, 1H), 1.86-1.77 (m, 1H), 1.41-1.30 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 159.1 (d, *J* = 242.4 Hz), 158.5, 152.3, 143.7, 141.9, 141.3, 129.9 (q, *J* = 32.6 Hz), 127.5, 125.8 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.1 Hz), 121.8, 120.8 (d, *J* = 8.3 Hz), 117.6, 116.5 (d, *J* =

23.4 Hz), 115.8, 51.3, 35.2, 20.7, 13.8 ppm. HRMS: calcd for $C_{24}H_{21}F_4O_3$, 433.1427 ($M+H^+$); found, 433.1419.

5.4 Experimental procedures for enantioselective C–H arylation of fluorobenzene chromium complex - Chapter 4

5.4.1 Experimental procedures for the synthesis of chiral phosphine ligands

Preparation of (*S*)-(2'-(naphthalen-2-ylmethoxy)-[1,1'-binaphthalen]-2-yl)diphenyl phosphane (L30)[170]



(*S*)-[1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (106). Under argon, pyridine (2.1 mL, 26 mmol, 2.6 equiv) was added into a solution of (*S*)-BINOL **L16** (2.94 g, 10 mmol, 1.0 equiv) in 100 mL of dry CH_2Cl_2. After stirring 5 minutes, the solution was cooled to 0 °C. Then Tf_2O (3.7 mL, 22 mmol, 2.2 equiv) was added slowly and the reaction mixture was stirred at room temperature for 16 h. After this time, the mixture was filtered through a pad of silica gel using EtOAc/hexane (1:30) as eluent. Concentrate of the filtrate afforded **106** as a white solid (5.2 g, 9.5 mmol, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.1 Hz, 2H), 8.01

(d, *J* = 8.2 Hz, 2H), 7.63-7.57 (m, 4H), 7.44-7.40 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 133.1, 132.3, 132.0, 128.4, 128.0, 127.3, 126.8, 123.5, 119.4, 118.1 (*q*, $J_{C\text{–}F}$ = 320.2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.6 ppm. MS (EI): m/z ($M+NH_4^+$) 568.1. The product **106** was previously reported.[182]

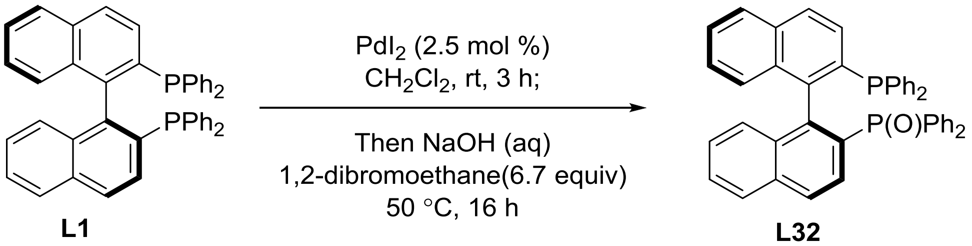
(*S*)-2'-(diphenylphosphoryl)-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (107). Under argon, to a solution of **106** (825 mg, 1.5 mmol, 1.0 equiv), diphenylphosphine oxide (606.6 mg, 3.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol, 10 mol %) and dppb (96.0 mg, 0.23 mmol, 10 mol %) in dry DMSO (7.0 mL) was added dry $^iPr_2NEt$ (1.1 mL, 6.0 mmol, 4.0 equiv), The reaction mixture was stirred at room temperature for 20 min and then at 110 °C for 16 h. After this time, the reaction mixture was cooled down to room temperature and 30 mL of H_2O was added. The resulting solution was extracted with Et_2O (3 x 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **107** (540 mg). The product **107** was was directly used in the next step without further purification. ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.1 ppm. These data consistent with those previously reported.[182]

(*S*)-(2'-(naphthalen-2-ylmethoxy)-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide (109). To a solution of **107** (482 mg, 0.8 mmol, 1.0 equiv) in dioxane/methanol (2:1, 7.0 mL) at 0 °C was added 2.5 mL of 3.0 N NaOH (aq.). The resulting mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting mixture was diluted with EtOAc (20 mL) and H_2O (10 mL), concentrated HCl was then slowly added to adjust the pH to ~3 at 0 °C. The resulting solution was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to afford crude **108** (300 mg). Then, a mixture of **108** (300 mg, 0.63 mmol, 1.0 equiv) and K_2CO_3 (331.8 mg, 2.4 mmol, 4.0 equiv) was dissolved in analytical-grade acetone (30 mL), 1-(bromomethyl)naphthalene (535 mg, 2.4 mmol, 4.0 equiv) was then added, the mixture was then heated at 60 °C for 40 h. After this time, the mixture was cooled to room temperature, and then filtered through Celite with Et_2O (3 x 10 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (EtOAc/hexane 2:1) to afford **109** as a white foam (210 mg, 0.35

mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.02 (m, 2H), 7.97-7.92 (m, 1H), 7.80-7.78 (m, 1H), 7.69-7.59 (m, 4H), 7.56-7.44 (m, 5H), 7.33-7.23 (m, 7H), 7.17-7.05 (m, 6H), 6.98-6.91 (m, 3H), 5.16-5.10 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 140.8 (d, *J* = 8.6 Hz), 135.0 (d, *J* = 2.2 Hz), 134.9, 134.2, 133.8, 133.3 (d, *J* = 11.7 Hz), 133.1, 132.7, 132.1, 132.0 (d, *J* = 9.7 Hz), 131.3 (d, *J* = 9.9 Hz), 131.1 (d, *J* = 2.7 Hz), 130.8, 130.7 (d, *J* = 2.8 Hz), 130.5, 129.8, 129.2 (d, *J* = 11.2 Hz), 128.6, 128.1 (d, *J* = 6.0 Hz), 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0, 126.3, 126.1, 125.8, 125.7, 125.3, 124.5, 123.5, 120.6 (d, *J* = 4.8 Hz), 113.7, 70.1 ppm. Some doublets due to C-P couplings can not be assigned due to complexity of the spectrum and they are listed as singlets. ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2 ppm. HRMS: calcd for $C_{43}H_{32}O_2P$, 611.2140 (M+H$^+$); found, 611.2145.

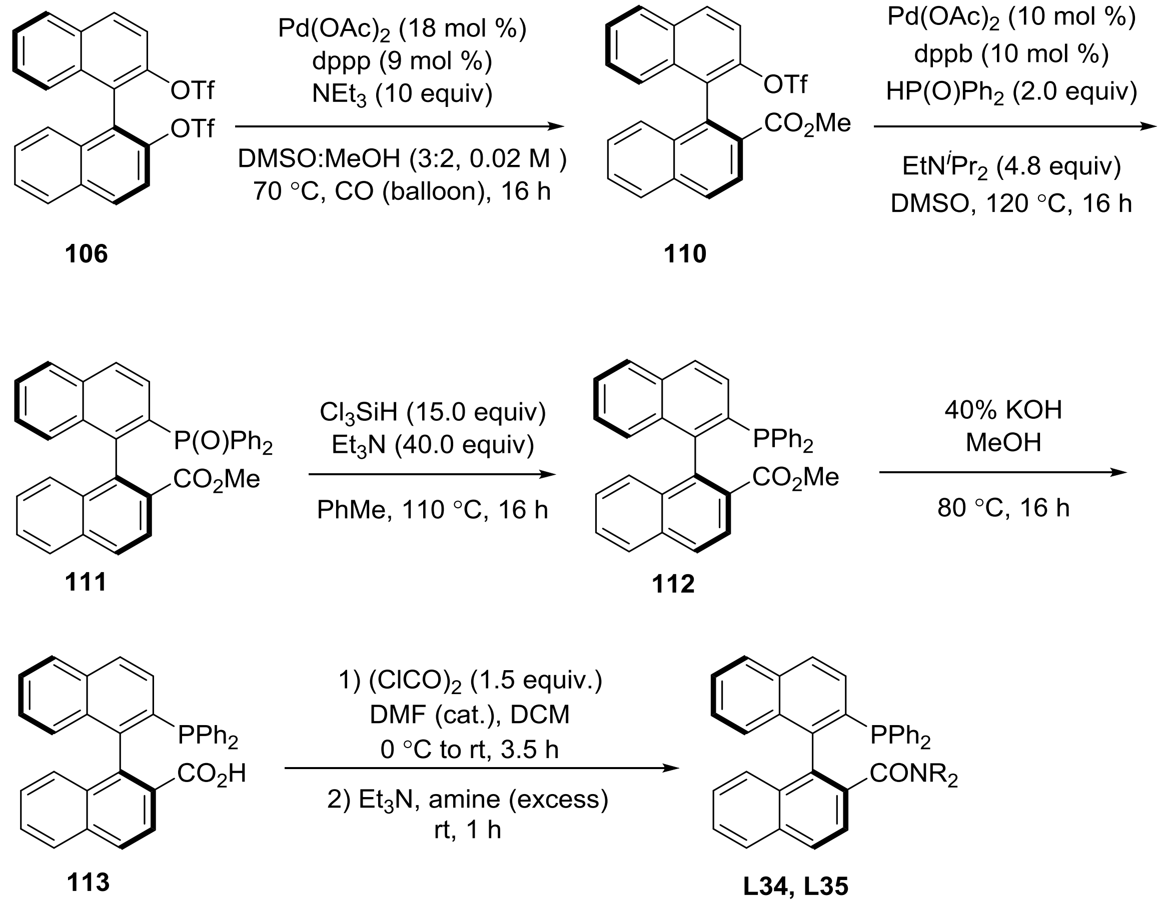
(*S*)-(2'-(naphthalen-2-ylmethoxy)-[1,1'-binaphthalen]-2-yl)diphenyl phosphane (L30). To a solution of **109** (120 mg, 0.16 mmol, 1.0 equiv), Et_3N (0.80 mL, 6.4 mmol, 40.0 equiv) in dry PhMe (3.2 mL) was slowly added trichlorosilane (0.16 mL, 1.6 mmol, 10 equiv) at 0 °C. The reaction mixture was stirred at rroom temperature for 30 min and then stirred at 110 °C for 16 h. After this time, the mixture was cooled down to room temperature and filtered through a pad of silica, the filtrate was concentrated and the resulting residue was purified by flash chromatography (Et_2O/hexane 1:10) to afford **L30** as white foam (95 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 3H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.76-7.74 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.54-7.47 (m, 2H), 7.47-7.40 (m, 3H), 7.35-7.33 (m, 2H), 7.31-7.25 (m, 3H), 7.22-7.09 (m, 9H), 7.02-6.98 (m, 4H), 5.08 (d, *J* = 13.1 Hz, 1H), 4.89 (d, *J* = 13.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (d, *J* = 1.9 Hz), 141.4, 141.1, 137.0 (d, *J* = 10.4 Hz), 136.8 (d, *J* = 9.9 Hz), 134.9 (d, *J* = 10.0 Hz), 134.0, 133.1 (d, *J* = 2.1 Hz), 132.7, 132.7, 132.5, 132.4, 132.2, 132.1, 132.1, 131.6, 129.3 (d, *J* = 1.7 Hz), 127.8, 127.1 (d, *J* = 2.8 Hz), 127.0, 126.9, 126.9, 126.8 (d, *J* = 1.1 Hz), 126.7, 126.6, 126.5, 125.8 (d, *J* = 2.6 Hz), 125.7, 125.3, 124.9, 124.6, 124.4, 123.9, 123.2, 122.5, 121.8 (d, *J* = 9.0 Hz), 113.3, 68.9 ppm. Some doublets due to C-P couplings can not be assigned due to complexity of the spectrum and they are listed as singlets. ^{31}P NMR (162 MHz, $CDCl_3$) δ -13.4 ppm. HRMS: calcd for $C_{43}H_{32}OP$, 595.2191 (M+H$^+$); found, 595.2157. Specific rotation: $[\alpha]_D$ (25.4 °C) = -135.9° (c = 0.05, CH_2Cl_2).

Preparation of *S*-BINAP(O) (L32)[171]



Under argon, to a dry Schlenk flask containing PdI_2 (3.7 mg, 0.010 mmol, 2.5 mol %) and (*S*)-BINAP (250 mg, 0.40 mmol, 1.0 equiv) was added 2.5 mL of dry CH_2Cl_2. The mixture was then stirred at room temperature for 3 h until PdI_2 was dissolved completely. A aqueous solution of NaOH (0.23 g, 5.75 mmol in 1.5 mL of H_2O) was then added, followed by 1,2-dibromoethane (0.50 g, 2.66 mmol, 6.7 equiv). The resulting mixture was stirred at 50 °C for 16 h. After this time, the mixture was cooled down and 20% H_3PO_4 solution was added to adjust the pH to ~4, followed by adding dppe (10 mg) and stirred at room temperature for 5 min to remove Pd. The resulting solution was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude was purified by flash chromatography (CH_2Cl_2:EtOAc = 10:1) to afford *S*-BINAP(O) (**L32**) as a white solid (130 mg, 0.2 mmol, 51%). ^1H NMR (400 MHz, CDCl3): δ 7.92 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.62-7.57 (m, 3H), 7.41 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.38-7.31 (m, 6H), 7.29-7.20 (m, 7H), 7.16-7.13 (m 1H), 7.10-7.01 (m, 4H), 6.97-6.93 (m, 2H), 6.90-6.87 (m, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.74-6.70 (m, 1H), 6.64 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (d, *J* = 7.5 Hz), 144.8 (d, *J* = 7.4 Hz), 142.8 (d, *J* = 4.6 Hz), 142.5 (d, *J* = 4.6 Hz), 138.7 (d, *J* = 12.8 Hz), 137.1 (d, *J* = 13.5 Hz), 136.8 (d, *J* = 11.3 Hz), 134.7 (d, *J* = 22.3 Hz), 134.5, 134.0 (d, *J* = 2.1 Hz), 133.6 (d, *J* = 3.0 Hz), 133.5, 133.4, 133.2, 133.14, 133.10, 133.06, 133.03, 132.98, 132.2, 132.1, 131.5 (d, *J* = 9.5 Hz), 131.2 (d, *J* = 2.7 Hz), 130.7 (d, *J* = 2.7 Hz), 129.9 (d, *J* = 2.1 Hz), 129.1 (d, *J* = 2.3 Hz), 128.8 (d, *J* = 12.9 Hz), 128.4 (d, *J* = 7.7 Hz), 128.1 (d, *J* = 2.0 Hz), 128.04, 128.01, 127.9 (d, *J* = 1.2 Hz), 127.8, 127.7, 127.63, 127.59, 127.5, 127.4, 127.0 (d, *J* = 2.6 Hz), 126.1, 126.0, 125.5. Some doublets due to C-P couplings can not be assigned due to complexity of the spectrum and they are listed as singlets. ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.1, -15.34 ppm. MS (EI): m/z ($M+H^+$) 639.3. Specific rotation: $[\alpha]_D$ (25.4 °C) = -113.7° (c = 0.05, CH_2Cl_2). The ^1H NMR and ^{31}P NMR are consistent with those previously reported.[180]

Preparation of L34 and L35.[172]



Methyl (*S*)-2'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-binaphthalene]-2-carboxylate (110). A mixture of **106** (2.00 g, 3.6 mmol), $Pd(OAc)_2$ (146 mg, 0.65 mmol, 18 mol %), and 1,3-bis(diphenylphosphino)propane (132 mg, 0.32 mmol, 9.0 mol %) was charged in a dry round bottle flask filled with CO. 3/2 mixture of DMSO and MeOH (167 mL) was added, followed by adding NEt_3 (6.7 mL, 36 mmol, 10.0 equiv). The mixture was stirred at 70 °C for 16 h. After this time, the mixture was cooled down and concentrated. The resulting red-brown residue was dissolved in Et_20 and washed with a large amount of H_20. The combined organic layer was dried over $MgS0_4$, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5:1) to afford **110** (817 mg, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 1H), 8.08 (t, *J* = 8.8 Hz, 2H), 8.00-7.97 (m, 2H), 7.60- 7.52 (m, 3H), 7.36-7.31 (m, 2H), 7.16 (t, *J* = 7.9 Hz, 2H), 3.57 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 144.3, 135.1, 133.7, 133.4, 132.5, 132.1, 130.3, 129.7, 129.4, 128.6, 128.3, 128.2, 128.1, 127.6, 127.4, 127.2, 126.9, 126.5, 126.1, 119.3, 118.1 (q, $J_{C\text{–}F}$ = 320.0 Hz), 52.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.8 ppm. MS (EI): m/z ($M+H^+$) 461.1. hese data are consistent with those previously reported.[181]

Methyl (*S*)-2'-(diphenylphosphoryl)-[1,1'-binaphthalene]-2-carboxylate (111). To a solution of **110** (690 mg, 1.5 mmol), diphenylphosphine oxide (606.6 mg, 3.0 mmol), $Pd(OAc)_2$ (33.6 mg, 0.15 mmol), and 1,3-bis(diphenylphosphino)propane (dppp) (64.2 mg, 0.075 mmol) in DMSO (10 mL) was added $^iPr_2NEt$ (1.26 mL, 7.2 mmol), and the mixture was stirred at 100 °C for 24 h. After the reaction, the mixture was cooled down and diluted with EtOAc, washed with a large amount of H_2O and extracted, the combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (*n*-hexane:EtOAc = 1:2) to afford **111** (420 mg). The product **111** was directly used in the next step without further purification. ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.7 ppm. MS (EI): m/z ($M+H^+$) 513.2. These data are consistent with those previously reported.[181]

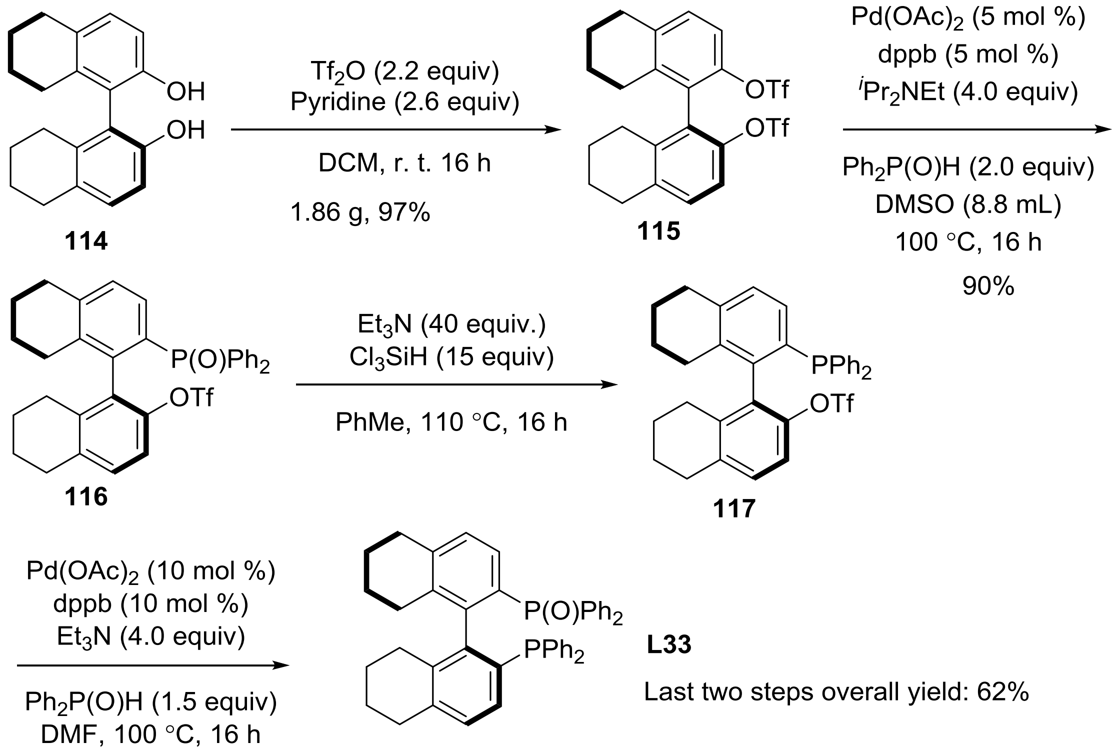
Methyl (*S*)-2'-(diphenylphosphanyl)-[1,1'-binaphthalene]-2-carboxylate (112). Under argon, to a solution of **111** (380 mg, 0.74 mmol) and Et_3N (4.0 mL, 29 mmol, 40 equiv) in dry PhMe (20 mL) was slowly added trichlorosilane (1.2 mL, 11 mmol, 15 equiv) at 0 °C, the mixture was stirred at room temperature for 30 min and then at 110 °C for 16 h. After this time, the mixture was cooled down to room temperature and diluted with Et_2O slowly. The resulting suspension was filtered through a pad of silica, and the combined organic layer was dried over $MgS0_4$ and concentrated under reduced pressure to afford **112** (320 mg). ^{31}P NMR (162 MHz, $CDCl_3$) δ -15.5 ppm. The product **112** was directly used in the next step without further purification. MS (EI): m/z ($M+H^+$) 497.2. These data are consistent with those previously reported.[181]

(S)-2'-(diphenylphosphanyl)-[1,1'-binaphthalene]-2-carboxylic acid (113). To a solution of **112** (300 mg, 0.60 mmol) in MeOH (7.5 mL) was added 1.5 mL of 40% KOH solution, and the mixture was stirred at 80 °C for 16 h. After this time, the mixture was cooled down and acidified (pH a 2) by addition of concentrated HCl at 0 °C. After extracting with EtOAc, the combined organic layer was dried over $MgS0_4$ and concentrated under reduced pressure to afford **113** (260 mg). The product **113** was directly used in the next step without further purification. ^{31}P NMR (162 MHz, $CDCl_3$) δ -15.0 ppm. MS (EI): m/z ($M+H^+$) 483.2. These data are consistent with those previously reported.[181]

(*S*)-(2'-(diphenylphosphanyl)-[1,1'-binaphthalen]-2-yl)(pyrrolidin-1-yl)methanone (L34). To a solution of **113** (97 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 was added a drop of DMF, and $(ClCO)_2$ (25 µL, 0.3 mmol, 1.5 equiv) at 0 °C, the mixture was then stirred at room temperature for 3.5 h. After this time, Et_3N (140 µL, 1.0 mmol, 5 equiv) and pyrrolidine (85 µL, 1.0 mmol, 5 equiv) was then added, the mixture was stirred at room temperature for an hour. The mixture was then directly concentrated under reduced pressure and the residue was purified by silica gel column chromatography to afford **L34** as a white solid (12 mg, 0.02 mmol, 10%) ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.47-7.39 (m, 3H), 7.30-7.20 (m, 5H), 7.17-7.07 (m, 8H), 6.87 (d, *J* = 8.2 Hz, 1H), 3.39-3.23 (m, 3H), 3.13-3.06 (m, 1H), 1.53-1.43 (m, 2H), 1.16-1.05 (m, 1H), 0.90-0.84 (m, 1H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ, -15.8 ppm. HRMS: calcd for $C_{37}H_{31}NOP$, 536.2143 ($M+H^+$); found, 536.2140. Specific rotation: $[\alpha]_D$ (26.3 °C) = -255.7° (c = 0.024, CH_2Cl_2).

(*S*)-2'-(diphenylphosphanyl)-*N,N*-diphenyl-[1,1'-binaphthalene]-2-carboxamide (L35). To a solution of **113** (97 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 was added a drop of DMF, and 1.5 equivalents of ClCOCOCl slowly at 0 °C, the mixture was then stirred at room temperature for 3.5 h. After this time, Et_3N (140 µL, 1.0 mmol, 5 equiv) and diphenylamine (67.7 mg, 0.4 mmol, 2.0 equiv) was then added, the mixture was stirred at room temperature for an hour. The mixture was then directly concentrated under reduced pressure and the residue was purified by silica gel column chromatography to afford **L35** as a white solid (15 mg, 0.02 mmol, 10%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.48-7.45 (m, 1H), 7.39-7.29 (m, 6H), 7.18-7.14 (m, 1H), 7.10-6.96 (m, 11H), 6.87-6.83 (m, 1H), 6.76-6.58 (m, 7H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ, -14.7 ppm. HRMS: calcd for $C_{45}H_{33}NOP$, 634.2300 ($M+H^+$); found, 634.2294. Specific rotation: $[\alpha]_D$ (26.3 °C) = -220.3° (c = 0.021, CH_2Cl_2).

Preparation of L33.[173]



(*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (115). Under argon, pyridine (0.7 mL, 8.8 mmol, 2.6 equiv) was added into a solution of (*S*)-*H₈*-BINOL **L16** (1.0 g, 3.4 mmol, 1.0 equiv) in 35 mL of dry DCM. After stirring 5 minutes, the solution was cooled to 0 °C. Then Tf_2O (1.3 mL, 7.5 mmol, 2.2 equiv) was added slowly and the reaction mixture was stirred at room temperature for 16 h. After this time, the mixture was filtered through a pad of silica gel using EtOAc/hexane (1:30) as eluent. Concentrate of the filtrate afforded **115** as a white solid (1.86 g, 3.3 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 2.85 (t, *J* = 6.3 Hz, 4H), 2.42 (dt, *J* = 17.0, 6.0 Hz, 2H), 2.29 (dt, *J* = 16.9, 6.2 Hz, 2H), 1.84-1.67 (m, 8H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 139.3, 138.3, 130.9, 127.1, 118.2 (q, $J_{C\text{–}F}$ = 319.8 Hz), 118.1, 29.4, 27.5, 22.4, 22.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74. 8 ppm. HRMS: calcd for $C_{22}H_{20}F_6O_6S_2Na$, 581.0503 (M+Na$^+$); found, 581.0505.

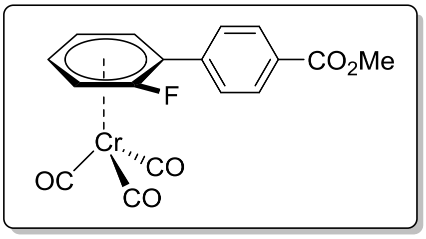
(*S*)-2'-(diphenylphosphoryl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (116). Under argon, To a solution of **115** (1.1 g, 2.0 mmol, 1.0 equiv), diphenylphosphine oxide (810 mg, 4.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 5 mol %) and dppb (42.6 mg, 0.1 mmol, 5 mol %) in dry DMSO (8.8 mL) was added $^{i}Pr_2NEt$ (1.4 mL, 8.0 mmol, 4.0 equiv). The reaction mixture was stirred at room temperature for 20 min and then at 110 °C for 16 h. After this time, the reaction mixture was cooled down to room temperature, and 30 mL of H_2O was added. The resulting solution was extracted with Et_2O at least 3 times. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was purified by silica gel column chromatography (*n*-hexane:EtOAc = 2:1) to afford **116** as a white solid (1.08 g, 1.8 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.59 (m, 2H), 7.50-7.38 (m, 6H), 7.32-7.28 (m, 2H), 7.18- 7.10 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 2.85-2.83 (m, 2H), 2.77-2.74 (m, 2H), 2.51-2.43 (m, 1H), 2.37-2.30 (m, 1H), 2.12-2.02 (m, 2H), 1.80-1.55 (m, 8H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 142.6 (d, *J* = 2.6 Hz), 139.3, 138.6 (d, *J* = 7.7 Hz), 137.6 (d, *J* = 9.9 Hz), 137.0, 134.1, 133.1, 132.1 (d, *J* = 9.3 Hz), 131.6 (d, *J* = 9.8 Hz), 131.4 (d, *J* = 2.7 Hz), 131.23, 131.18 (d, *J* = 2.8 Hz), 131.1, 131.02 (d, *J* = 4.0 Hz), 130.13, 128.71, 128.66 (d, *J* = 13.2 Hz), 128.3 (d, *J* = 11.9 Hz), 128.0 (d, *J* = 12.2 Hz), 127.7, 118.1 (q, $J_{C–F}$ = 319.7 Hz), 117.0, 30.3, 29.5, 27.9, 26.9, 22.9, 22.48, 22.45, 22.4 ppm. Some doublets due to C-P couplings can not be assigned due to complexity of the spectrum and they are listed as singlets. ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.1 ppm. MS (EI): m/z ($M+H^+$) 611.2.

(S)-2'-(diphenylphosphanyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (117). Under argon, to a solution of **116** (1.0 g, 1.6 mmol), Et_3N (8.0 mL, 64 mmol, 40 equiv) in dry PhMe (32 mL) was slowly added trichlorosilane (1.6 mL, 16 mmol, 10 equiv). The reaction mixture was stirred at 0 °C for 10 min and then at 110 °C for 16 h. After this time, the reaction mixture was cooled down to room temperature and filtered through a pad of silica, the filtrate was concentrated under reduced pressure to afford **117** (1.5 g). ^{31}P NMR (162 MHz, $CDCl_3$) δ -14.4 ppm. MS (EI): m/z ($M+H^+$) 595.3. The product was directly used in the next step without further purification.

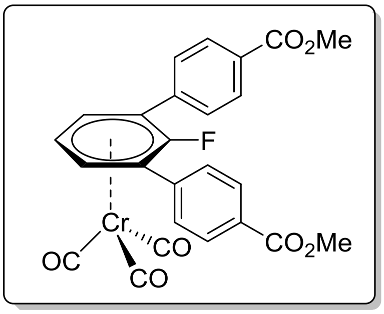
(*S*)-*H_8*-BINAP(O) (L33). Under argon, to a solution of **117** (595 mg, 1.0 mmol, 1.0 equiv), diphenylphosphine oxide (303.0 mg, 1.5 mmol, 1.5 equiv), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol, 10 mol %) and dppb (42.6 mg, 0.1 mmol, 10 mol %) in dry DMSO (7.0 mL) was added dry $^{i}Pr_2NEt$

(0.7 mL, 4.0 mmol, 4.0 equiv), The reaction mixture was stirred at room temperature for 20 min and then at 110 °C for 16 h. After this time, the reaction mixture was cooled down to room temperature and 20 mL of H_2O was added. The resulting solution was extracted with Et_2O (3 x 20 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography (CH_2Cl_2:EtOAc = 10:1) to afford *S*-*H_8*-BINAP(O) (**L33**) as a white solid (250 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.57 (m, 4H), 7.46-7.15 (m, 16H), 7.13-7.10 (m, 1H), 7.06-7.01 (m, 2H), 6.98-6.96 (m, 1H), 2.76-2.62 (m, 4H), 1.88-1.67 (m, 3H), 1.55-1.30 (m, 6H), 1.25-1.08 (m, 2H), 0.78-0.68 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (app. t, *J* = 8.2 Hz, 2C), 144.9 (d, *J* = 3.7 Hz), 144.6 (d, *J* = 3.7 Hz), 141.4 (d, *J* = 2.6 Hz), 140.2 (d, *J* = 13.7 Hz), 138.0, 137.9 (d, *J* = 2.5 Hz), 137.8 (d, *J* = 2.4 Hz), 137.3 (d, *J* = 14.7 Hz), 135.5, 135.5, 135.3, 134.8 (d, *J* = 8.4 Hz), 134.6 (d, *J* = 6.6 Hz), 134.4 (d, *J* = 12.8 Hz), 133.4, 132.9 (d, *J* = 16.6 Hz), 132.3 (d, *J* = 2.4 Hz), 132.3 (d, *J* = 2.4 Hz), 132.2 (d, *J* = 9.3 Hz), 131.3 (d, *J* = 2.1 Hz), 131.2, 131.1 (x2), 131.0 (d, *J* = 2.6 Hz), 128.8 (d, *J* = 3.6 Hz), 128.2 (d, *J* = 7.8 Hz), 128.1 (d, *J* = 4.4 Hz), 128.0 (d, *J* = 4.1 Hz), 127.9 (d, *J* = 4.7 Hz), 127.4 (d, *J* = 13.8 Hz), 126.9, 126.4 (d, *J* = 2.3 Hz), 30.2, 29.9, 27.7 (d, *J* = 2.2 Hz), 26.9, 22.9, 22.6, 22.4, 22.2 ppm. Some doublets due to C-P couplings can not be assigned due to complexity of the spectrum and they are listed as singlets. ^{31}P NMR (162 MHz, $CDCl_3$) δ, 27.9, -17.2 ppm. HRMS: calcd for $C_{44}H_{41}OP_2$, 647.2633 (M+H$^+$); found, 647.2619. Specific rotation: $[\alpha]_D$ (25.4 °C) = -119.2° (c = 0.05, CH_2Cl_2).

5.4.2 Enantioselective C-H arylation of fluorobenzene chromium tricarbonyl complex

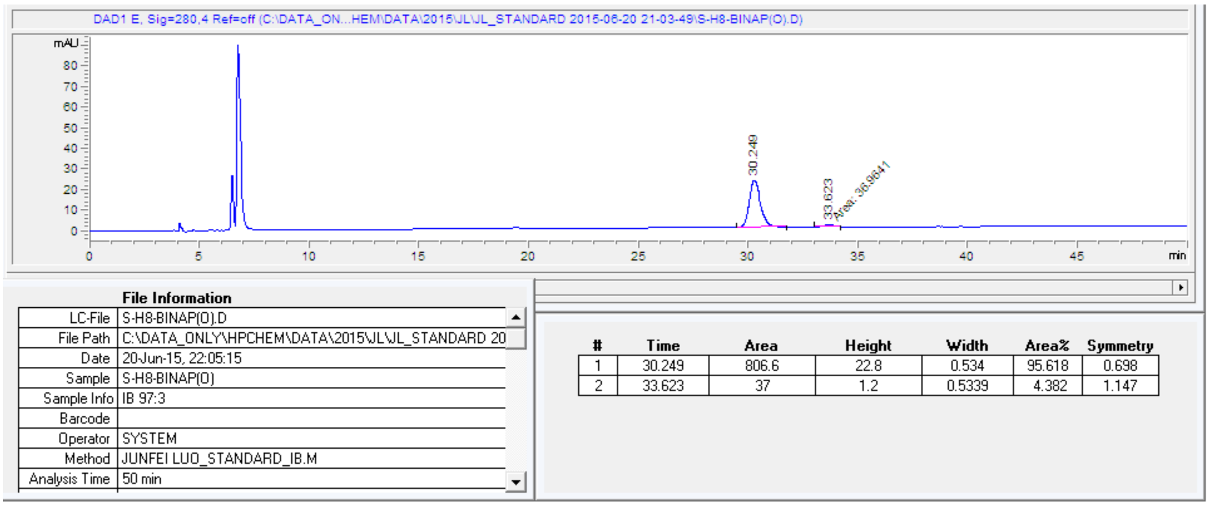


Under argon, to a mixture of Pd(dba)$_2$ (1.7 mg, 3.0 μmol, 3.0 mol %), *S-H$_8$*-BINAP(O) (2.2 mg, 3.3 μmol, 3.0 mol%), dicyclohexylacetic acid (11.2 mg, 0.050 mmol, 0.50 equiv), K_2CO_3 (28.0 mg, 0.20 mmol, 2.0 equiv), Ag_2CO_3 (28.0 mg, 0.10 mmol, 1.0 equiv), [(fluorobenzene)Cr(CO)$_3$] (23.2 mg, 0.10 mmol, 1.0 equiv), methyl *p*-iodobenzoate (52.4 mg, 0.20 mmol, 2.0 equiv) and 2,2,6,6-tetramethylpiperidine (34 μl, 0.20 mmol, 2.0 equiv) was added $PhCH_3$ (100 μL). The mixture was covered by aluminium foil and stirred at 40 °C for 40 h. After this time, the reaction mixture was filtered through a plug of silica and washed with acetone. The filtrate was evaporated to dryness and purified by preparative TLC (hexane:Et_2O = 50:50), affording pure desired product **102** as a yellow solid (13.8 mg, 38%). mp: 134-136 °C. IR: 2970, 1737, 1366, 1217 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d$_6$): δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.79 (dd, *J* = 8.2, 1.4 Hz, 2H), 6.27-6.24 (m, 1H), 6.05-6.00 (m, 1H), 5.94-5.90 (m, 1H), 5.45-5.43 (m, 1H), 3.92 (s, 3H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$): δ 233.0 (d, *J* = 1.8 Hz), 166.6, 145.9 (d, *J* = 265.0 Hz), 137.9, 131.6, 130.6 (d, *J* = 2.6 Hz), 130.4, 99.2 (d, *J* = 12.7 Hz), 97.3 (d, *J* = 3.6 Hz), 96.2 (d, *J* = 7.8 Hz), 88.9, 81.0 (d, *J* = 22.0 Hz), 52.6 ppm. HRMS calcd for $C_{17}H_{11}O_5{}^{50}CrF$: 364.0046 (M$^+$); found, 364.0041. HPLC: Chiralpak IB, hexane/isopropanol = 97:3, flow rate 0.8 ml/min, λ = 280 nm, ret. times: 30.249 min (95.618 %), 33.623 min (4.382 %). Specific rotation: $[\alpha]_D$ (27 °C) = +75.4° (c = 0.05, CH_2Cl_2).



Bisarylation product **103** was obtained as a main by-product in the reaction above (20.8 mg, 42%). IR: 2970, 1877, 1739, 1366, 1217 cm^{-1}. mp: 198 °C (decomposition). ^{1}H NMR (400 MHz, acetone-d$_6$) δ 8.13 (d, *J* = 8.5 Hz, 4H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 4H), 6.37-6.34 (m, 2H), 5.62-5.59 (m, 1H), 3.93 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d$_6$) δ 232.6 (d, *J* = 1.8 Hz), 166.7, 143.8 (d, *J* = 265.6 Hz), 137.9 (d, *J* = 2.2 Hz), 131.8, 131.0 (d, *J* = 2.6 Hz), 130.4, 98.8 (d, *J* = 14.2 Hz), 97.8 (d, *J* = 3.7 Hz), 88.2, 52.6 ppm. HRMS calcd for $C_{25}H_{17}O_{7}{}^{50}CrF$: [M]+ 498.0413; found: [M]+ 498.0415.

HPLC spectra of **102** separation



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File Information

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Sample	S-H8-BINAP(O)
Sample Info	IB 97:3
Barcode	
Operator	SYSTEM
Method	JUNFEI LUO_STANDARD_IB.M
Analysis Time	50 min

#	Time	Area	Height	Width	Area%	Symmetry
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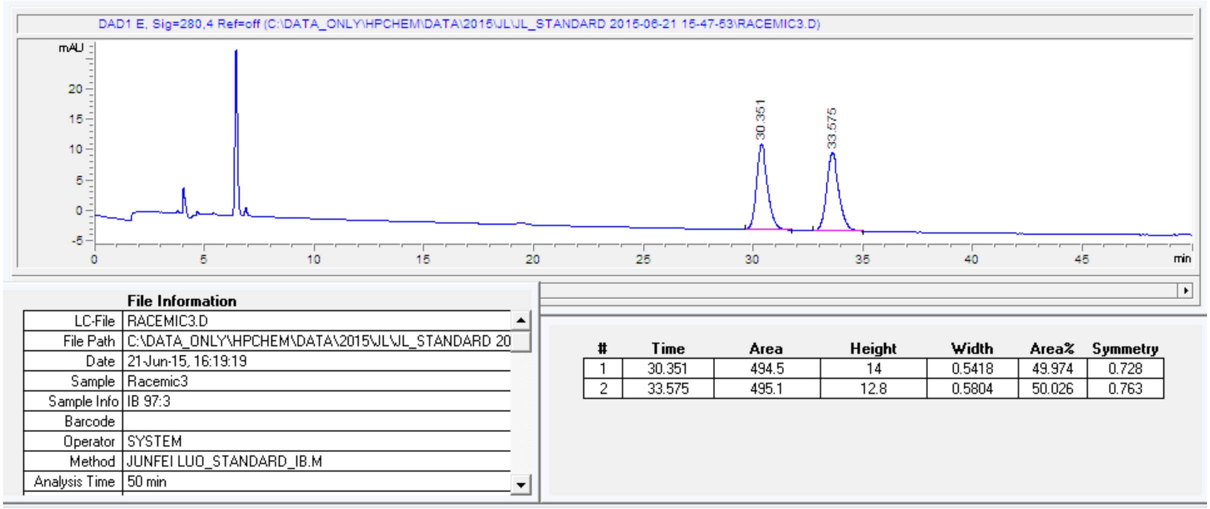
HPLC spectra of racemic **102** separation



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File Information

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Barcode	
Operator	SYSTEM
Method	JUNFEI LUO_STANDARD_IB.M
Analysis Time	50 min

#	Time	Area	Height	Width	Area%	Symmetry
1	30.351	494.5	14	0.5418	49.974	0.728
2	33.575	495.1	12.8	0.5804	50.026	0.763

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