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Iron-Catalysed Hydride and Radical Transfer Reactions

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THE UNIVERSITY of EDINBURGH

A thesis submitted for the degree of Doctor of Philosophy

2016
Abstract

Iron-catalysed carbonyl reduction, nitro reduction, formal hydroamination, and the radical alkenylation of alkyl halides have been developed. A simple, easy-to-make, air- and moisture-stable iron(III) amine-bis(phenolate) complex catalysed the hydrosilylation of carbonyl compounds efficiently using triethoxysilane as the reducing agent. The reaction tolerated a wide range of substrates to give the corresponding alcohol products in good to excellent yields after hydrolysis of the hydrosilylated products (Scheme A1).

**Scheme A1. Iron-Catalysed Hydrosilylation of Carbonyl Compounds.**

The same catalyst was also an active catalyst for the chemoselective reduction of nitro arenes into corresponding amines using triethoxysilane as reducing agent. The method exhibited excellent chemoselectivity as other reducible functional groups such as halogen, ester, nitrile all kept unchanged during the reaction. This catalytic system was then successfully applied to the formal hydroamination of alkene to give substituted amine in synthetic useful yields under mild condition. The reaction is hypothesised to proceed through a radical intermediate (Scheme A2).

**Scheme A2. Iron-Catalysed Nitro Reduction and Alkene Formal Hydroamination.**

Finally, FeCl$_2$-catalysed formal Heck cross-coupling has been developed between alkyl halides and styrenes. The reaction tolerated both electron-rich and electron-neutral substrates to give the products in moderate to excellent yields. Initial studies revealed that the reaction also proceeds through a radical intermediate (Scheme A3).

**Scheme A3. Iron-Catalysed Formal Heck Cross-Coupling of Functionalised Alkyl Halides.**
Lay Summary

The use of transition metals as catalysts has revolutionised modern synthetic chemistry profoundly, as many otherwise unimaginable reactions have become possible with the help of transition metals. However, although being highly active, most of the transition metals that have found wide application in synthetic chemistry are toxic and expensive, which will undoubtedly limit their applications in large-scale production.

As the most abundant transition metal in the Earth’s crust, iron is inexpensive, non-toxic and environmentally benign, making it an ideal catalyst when it comes to industrial production. In this work, several easy-to-make iron-based catalysts have been used in the synthesis of industrially relevant molecules. In most cases, the reactions proceeded in a controlled manner under simple reaction conditions, giving the products in good yields.
Declaration

I certify:

a) that the thesis has been composed by me, and

b) either that the work is my own, or, where I have been a member of a research group, that I have made a substantial contribution to the work, such contribution being clearly indicated, and

c) that the work has not been submitted for any other degree or professional qualification except as specified.

Kailong Zhu
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<td>Phenanthroline</td>
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<td>PMDTA</td>
<td>N,N,N',N'''-Pentamethyldiethylenetriamine</td>
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<tr>
<td>ppy</td>
<td>2-Phenylpyridinato</td>
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<tr>
<td>Pr</td>
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<tr>
<td>py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>r.t.</td>
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<td>Rate-determining step</td>
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<td>Single-electron transfer</td>
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<td>Trifluoroacetic acid</td>
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<td>Tetrahydrofuran</td>
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<td>TMDS</td>
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<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
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<tr>
<td>TOF</td>
<td>Turnover frequency</td>
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1. Introduction

Modern synthetic chemistry has been profoundly influenced by the use of organometallic catalysts since the 1950s. Platinum-group metals such as ruthenium,\textsuperscript{1-3} palladium,\textsuperscript{4-7} rhodium\textsuperscript{8-10} and iridium\textsuperscript{11-13} are among the most widely used transition metals. However, the high toxicity and high price of these metals have limited their applications in large scale industrial production. As a result, chemists continue to search for metals that are earth-abundant, inexpensive and environmentally benign as substitutions of those noble metals. As the most abundant transition metal in the Earth’s crust, iron has emerged as an important candidate that meets all the above criteria. Recently, we have witnessed a huge development in iron catalysis and numerous iron-based catalysts have been reported by various research groups, covering almost all kinds of reactions that have been done previously using noble metals.\textsuperscript{14-19} Among those reactions, iron-catalysed hydride transfer and radical transfer reactions are particularly useful as they have been involved in the synthesis of many industrially relevant molecules. Iron-catalysed hydride transfer reactions are associated with synthetically useful transformations such as the hydrogenation\textsuperscript{14-15} or hydrofunctionalisation\textsuperscript{17} of alkenes and alkynes, the reduction of carbonyl compounds and their derivatives\textsuperscript{14-15,20} and the reduction of nitro compounds.\textsuperscript{14,21} Commonly used hydride sources include molecular hydrogen, metal hydrides such as lithium aluminium hydride and sodium borohydride, formic acid, isopropanol and hydrosilanes. In most cases, an iron hydride species is thought to be involved in the hydride transfer process. In such reactions, the essential role of iron is as the ‘hydride shuttle’, transferring a hydride from the hydride source to the product. In some less common examples, the iron catalysts act simply as Lewis acids, which can activate the unsaturated substrates to make them more susceptible to the nucleophilic attack from an external hydride source. In those reactions, no iron hydride species need to be formed during the reaction process. The relative ease of iron to undergo a single-electron transfer (SET) makes it an ideal candidate for radical reactions. Particularly, the iron-catalysed generation of alkyl radicals from corresponding alkyl halides through a SET process has been utilised in a large number of reactions including atom transfer radical polymerisation (ATRP) of vinyl monomers and cross-coupling reactions between various coupling partners.

1.1 Iron-Catalysed Hydride Transfer

1.1.1 Hydrogenation/Hydrofunctionalisation of Alkenes and Alkynes

In a typical hydrogenation or hydrofunctionalisation of alkenes and alkynes catalysed by a low oxidation-state iron complex, the alkenes or alkynes are normally activated through
coordination to the iron complex. On the other hand, hydride sources can be activated either by oxidative addition or σ-bond coordination. Insertion of the alkenes or alkynes into the iron-hydride bond followed by reductive elimination give the hydrogenation or hydrofunctionalisation products (Scheme 1.01).\[17\] In some cases, such as the hydrosilylation of alkenes, the insertion of the substrates into the iron-silyl bond rather than the iron-hydride bond has also been reported.\[22\] However, higher oxidation state iron complexes usually act as Lewis acids in such reactions. In these cases, the coordination of an alkene or alkyne to the iron catalyst makes it more susceptible to a nucleophilic attack.\[17\]

**Scheme 1.01.** General mechanism for low-oxidation state iron-catalysed hydrogenation or hydrofunctionalisation of alkenes and alkynes.

[Chemical structure diagram]

Hydrogen is the most widely used hydride sources for such reactions. Iron-catalysed hydrogenation of alkenes dates back to the 1960s when Frankel and co-workers realised the hydrogenation of methyl linoleate using Fe(CO)$_5$ as the catalyst.\[23-24\] In early examples of iron-catalysed hydrogenation of alkenes, iron carbonyl complexes were the most widely used catalysts, usually requiring continued photo-irradiation\[25\] or high temperatures and high hydrogen pressures.\[23-24,26\] A major breakthrough in this field was made by the group of Chirik in 2004 when they reported the highly efficient hydrogenation of alkenes at room temperature by using the bis(imino)pyridine iron(0) complex 1 as the catalyst. In the reduction of 1-hexene 2, 98% conversion (GC) to hexane 3 was obtained in toluene at ambient temperature in 12 minutes with just 0.3 mol% catalyst loading (Scheme 1.02).\[27\]

**Scheme 1.02.** Bis(imino)pyridine iron(0) complex as an efficient catalyst for alkene hydrogenation.

[Chemical structure diagram]
Mechanistically, dissociation of the dinitrogen ligands is followed by alkene coordination. Dihydrogen cleavage then proceeds to form the iron dihydride complex, followed by the insertion of the coordinated alkene to give an iron-alkyl species. The hydrogenated product and the active iron(0) species are reformed by reductive elimination (Scheme 1.03).27

Scheme 1.03. Mechanism of the bis(imino)pyridine iron(0)-catalysed alkene hydrogenation.

Compared to alkenes, the hydrogenation of alkynes is more challenging to control as alkynes can be reduced to either alkanes or alkenes. Moreover, in the semi-hydrogenation of internal alkynes, the control of stereo-selectivity presents another big challenge. Thus, the hydrogenation of alkynes with good product- and stereo-selectivity is highly desirable.

The semi-hydrogenation of internal alkynes was reported using a novel PNP pincer ligand-supported imino borohydride iron complex 4. The catalyst exhibited excellent (E)-selectivity for a variety of substrates when the reactions were conducted in THF at 90 °C with 4-10 bar of hydrogen (Scheme 1.04). Substrates with electron-withdrawing substituents required longer reaction times, higher catalyst loadings and hydrogen pressures to reach full conversion, probably due to the weaker bonding between electron deficient alkynes and the iron complex.28

Scheme 1.04. Iron-catalysed (E)-selective semi-hydrogenation of internal alkyne.
The (Z)-selective hydrogenation of alkynes was reported using FeCl₃ as the precatalyst in ionic liquids in the presence of a Grignard reagent. Iron(0) nanoparticles, generated \textit{in situ} from the reduction of FeCl₃ with the Grignard reagent were proposed to be the active catalyst. The presence of a nitrile group in the ionic liquid or a nitrile-group-containing additive was necessary for the reactivity.³⁹ Transfer hydrogenation of terminal alkynes to alkenes was reported by Beller and co-workers³⁰ using formic acid as the hydride source. The combination of iron(II) tetrafluoroborate hexahydrate and the phosphine ligand 7 catalysed the semi-reduction of phenylacetylene 8 to styrene 9 with high efficiency under mild reaction conditions (Scheme 1.05).

**Scheme 1.05.** Transfer hydrogenation of alkynes catalysed by phosphine-supported iron complex.

The active catalyst is formed \textit{in situ} by the dissociation of one equivalent of BF₄⁻ ligand and one equivalent of BF₃. The active catalytic species then dehydrogenates formic acid to form an iron dihydrogen complex with the release of carbon dioxide. Coordination of the alkyne to the iron dihydrogen complex is then followed by an insertion reaction to give the alkenyl iron complex, which then undergoes reductive elimination to give the product (Scheme 1.06).³⁰

**Scheme 1.06.** Proposed mechanism for the transfer hydrogenation of terminal alkynes
In recent years, hydrosilylation of alkenes and alkynes has received tremendous attention as the products of such reactions are versatile building block in synthetic chemistry.\textsuperscript{31-33} Chirik’s bis(imino)pyridine iron(0) complex, 1, which has been proved to be highly active in alkene hydrogenation, is also applicable to the hydrosilylation of alkenes.\textsuperscript{27} In the reaction of 1-hexene 2, linear product 10 was obtained in 98% conversion in 1 hour with 0.3 mol% of catalyst. The reaction mechanism was believed to be similar to that of alkene hydrogenation (Scheme 1.07).

**Scheme 1.07.** Bis(imino)pyridine iron(0) complex as an efficient catalyst for alkene hydrosilylation.

\[ \begin{align*}
\text{2 (pentane, 22 °C, 60 min, >98 conv)} & \rightarrow \text{10 (PhSiH$_3$)} \\
\text{1 (0.3 mol%) FeCl$_2$/bis(imino)pyridine - catalysed hydrosilylation of alkenes and alkynes.} \\
\end{align*} \]

Although highly active, bis(imino)pyridine iron(0) complex 1 is highly sensitive towards air and moisture, which makes it difficult to handle. To address this problem, \textit{in situ} generation of the active iron(0) species from the corresponding iron(II) complex of the bis(imino)pyridine ligand 11 was reported by our group for the hydrosilylation of alkenes and alkynes, using Grignard reagent as the activator. A wide range of substrates including alkynes were tolerated, to give the hydrosilylation products in up to 96% yield (Scheme 1.08).\textsuperscript{34}

**Scheme 1.08.** FeCl$_2$/bis(imino)pyridine-catalysed hydrosilylation of alkenes and alkynes.

\[ \begin{align*}
\text{R$_1$=C=CR$_2$ + R$_3$SiH & $\xrightarrow{\text{FeCl$_2$ (1.0 mol%) 11 (1.0 mol%)}}$ R$_1$=C=CR$_2$SiR$_3$} \\
\text{EtMgBr (2.0 mol%) THF, r.t, 1 h} & \rightarrow \text{36 examples up to 96% yield} \\
\end{align*} \]

In addition to hydrogenation and hydrosilylation, other hydrofunctionalisation reactions of alkenes and alkynes involving a hydride transfer process such as hydromagnesiation\textsuperscript{35-36} and hydroboration\textsuperscript{37} have also emerged as powerful tools for the construction of synthetically useful products.
1.1.2 Reduction of Carbonyl Compounds

Iron-catalysed hydride transfer is also widely observed in the reduction of carbonyl compounds. Hydrogenation, transfer hydrogenation and hydrosilylation are most widely employed methods. The first example of iron-catalysed efficient hydrogenation of ketones was reported in 2007 using iron complex 12, which is essentially the iron analogue of Shvo’s ruthenium complex. An outer sphere mechanism was proposed by the authors, in which the proton of the hydroxyl group was added to the oxygen of the ketone while the hydride of the iron-hydride bond was transferred to the carbon of the ketone. The catalyst was then regenerated by the oxidative addition of one equivalent of dihydrogen (Scheme 1.09).

Scheme 1.09. Iron-catalysed hydrogenation of ketone through an outer sphere mechanism.

Chemoselective transfer hydrogenation of α,β-unsaturated ketones has been reported using iron dihydrogen complex 15 as the catalyst. In the reduction of benzylideneacetone 16, the corresponding α,β-unsaturated alcohol 17 was isolated in 95% yield using cyclopentanol as the hydride source, with just 1.0 mol% catalyst loading (Scheme 1.10).

Scheme 1.10. Iron hydride complex catalysed chemoselective transfer hydrogenation of α,β-unsaturated ketone and its mechanism.

In contrast to the outer-sphere mechanism as suggested by Guan and co-workers, in this reaction, an inner-sphere mechanism is implicated by the authors: the cleavage of the η²-
dihydrogen ligand is followed by the coordination of the ketone substrate. The insertion of the carbonyl substrate gives an iron alkoxide species. Protonation of the alkoxide with cyclopentanol releases the alcohol product and gives an iron cyclopentoxide complex. β-Hydride elimination gives cyclopentanone as the by-product and regenerated the active iron hydride complex (Scheme 1.11). 40

**Scheme 1.11.** Mechanism of the iron hydride complex-catalysed chemoselective transfer hydrogenation.

A major breakthrough in iron-catalysed carbonyl transfer hydrogenation was achieved by the group of Morris, who developed a series of highly efficient diiminediphosphine iron(II) complexes and amine(imine)diphosphine iron(II) complexes for the asymmetric transfer hydrogenation of ketones (Figure 1.01). In the asymmetric transfer hydrogenation of acetophenone using isopropanol as the reducing agent, a TOF of 3000 h⁻¹ was achieved when diiminediphosphine iron(II) complexes 18-19 were used, while the amine(imine)diphosphine complexes 20-21 gave even higher TOFs of up to 5000 h⁻¹. 41

**Figure 1.01.** The diiminediphosphine and amine(imine)diphosphine iron(II) complexes for the asymmetric ketone transfer hydrogenation.
Another widely used method for the reduction of carbonyl compounds into alcohols is hydrosilylation followed by aqueous workup. The history of iron-catalysed hydrosilylation of carbonyl compounds can be dated back to 1990, when Brunner first reported the hydrosilylation of benzophenone catalysed by \([\text{Cp}^*\text{Fe} (\text{CO})(\text{COCH}_3)L]\) \([L = (\text{S})-(+)-\text{Ph}_2\text{PN} (\text{CH}_3)\text{CH} (\text{CH}_3)\text{Ph}]\) under photo-irradiation conditions.\(^{42,43}\) However, only one example of substrate was included in this study. In 2007, a general method for the hydrosilylation of carbonyl compounds was reported using a combination of \(\text{Fe(OAc)}_2\) and tetramethylethylenediamine (TMEDA) as the catalyst (Scheme 1.12).\(^{44}\) Since then, many highly efficient iron-based catalysts have been designed and synthesised for the hydrosilylation of carbonyl compounds.\(^{14-15}\) Recent developments in iron-catalysed hydrosilylation of carbonyl compounds will be discussed in detail in Chapter 2 of this thesis.

**Scheme 1.12.** Multi-nitrogen-based ligand supported iron complex as an efficient catalyst for the hydrosilylation of ketones.

\[
\begin{align*}
\text{TMEDA} &= \text{Me}_2\text{N} - \text{NMe}_2 \\
\text{ThF}, 65 ^\circ \text{C}, \text{work up with H}_2\text{O}^+ &\rightarrow \\
\text{up to 94% yield}
\end{align*}
\]

### 1.1.3 Reduction of Nitro Compounds

Iron-catalysed nitro reduction represents another key industrially relevant transformation. Reductants that have been successfully used in this reaction include gaseous hydrogen, formic acid, isopropanol, hydrazine hydrate and hydrosilane. Compared to hydrogenation and hydrofunctionalisation of alkenes and alkynes and the reduction of carbonyl compounds, the iron-catalysed reduction of nitro compounds has been much less explored.\(^{14,16,19}\) The mechanism of this type of reaction is largely unclear, however, it is hypothesised to proceed by a hydride transfer process (Scheme 1.13). Recent advancements in iron-catalysed reduction of nitro compounds will be discussed in detail in Chapter 3 of this thesis.

**Scheme 1.13.** General mechanism of iron-catalysed reduction of nitro compounds.
1.2 Iron-Catalysed Radical Transfer

1.2.1 Atom Transfer Radical Polymerisation

Perhaps the most important application of iron-catalysed radical transfer is in the ATRP of vinyl monomers such as styrene and methyl methacrylate (MMA). In a typical iron-catalysed ATRP reaction, chain propagation is initiated by an alkyl radical, which is generated by an iron catalyst in a lower oxidation state through a single-electron transfer process from the alkyl halide (Scheme 1.14).


Since the first example of iron-catalysed ATRP of methyl methacrylate as reported in 1997 by Sawamoto and co-workers, in which a phosphine-ligated iron(II) complex was used as catalyst, extensive efforts have been devoted to the development of this type of reaction, as the low-toxicity and bio-compatibility of iron make it particularly advantageous for the preparation of polymers that are bio-relevant.

1.2.2 Cross-Coupling Reactions

Iron-catalysed radical transfer reactions are also widely involved in cross-coupling reactions, particularly the Kumada-type reaction between alkyl halides and Grignard reagents. In the iron-catalysed Kumada reaction of vinyl or aryl halides with Grignard reagents, a similar mechanism to the palladium-catalysed version of the reaction has been proposed, which involves the oxidative addition of a vinyl or aryl halide to an iron centre. The oxidative addition of an alkyl halide to the iron complex was also suggested by Hayashi and co-workers in their investigation of Fe(acac)_3-catalysed cross-coupling between alkyl halides and aryl Grignard reagents. However, some later experimental observations in the reaction of alkyl halides cannot be explained by such a mechanism. For instance, in the Kumada-type cross-coupling of chiral 2-bromo-octane and an aryl Grignard reagent catalysed by a low oxidation-state iron complex, racemic product was obtained, which was inconsistent with the above-mentioned mechanism as configuration of the chiral centre should be retained in an oxidative addition step (Scheme 1.15).
Scheme 1.15. Racemisation of the product in the Kumada-type reaction of chiral alkyl halide.

Based on those experimental results and the propensity of iron to undergo a single-electron transfer process, several radical-based mechanisms were outlined, in which the alkyl radical was generated from alkyl halide through a single-electron transfer process from the iron catalyst to the alkyl halide. One simplified example of the radical mechanism was suggested by the group of Bedford in their work on iron-catalysed coupling of alkyl halides with aryl Grignard reagents.\(^{52}\) The iron precatalyst was first reduced by the Grignard reagent, followed by alkyl radical generation from alkyl halide through a single-electron transfer process. Transmetalation between the Grignard reagent and the iron halide complex gave the iron aryl species. The formal Kumada cross-coupling product was obtained by the abstraction of the aryl radical from the iron aryl complex by the alkyl radical, with the concomitant regeneration of the active catalyst (Scheme 1.16).

Scheme 1.16. Bedford’s mechanism for iron-catalysed Kumada-type reaction of alkyl halides.

The group of Nagashima reported a FeCl\(_3\)-catalysed radical cross-coupling reaction between alkyl halides and aromatic Grignard reagents in the presence of excess TMEDA.\(^{53}\) The TMEDA-ligated diaryl iron(II) species was supposed to be the active catalyst which would then enter into a similar catalytic cycle as proposed by Bedford, with a slight modification as in this case the elimination reaction to release the coupling product took place before the transmetalation between the aryl(halogeno)iron complex and the Grignard reagent (Scheme 1.17). The TMEDA-ligated diaryl iron(II) species was able to be isolated from the reaction of FeCl\(_3\) and Grignard reagent in the presence of TMEDA. Treatment of this isolated iron complex with alkyl halide afforded a new iron complex, which was confirmed by NMR to be the aryl(halogeno)iron(II) complex.
In the mechanisms proposed by Bedford and Nagashima, the oxidation state of the active iron catalyst differed only by one electron. Cahiez suggested a different mechanism in their work on iron-catalysed alkylation of aryl Grignard reagents, in which two consecutive single-electron transfer processes took place. The active iron(0) species was generated in situ from the reduction of the iron(III) precatalyst by the Grignard reagent, followed by the addition of the Grignard reagent to give a diaryl iron(0) species. Single-electron transfer gave the alkyl halide radical anion and an iron(I) intermediate. Instead of a direct elimination to give the coupling product, the alkyl radical was added to the iron centre to give an iron(II) species which then underwent the elimination to give the product, regenerating the iron(0) catalyst (Scheme 1.18). In such a mechanism, the oxidative addition of the alkyl halide to the iron complex is split into two separate steps. However, no strong experimental evidence was acquired to support this mechanism.

Scheme 1.17. Mechanism for the Kumada-type reaction in the presence of TMEDA.

Scheme 1.18. The Fe(0)/Fe(I)/Fe(II) catalytic cycle in iron-catalysed Kumada-type reaction.

Iron-catalysed radical transfer reactions have also been implicated in other types of cross-coupling reaction such as the Heck-type reaction, the cross-dehydrogenative-coupling reaction and the radical cross-coupling between aryl halides and aryl compounds.
1.3 Interplay of Iron-Catalysed Radical and Hydride Transfer

In some reactions, both iron-catalysed hydride transfer and radical transfer may be involved in the reaction process. In such reactions, an iron hydride species is initially formed through a hydride transfer process from the hydride source to the iron centre, which can then donate a hydrogen atom to unsaturated systems such as alkenes to give radical intermediates. A variety of products can then be accessed using different radical traps (Scheme 1.19).^58

Scheme 1.19. Interplay of iron-catalysed radical and hydride transfer.

One typical example of this type of reaction is the iron-mediated radical hydrofluorination of an unactivated alkene, as reported by the group of Boger^59-60 Using sodium boron hydride as the hydride source and Selectfluor as the fluorine radical source, the reaction tolerated a wide range of substrates under mild reaction conditions. The hydrofluorination products were isolated in 41-79% yields in just 5-30 minutes. In the reaction of substrate 25, cyclised product 26 was isolated in 40% yield, which was supportive of a radical mechanism (Scheme 1.20).

Scheme 1.20. Iron-mediated radical hydrofluorination of olefins.
Inspired by this work, Baran and co-workers\textsuperscript{61-62} reported their work in iron-catalysed reductive coupling of alkenes using hydrosilane as the hydride source. Hydride transfer from the hydrosilane to the iron complex gave an iron hydride species. A hydrogen atom transfer (HAT) from the iron hydride to the alkene afforded the alkyl radical, which was added to a functionalised alkene. The radical addition product then underwent a single-electron transfer process to give a carbanion, regenerating the iron(III) catalyst. Protonation of the anion with solvent gave the reductive coupling product (Scheme 1.21). More recently, the same group extended this protocol to the formal hydroamination of alkenes with nitroarenes.\textsuperscript{63} In this work, nitrosoarenes, that were generated \textit{in situ} from the partial reduction of nitroarenes, acted as the radical traps. A wide range of functional groups were well tolerated to give heavily substituted aniline derivatives in synthetically useful yields.

\textbf{Scheme 1.21.} Iron-catalysed reductive coupling of alkenes.

The interplay of iron-catalysed hydride and radical transfer has also been explored in iron-catalysed controlled radical polymerisation (Scheme 1.22). This interplay is especially apparent in the $\alpha$-diimine iron(II)-catalysed ATRP of styrene using an alkyl chloride initiator.\textsuperscript{64-65} The alkyl radical, generated from the corresponding alkyl chloride through a single-electron transfer process, can be trapped directly by the low oxidation-state iron species to form an iron-alkyl complex. $\beta$-Hydride elimination of the iron-alkyl complex afforded an iron-hydride species. Alternatively, the iron-hydride complex could be formed through the direct hydrogen atom transfer from the alkyl radical to the low oxidation-state iron complex. These hydride transfer reactions compete against radical propagation, meaning that catalyst design determines whether ATRP or a catalytic chain transfer mechanism dominates.
**Scheme 1.22.** Interplay of hydride transfer and radical transfer in iron-catalysed ATRP of styrenes.

1.4 Objectives

It can be concluded that iron-catalysed hydride transfer has been involved in the reduction or hydrofunctionalisation of a variety of substrates. Among the substrates that have been exploited, alkenes, alkynes and carbonyl compounds are the most extensively studied. For the hydrogenation or hydrofunctionalisation of alkenes and alkynes, tremendous advances have been achieved in the past several decades. The highly sensitive iron-based catalysts used by Chirik and co-workers in their seminal works have been simplified, with many easy-to-make, air and moisture stable iron complexes being developed. On the other hand, in iron-catalysed hydrogenation or hydrosilylation of carbonyl compounds, the iron complexes used are either difficult-to-make or sensitive towards air and moisture, particularly those hydridoiron complexes and N-heterocyclic carbene (NHC)/iron complexes: simplification of catalyst in these cases should be prioritised. Thus, in this thesis, hydrosilylation of carbonyl compounds using a simple, air and moisture stable iron(III) complex is developed.

Compared to iron-catalysed reduction of alkene/alkyne and carbonyl compounds, much less attention has been paid to the reduction of nitro compounds even though it is a process of great industrial importance. While iron-catalysed reduction of nitro compounds via hydrogenation and transfer hydrogenation have been widely studied, very few examples have been reported using hydrosilane as the reducing agent, which is easily available, easy-to-handle and inexpensive. Furthermore, as a milder reducing agent, using hydrosilane as reductant may help
increasing the chemoselectivity, which has always been a challenge in the reduction of nitro compounds bearing other reducible functionalities.

As for the iron-catalysed radical transfer reactions, focus has always been on iron-catalysed ATRP and Kumada-type cross-coupling reaction, using alkyl halides as the radical source. However, alkyl halides as radical source have rarely been applied in other types of reactions. Recent advances in transition-metal-catalysed formal Heck cross-coupling between alkyl halides and styrenes prompted us to investigate iron-based catalysts for this important transformation.

Recent work from the group of Baran has demonstrated that hydride transfer and radical transfer can be incorporated into one single reaction under iron catalysis, and has thus reported iron-catalysed formal hydroamination of alkenes using nitroarenes. However, high catalyst loading and high reaction temperature are required in order to obtain good yields. Thus, the simplification of the reaction conditions of this synthetically useful transformation has also been selected as a target of this thesis.
2. Amine-bis(phenolate) Iron(III)-Catalysed Hydrosilylation of Carbonyl Compounds

2.1 Introduction

The catalytic reduction of carbonyl compounds, particularly aldehydes and ketones, to the corresponding primary and secondary alcohols is among the most important organic transformations as alcohols are important intermediates for the synthesis of many industry-relevant products such as agrochemicals and pharmaceuticals. Among all the methods that have been well established for the reduction of ketones and aldehydes, catalytic transfer hydrogenation using alcohols or formic acid as hydride transfer reagents and direct hydrogenation using molecular hydrogen are the most widely used. Alternatively, the reduction of ketones and aldehydes into the corresponding alcohol products can be realised by catalytic hydrosilylation, followed by the cleavage of the formed Si-O bond upon aqueous workup, as hydrosilanes are inexpensive and easy-to-handle. Traditionally, this type of transformation is largely catalysed by the noble transition metals, particularly rhodium. However, considering the high cost and potential toxicity of these metals, it would be highly desirable to develop alternative catalysts for carbonyl hydrosilylation. Among all the metals available, iron seems to be the best choice as it is both abundant and significantly less toxic. Indeed, many successful catalytic systems have now been developed for the hydrosilylation of carbonyl compounds using iron-based catalysts.

2.1.1 Noble-Metal-Catalysed Carbonyl Hydrosilylation

Historically, the catalytic hydrosilylation of carbonyl compounds has been dominated by precious metals, particularly rhodium. Wilkinson’s catalyst was the first rhodium-based catalyst to be used for the hydrosilylation of carbonyl compounds. In the hydrosilylation of acetophenone with triethylsilane, the corresponding silyl ether product was obtained in 97% yield (Scheme 2.01). The active catalytic species was isolated as (PPh₃)₂Rh(H)(SiEt₃)Cl, which is formed by the oxidative addition of triethylsilane to the catalyst after the dissociation of one PPh₃ ligand.

Scheme 2.01. Wilkinson’s catalyst as an efficient catalyst for carbonyl hydrosilylation.
Shortly after this seminal work in rhodium-catalysed carbonyl hydrosilylation, the groups of Ojima,\(^7\) Kumada\(^7\) and Kagan\(^6\) reported the asymmetric version of this reaction by the introduction of chiral ligands. Since then, a large number of chiral rhodium-based complexes have been reported for asymmetric ketone reduction.\(^7\)-\(^8\) Other noble metals such as ruthenium\(^8\)-\(^8\) and iridium\(^6\)-\(^8\) are also widely used as catalysts for the hydrosilylation of carbonyl compounds.

### 2.1.2 Iron-Catalysed Carbonyl Hydrosilylation

In 1990, Brunner first reported the hydrosilylation of benzophenone using [Fe(Cp)(CO)] as the catalyst under photo-irradiation conditions.\(^4\)-\(^4\)\(^2\)\(^3\) In 2007, the group of Nishiyama reported the first general iron-catalysed hydrosilylation of ketones.\(^4\)\(^4\) In the same year, Beller and co-workers\(^8\)\(^7\) reported a general and highly chemoselective hydrosilylation of aldehydes using polymethylhydrosiloxane (PMHS) as the reductant. Fe(OAc)\(_2\) together with tricyclohexylphosphine (PCy\(_3\)) acted as an efficient catalytic combination for the hydrosilylation of a variety of aldehydes, with up to 99\% isolated yields (Scheme 2.02). This catalytic system was then extended to the hydrosilylation of ketones.\(^8\)\(^8\) Replacing the tricyclohexylphosphine ligand with a chiral phosphine ligand helped realise the asymmetric hydrosilylation of ketones with moderate to excellent enantioselectivities.\(^8\)\(^8\)-\(^8\)\(^9\)

**Scheme 2.02.** Aldehyde hydrosilylation catalysed by iron/phosphine.

![Scheme 2.02](image)

In the following year, Nishiyama and Furuta\(^9\) demonstrated that sodium thiophene-2-carboxylate 34 was a superior ligand for Fe(OAc)\(_2\) in the hydrosilylation of acetophenones. Compared to their previous work in which TMEDA was used as the ligand, significant improvements in both yields and selectivities were achieved (Scheme 2.03). The stronger bonding between the sulphur-containing ligand 34 and the iron centre may contribute to the improved activity. This catalytic combination was then tested in the hydrogenation and transfer hydrogenation of carbonyl compounds, though in this case catalytic efficiency was dramatically decreased.
Scheme 2.03. Thiophene derivatives as ligands for iron-catalysed hydrosilylation of ketones.

Bis(imino)pyridine iron(0) complex 1, which had been shown to be a potent catalyst for the hydrosilylation of alkenes,\textsuperscript{27} also exhibited high activity in the hydrosilylation of carbonyl compounds.\textsuperscript{89} In the hydrosilylation of 4-methylbenzaldehyde and acetophenone with Ph\textsubscript{2}SiH\textsubscript{2}, the substrates were quantitatively hydrosilylated in less than 1 hour at room temperature in pentane. Complexes 35 and 36, which are more stable than the dinitrogen complex 1, also catalysed the hydrosilylation of various ketones and aldehydes with high efficiency in the absence of an activator. The catalyst loading can be lowered to 0.1 mol\% when complex 36 is used as the catalyst (Scheme 2.04).\textsuperscript{91}

Scheme 2.04. Bis(imino)pyridine iron(II) complex-catalysed hydrosilylation of carbonyls.

Hydridoiron complexes have found wide application in a variety of catalytic reactions. In fact, in many iron-catalysed reduction reactions, hydridoiron species are always thought to be the active intermediates. A number of representative examples of iron-hydrido complexes that have been reported in the past decade for the carbonyl hydrosilylation are outlined in Figure 2.01.\textsuperscript{92-95}
In 2008, Nikonov and co-workers\(^92\) synthesised a non-classical silyl iron dihydride complex 37 by reaction of iron hydride complex \([\text{Cp}^*(\text{iPr}_2\text{MeP})\text{FeH}]\) with \(\text{H}_2\text{SiMePh}\). The complexation of hydrosilane was not realised through Si-H oxidative addition or \(\sigma\)-coordination. Instead, the donation of the hydride of the silane to the iron centre and an interaction between the silyl and the metal-bonded hydride were involved to form a non-classical H-Si-H bonding interaction. The complex was tested in the catalytic hydrosilylation of benzaldehyde. In the presence of 5 mol\% of catalyst 37, the starting benzaldehyde was consumed within 12 hours at 50 °C using \(\text{H}_2\text{SiMePh}\) as the reducing agent.

Guan and co-workers developed a POCOP pincer-type ligand supported iron hydrido complex 38 for the hydrosilylation of both ketones and aldehydes (Scheme 2.05).\(^93\) The reactions of aldehydes proceeded well, to give the corresponding primary alcohols in good to excellent yields within 3 hours in most cases. Ketones turned out to be more difficult substrates as lower yields were obtained even at higher temperatures and prolonged reaction times.

**Scheme 2.05.** Iron hydrido complex supported by a POCOP pincer ligand for carbonyl hydrosilylation.

\[
\text{RCHO} + \text{(ETO)}_2\text{SiH (1.1 equiv)} \xrightarrow{\text{THF, 50-65 °C}} \text{1.0 mol\% 38} \xrightarrow{\text{10\% NaOH, 50 °C, MeOH}} \text{RCH}_2\text{OH} \text{ up to 92\%}
\]

\[
\begin{align*}
\text{R}^\prime & \text{R}'' & \xrightarrow{\text{THF, 50-80 °C}} \xrightarrow{\text{1.0 mol\% 38}} \text{10\% NaOH, 50 °C, MeOH} & \text{OH} \\
\text{R}^\prime & \text{R}'' & & \end{align*}
\]

Bis(diphenylphosphinoethane)iron dihydride complex 39 was used for the hydrosilylation of both aldehydes and ketones using PMHS as the reducing agent under visible light irradiation.\(^94\) NaB(OEt)₄ as a co-catalyst was necessary for the reaction to occur, as no hydrosilylation product was obtained in the absence of it. One significant feature of this system is that the catalyst loading can be lowered to 0.1 mol\% (Scheme 2.06).
Scheme 2.06. Hydridoiron complex-catalysed hydrosilylation under visible light irradiation.

\[
\begin{align*}
\text{R'CO} & \xrightarrow{\text{Fe(OAc)}_2 \ (2.5 \text{ mol\%})} \text{PMHS (2.0 equiv)} \xrightarrow{\text{NaB(OE)I}_4 (1.0 \text{ mol\%})} \text{toluene, 100 °C} \xrightarrow{\text{2 N NaOH, MeOH}} \text{R'COH} \\
\text{visible light} & & \text{r.t, overnight}
\end{align*}
\]

N-Heterocyclic carbene(NHC)/iron complexes constitute another important catalyst family for carbonyl hydrosilylation (Figure 2.02). Darcel and Sortais \(^{96}\) reported the first NHC/iron(II) complex-catalysed hydrosilylation of aldehydes and ketones in 2011, where both neutral and cationic cyclopentadienyl(NHC) iron complexes 41 and 42 were used as catalysts. When the cationic complex 41 was used, visible light activation was necessary for the generation of the active catalytic species, whereas the neutral one worked well at 30 °C without any activation.

Figure 2.02. Selected examples of N-heterocyclic carbene(NHC)/iron complexes for the hydrosilylation of carbonyl compounds.

In the same year, Adolfsson and co-workers \(^{97}\) employed the commercially available NHC precursor [IPr][HCl] \(^{43}\) [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazo-2-ylidene] for the hydrosilylation of ketones together with a catalytic amount of Fe(OAc)\(_2\) (Scheme 2.07). The carbene precursor was deprotonated in situ using n-BuLi. A reaction time of 16-18 hours was required in most cases for the full conversion of the starting material, suggesting a relatively low catalyst activity, which was attributed to the steric hindrance provided by the carbene ligand.

Scheme 2.07. Carbonyl hydrosilylation with sterically hindered NHC/iron complex.

\[
\begin{align*}
\text{13} & \xrightarrow{\text{1. Fe(OAc)}_2 (2.5 \text{ mol\%}) \ [\text{IPr}][\text{HCl}] (3.0 \text{ mol\%}), \text{n-BuLi (3.0 mol\%)} \ PMHS (3.0 equiv), \text{THF, 65 °C, 18 h}} \text{14, 99\% conversion} \\
\text{14} & \xrightarrow{\text{2. NaOH (aq), MeOH, r.t, 2 h}} \text{14, 99\% conversion}
\end{align*}
\]
In a follow-up study, the authors evaluated other less sterically hindered NHC precursors for the hydrosilylation of ketones and aldehydes in order to obtain increased activity.98 Substantial improvements in terms of activity were observed when [HEMIM][OTf] 44 [HEMIM = 1-(2-hydroxyethyl)-3-methylimidazolium] was used as the ligand precursor. The corresponding primary or secondary alcohols were obtained in good to excellent yields within a short reaction time (0.5-3 h) with a catalyst loading of 1.0 mol%.

The group of Royo synthesised a cyclopentadienyl-functionalised NHC/iron(II) complex 46 for the hydrosilylation of carbonyl compounds.99 Structurally, the carbene moiety and the cyclopentadienyl ring are connected by a linker. The catalyst exhibited excellent activity and chemoselectivity towards the hydrosilylation of benzaldehydes bearing electron-withdrawing groups. However, substrates with electron-donating groups were not included in this study. Aromatic ketones and aliphatic aldehydes were not suitable substrates, since no hydrosilylated products were obtained (Scheme 2.08).

**Scheme 2.08.** Cp*-NHC/iron(II) complex catalysed hydrosilylation of carbonyl compounds.

A series of [Fe(NHC)(CO)₄] complexes were synthesised by the reaction of Fe₃(CO)₁₂ with imidazolium halides by the same group.100 The activity of the resulting complexes in the hydrosilylation of benzaldehyde was then evaluated. [Fe(IMes)CO₃] 47 [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene] turned out to be the most active catalyst, giving the benzyl alcohol product in 94% isolated yield under optimised reaction conditions.

Ohki, Tatsumi and Glorius101 have synthesised bis(N-heterocyclic carbene) iron(II) complexes for the hydrosilylation of carbonyl compounds. Although the NHC adduct of FeCl₂ 48 has a tetrahedral geometry, treating 48 with MeLi gave complex 49 with square-planar geometry (Figure 2.02). In terms of activity, [(IMes)₂FeCl₂] 48 exhibited no activity towards the
hydrosilylation of acetophenone derivatives while [(IMes)$_2$FeMe$_2$]$_4$ gave excellent yields, with the catalyst loading being as low as 0.1 mol% (Scheme 2.09).

**Scheme 2.09.** Carbonyl hydrosilylation with bis(N-heterocyclic carbene) iron(II) complexes.

In 2010, Tilley and Yang$^{102}$ reported a simple amido iron(II) catalyst [Fe{N(SiMe$_3$)$_2$}]$_2$ for the hydrosilylation of carbonyl compounds at ambient temperature. No external ligand was needed and in some cases, even a catalyst loading of 0.01 mol% led to complete conversion of the starting materials (Scheme 2.10, upper equation). A catalyst formed *in situ* from FeBr$_2$ and KN(SiMe$_3$)$_2$ exhibited almost equal activity in the hydrosilylation of 4-methoxyacetophenone 59 (Scheme 2.10, lower equation). The detailed mechanism of the reaction is still unknown, though, *in situ* monitoring of the reaction mixture by $^1$H NMR suggested the formation of HN(SiMe$_3$)$_2$ during the reaction process.

**Scheme 2.10.** Simple iron-amido complex as an efficient catalyst for carbonyl hydrosilylation.

In their seminal work on iron-catalysed carbonyl hydrosilylation, Nishiyama and Beller realised asymmetric hydrosilylation by the introduction of chiral ligands.$^{44,88-89}$ For example, up to 79% ee was obtained by Nishiyama using chiral ligands 62-64 (Scheme 2.11)$^{44}$

**Scheme 2.11.** Chiral bisoxazoline ligand supported iron complex in ketone hydrosilylation.
Since these pioneering works in asymmetric hydrosilylation of ketones, a large number of chiral ligand-supported iron complexes have been designed and synthesised for this type of reaction, with selected examples shown in Figure 2.03.103-108

**Figure 2.03.** Chiral ligands and complexes in iron-catalysed asymmetric hydrosilylation of carbonyl compounds.
2.2 Results and Discussion

2.2.1 Project Aims

The hydrosilylation of carbonyl compounds followed by aqueous workup represents a practical method for the preparation of alcohols. The iron-catalysed version of this reaction has attracted extensive attention over the past several decades. However, the most efficient catalysts that have been developed so far are either difficult to make or highly sensitive towards air and moisture. Thus, the development of iron complexes that combine both structural simplicity and high reactivity would be highly desirable. Amine-bis(phenolate) iron(III) complexes, which have been extensively studied for iron-catalysed ATRP reactions,\cite{109,110,111} seem to be a good choice as they are simple, easy-to-make and more importantly, air- and moisture-stable. Thus, the aim of this project is the methodology development of carbonyl hydrosilylation using amine-bis(phenolate) iron(III) complexes as catalysts.

2.2.2 Condition Screening

Methodology development began with the hydrosilylation of benzophenone 81 with triethoxysilane. No desired product 82 was obtained when the reactions were conducted in non-coordinating solvents such as hexanes and benzene, using amine-bis(phenolate) iron(III) complex 83 as the catalyst (Table 2.01, entries 1 and 2). However, when the reactions were conducted in coordinating solvents such as THF and acetonitrile, 30% and 70% yields were obtained, respectively, after 24 hours at 60 °C (entries 3 and 4). Conversion of 96% for benzophenone was obtained when the reaction temperature was increased to 100 °C under otherwise identical conditions (entry 5). The reaction time was further reduced to 30 minutes when amine-bis(phenolate) iron(III) complex 84 was used as the catalyst (entry 6). Amine-bis(phenolate) iron(III) complexes 85 and 86 only gave the product in 5% yield even after 24 hours (entries 7 and 8), suggesting that an iron complex that is electron-rich is needed for efficient catalytic activity. Although a longer reaction time was needed, polymethylhydrosiloxane, an inexpensive, environmentally benign hydride source, was found to be a suitable reducing agent, giving the alcohol product in 96% yield (entry 9). A longer reaction time of 6 hours was required when the amount of triethoxysilane was reduced from 3.0 equivalents to 1.5 equivalents (entry 10). Reducing the catalyst loading also led to a prolonged reaction time (entry 11). When the reaction temperature was lowered to 80 °C, a longer reaction time of 3 hours was needed (entry 12). No reaction occurred when FeCl₃ was used as the catalyst, suggesting that the amine-bis(phenolate) ligand is necessary for activity (entry 13).
### Table 2.01. Condition optimisation of the iron-catalysed carbonyl hydrosilylation

<table>
<thead>
<tr>
<th>entry</th>
<th>cat</th>
<th>T/°C</th>
<th>solvent</th>
<th>silane</th>
<th>Time/h</th>
<th>Conv%b</th>
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<td>CD3CN</td>
<td>HSi(OEt)3</td>
<td>24</td>
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</table>

*a* Unless otherwise noted, all reactions were carried out using 3.0 equiv. of hydrosilane (0.9 mmol), 1.0 equiv. of benzophenone 81 (0.3 mmol), 0.02 equiv. of catalyst (0.006 mmol) in 0.3 mL solvent.  
b Determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard.  
c 1.5 equiv of HSi(OEt)3 was used.  
d 0.01 equiv of catalyst was used.  
*e* Isolated yield. N.R = no reaction.

By comparing the activity of complexes 83 and 84, it seems that a weaker donating group on the side-arm of the ligand increases the reactivity. Thus, we hypothesise that the dissociation of the side-arm is essential to the catalytic activity by providing a vacant coordinating site for the carbonyl compound. The huge difference between activities of complexes 83 and 86 suggests electron-withdrawing group on the benzene ring of the ligand is inhibitory to the
activity, as the electron-withdrawing groups decrease the coordinating of the phenolate oxygen to the iron, which would in turn increases the donating of the side-arm to the iron.

### 2.2.3 Substrate Scope and Limitations

The substrate scope of the hydrosilylation of ketones was then examined using the reaction conditions of 1 mol % of catalyst 84, 3.0 equiv of triethoxysilane in MeCN (1.0 M) at 80 °C. In all the reactions, the reaction mixture was treated with a 1M NaOH solution after completion to convert the hydrosilylated products into alcohols (Scheme 2.12). In most cases, good to excellent yields of the alcohol products were obtained, demonstrating the potential utility of this methodology in synthesis. Non-substituted acetophenone was readily reduced to give the product 14 in 91% isolated yield. Acetophenone derivatives bearing electron-donating groups were well tolerated to give the alcohol products 87-89 with 90-93% isolated yields. Acetophenone with a strongly electron-withdrawing CF₃ group turned out to be much less reactive, with only a 55% yield of the product 90 being obtained, even after 24 hours. In the case of the reduction of 4-bromoacetophenone, no protodehalogenation was observed and the alcohol product 91 was isolated in 87% isolated yield after a slightly longer reaction time. As iron-catalysed protodehalogenation always proceeds through the oxidative addition of the substrate to the *in situ* generated low-valent iron species, we suggest in our system, iron-species with low oxidation-state are not formed. 4-Acetylbiphenyl 29 was readily reduced to give the alcohol product 30 in 90% isolated yield. Cyclohexanol 92 was obtained from the reduction of cyclohexanone in 55% yield as determined by ¹H NMR.

**Scheme 2.12.** Substrate scope for the iron-catalysed hydrosilylation of ketones

*Unless otherwise noted, all reactions were carried out using 3.0 equiv. of hydrosilane (1.8 mmol), 1.0 equiv. of ketone (0.6 mmol), 0.01 equiv. of catalyst 84 (0.006 mmol) in 0.6 mL solvent at 80 °C.*

---

---
Isolated yields. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard are given in parenthesis.

With the success in the hydrosilylation of ketones, attention was then paid to aldehyde substrates (Scheme 2.13). Benzaldehyde was readily reduced to give benzyl alcohol 93 in 84% isolated yield. No protodehalogenation$^{112}$ was observed in the reactions of halogenated substrates, suggesting good chemoselectivity of the catalyst towards the hydrosilylation of carbonyl groups. The good chemoselectivity of this catalytic system was further demonstrated in the hydrosilylation of 4-acetylbenezonitrile. The nitrile group remained intact during the reaction and the corresponding 4-(hydroxymethyl)benzonitrile 96 was isolated in 81% yield. Electron-neutral substituents such as a methyl group and an electron-donating methoxy group were well tolerated to give the alcohol products 97 and 98 in excellent yields. A longer reaction time was needed for an aldehyde with a moderately electron-withdrawing F$_3$CO group, but without a significant decrease in yield. No ring-opening product was observed in the reaction of a heterocyclic substrate to give 5-ethyl-2-furanmethanol 100 in 86% yield. Unlike the hydrosilylation of an aliphatic ketone, that led to a significantly decreased yield, cyclohexylmethyl alcohol 101 was obtained in 91% yield.

Scheme 2.13. Substrate scope of the iron-catalysed hydrosilylation of aldehydes$^a$

$^a$ Unless otherwise noted, all reactions were carried out using 3.0 equiv. of hydrosilane (1.8 mmol), 1.0 equiv. of aldehyde (0.6 mmol), 0.01 equiv. of catalyst 84 (0.006 mmol) in 0.6 mL solvent at 80 °C. $^b$ Isolated yields. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard are given in parenthesis.

Currently, this system only works for the hydrosilylation of ketones and aldehydes, since other carbonyl derivatives such as esters and imines could not be reduced under the optimised reaction conditions (Scheme 2.14).
**Scheme 2.14.** Hydrosilylation of ester and imine.

![Scheme 2.14](image)

Hydrosilylation of CO₂ has recently emerged as a powerful tool for the synthesis of silyl formate, which is a versatile intermediate for the synthesis of a large number of fine chemicals. Compared to noble-metal-catalysed hydrosilylation of CO₂, iron-catalysed hydrosilylation of CO₂ is still largely unexplored. The current system was also tested in the hydrosilylation of CO₂, though only a 5% yield of the silyl formate product 104 was obtained (Scheme 2.15).

**Scheme 2.15.** Iron-catalysed hydrosilylation of CO₂

![Scheme 2.15](image)

In the hydrosilylation of α,β-unsaturated ketone 105, although a lower yield was obtained, no reduction of the C-C double bond was detected, suggesting good chemoselectivity in this catalytic system (Eq 1, Scheme 2.16). Cinnamaldehyde 107 was reduced exclusively into the corresponding cinnamyl alcohol 108 in 81% isolated yield, and no reduction of the C-C double bond was detected (Eq 2, Scheme 2.16).

**Scheme 2.16.** Chemoselective hydrosilylation of unsaturated carbonyl compounds.

![Scheme 2.16](image)

*a The reactions were carried out using 3.0 equiv. of hydrosilane (1.8 mmol), 1.0 equiv. of substrate (0.6 mmol), 0.01 equiv. of catalyst 84 (0.006 mmol) in 0.6 mL solvent at 80 °C for 3 h. *b Isolated yields.
Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard are given in parenthesis.

Gram-scale hydrosilylation of benzophenone was carried out using PMHS as the reducing agent, which is environmentally benign and inexpensive. The alcohol product, which is a key building block for the synthesis of vigilance promoting drug Modafinil (Brand name: Provigil), was obtained in 90% yield with 2.0 mol% of catalyst 84 (Scheme 2.17).

Scheme 2.17. Gram-scale hydrosilylation of benzophenone with PMHS$^a$

\[ \text{Scheme 2.17. Gram-scale hydrosilylation of benzophenone with PMHS$^a$} \]

$^a$ The reactions were carried out using 3.0 eq. of PMHS (36.0 mmol), 1.0 eq. of benzophenone (12.0 mmol), 0.02 eq. of catalyst 84 (0.024 mmol) in 12 mL MeCN at 100 °C for 4 h. $^b$ Isolated yields.
2.2.4 Mechanistic Considerations

Although iron-catalysed carbonyl hydrosilylation has advanced tremendously in the past several decades, mechanistic study of this reaction is still in its infancy and only a very limited examples are available in the literature. In their work on carbonyl hydrosilylation catalysed by a POCOP pincer-type ligand supported iron-hydrido complex 38, Guan and co-workers\textsuperscript{93} proposed an outer sphere mechanism. One PMe\textsubscript{3} ligand was proposed to dissociate during the reaction, thus providing a vacant binding site for either the carbonyl compound or the hydrosilane. The hydride ligand remains bound to the metal centre during the reaction process (Scheme 2.18).

Scheme 2.18. Iron-catalysed carbonyl hydrosilylation through an outer sphere mechanism.

However, a recent DFT study suggested a completely different reaction pathway, in which the hydride ligand directly participated in the reaction to form an alkoxide complex. This then undergoes \(\sigma\)-metathesis with one equivalent of hydrosilane to give the hydrosilylated product, regenerating the iron hydride complex.\textsuperscript{113}

Shortly after their report on the highly enantioselective ketone hydrosilylation catalysed by a bis(oxazolinylmethylidene)isoindoline ligand supported iron(II) precatalyst 80,\textsuperscript{108} Gade and co-workers elucidated the mechanism of the reaction.\textsuperscript{114} \(\sigma\)-Metathesis between the precatalyst and hydrosilane was thought to be the rate-determining step (RDS), forming an iron hydride species. The coordination and subsequent insertion of the ketone substrate to the iron hydride
species regenerated the alkoxide iron complex and released the hydrosilylation product (Scheme 2.19).

**Scheme 2.19.** Proposed mechanism of bis(oxazolinylmethylidene)isoindoline-supported iron(II)-catalysed carbonyl hydrosilylation.

A non-classical peripheral mechanism was proposed by Driess and Oestreich for carbonyl hydrosilylation catalysed by an iron(0) pincer complex 109$^{115}$. In this mechanism, the silyl group that was attached to the iron centre acted as Lewis acid for the activation of the carbonyl compound. The coordination of another equivalent of hydrosilane to the carbonyl released the hydrosilylation product and the active catalyst (Scheme 2.20).

**Scheme 2.20.** The non-classical peripheral mechanism for carbonyl hydrosilylation.
It can be concluded from those previous studies, iron-catalysed hydrosilylation of carbonyl compounds generally involves the formation of an iron-hydride species, the coordination of the carbonyl substrate to the iron centre, the insertion of the carbonyl substrate into the Fe-H bond and finally dissociation of the iron-alkoxide complex. Inspired by this, a mechanism involving an iron-hydride intermediate is proposed as shown in Scheme 2.21. The active iron-hydride species 110 is formed by the metathesis between complex 84 and hydrosilane, followed by the coordination of the carbonyl substrate to the iron centre. Insertion of the substrate into the Fe-H bond gives an iron-alkoxide intermediate. Metathesis between the iron-alkoxide complex and hydrosilane gives the product and regenerates the active iron-hydride complex.

Scheme 2.21. Proposed mechanism of amine-bis(phenolate) iron(III)-catalysed carbonyl hydrosilylation.

To test the feasibility of such a mechanism, the direct reaction between catalyst 84 and triethoxysilane was carried out as an effort to isolate the iron-hydride complex. A colour change of the reaction mixture was observed. Before heating, the reaction mixture featured the colour of the iron complex, which was dark blue. After being heated at 80 °C for about 30 minutes, the reaction mixture turned colourless. To isolate the colourless iron species, the reaction of complex 84 and triethoxysilane in hexanes was carried out, since we hypothesised that the insolubility of the catalyst in hexanes would give a precipitate containing the iron species, thus facilitating the isolation process. As expected, the decolourisation of the complex in hexanes turned out to be much lower than that in acetonitrile due to the poor solubility of the complex. After being stirred at 80 °C for 24 hours, the dark blue colour of the suspension disappeared completely to give a highly air- and moisture-sensitive colourless precipitate (Scheme 2.22), which was collected by decanting the solvents, washed with hexanes and analysed by ³¹H NMR. Unlike the iron(III) complex which is ¹H NMR silent, three broad peaks
were obtained for this colourless species with chemical shifts of 25.31(s), 32.80 (s) and 80.02 (br), suggesting the possible formation of an iron(II) species. Furthermore, ClSi(OEt)_3 was not observed in the reaction mixture, which is supposed to be observed if the reaction proceeds through the mechanism as depicted in **Scheme 2.21**.

**Scheme 2.22.** Reaction of complex 84 and triethoxysilane.

Previous studies have demonstrated that iron(III) can be reduced in the presence of reductant during the hydrosilylation of carbonyl compounds. In their work on iron(III)-catalysed asymmetric hydrosilylation of ketones, Nishiyama and co-workers suggested that the iron(III) was reduced *in situ* by zinc to give the active species. Treatment of the catalyst solution in THF with zinc led to a colour change of the solution from green to yellow. The colour change corresponded with a decrease in the magnetic moment of the complex from 5.9 µB to 4.8 µB, suggesting the formation of a high-spin iron(II) species. Based on the experimental results, it is highly possible that in our system, the iron(III) precatalyst was also reduced before entering the catalytic cycle, probably by hydrosilane. The elucidation of the mechanism of the reduction of the catalyst and the full identification of the structure of this iron intermediate will be the focus of future work.

### 2.3 Conclusions

The highly efficient hydrosilylation of carbonyl compounds was established using a simple, easy-to-handle, air- and moisture-stable iron(III) amine-bis(phenolate) complex 84 as the catalyst. By using triethoxysilane as the reducing agent, a wide range of substrates were tolerated, giving the corresponding alcohol products in good to excellent yields after hydrolysis of the hydrosilylated products (**Scheme 2.23**). Initial results show that the current system is reactive towards the hydrosilylation of CO2, although with low conversion. Initial results also suggest that the amine-bis(phenolate) iron(III) complex 84 is reduced by silane under the same reaction conditions, to give an iron(II) species, although the structure of this has not yet been established.
Scheme 2.23. Iron-catalysed hydrosilylation of carbonyl compounds.

\[
\begin{align*}
\text{Scheme 2.23. Iron-catalysed hydrosilylation of carbonyl compounds.} \\
\text{[Chemical Structures]} \\
\text{3 h, 84% (90%)} & \quad \text{3 h, 92% (95%)} & \quad \text{3 h, 88% (93%)} & \quad \text{4 h, 81% (86%)} & \quad \text{3 h, 90% (96%)} \\
\text{3 h, 88% (94%)} & \quad \text{6 h, 89% (92%)} & \quad \text{6 h, 86% (90%)} & \quad \text{3 h, 91% (96%)} & \quad \text{3 h, 91% (97%)} \\
\text{3 h, 90% (97%)} & \quad \text{3 h, 90% (94%)} & \quad \text{3 h, 93% (96%)} & \quad \text{24 h, 55% (60%)} & \quad \text{4 h, 87% (92%)} \\
\text{3 h, 90% (94%)} & \quad \text{3 h, (55%)} & \quad \text{3 h, 55% (65%)} & \quad \text{3 h, 81% (87%)} & \quad \text{12 h, (5%)}
\end{align*}
\]
3. Amine-bis(phenolate) Iron(III)-Catalysed Reduction of Nitro Compounds and Formal Hydroamination

3.1 Introduction

The reduction of nitro compounds, especially the reduction of nitroarenes to the corresponding aniline and aniline derivatives, represents one of the most important transformations in industry, as aniline and its derivatives are versatile intermediates for the synthesis of fine chemicals such as polymers, dyes and pigments and rubber additives. As one of the most fundamental organic reactions, the early examples of this reaction largely depended on the use of stoichiometric metal, together with acids, a process that is known as the Bechamp reduction (Scheme 3.01).

Scheme 3.01. Nitro reduction with stoichiometric metals.

Although highly active, the generation of large amounts of metal waste make this method less than ideal for large-scale industrial production. Thus, the development of a catalytic process is highly desired. The catalytic reduction of nitro compounds has been dominated by noble metals to date, particularly platinum and palladium, using gaseous hydrogen as the reducing agent. However, the high cost and high toxicity of those metals have limited their application in industry. Furthermore, those methods always exhibit poor chemoselectivity when other reducible functionalities are present, affording undesired by-products.

Thus, the development of catalytic methods for the reduction of nitro compounds with high chemoselectivity using inexpensive and environmentally benign catalysts has always been a hot topic in synthetic chemistry. As a result, iron-catalysed reduction of nitro compounds has attracted extensive attention in recent years.

3.2 Iron-Catalysed Nitro Reduction

As an alternative to precious metals, the high abundance, low cost and bio-compatibility of iron make the iron-catalysed version of nitro reduction more advantageous than a reaction catalysed by precious metals. Many successful iron-based catalytic systems have been
developed in the past decades for nitro reduction, using various reducing agents such as gaseous hydrogen, hydrazine hydrate, hydrosilanes and formic acid, amongst others.14, 16, 19

3.2.1 Hydrogen as the Reducing Agent

The group of Chaudhari119 has reported a catalytic combination of FeSO₄∙7H₂O and EDTANa₂ (EDTA = ethylenediaminetetraacetic acid) for the highly chemoselective hydrogenation of nitroarenes. The good solubility of the catalyst in water made it possible to carry out the reactions in an aqueous/organic biphasic medium. At the end of the reaction, the catalyst remained in the aqueous phase, while the product was in the organic phase, which allows it to be easily separated from the catalyst. The aqueous phase, containing the catalyst, can be reused for 8 cycles without significant loss of either reactivity or chemoselectivity (Scheme 3.02).

**Scheme 3.02.** Iron-catalysed hydrogenation of nitroarenes in a biphasic medium.

Beller and co-workers120 reported a carbon-supported Fe₂O₃-based heterogeneous catalyst for the chemoselective hydrogenation of aromatic nitro compounds. More than 80 examples were investigated, and in most cases both high yields and high chemoselectivities were obtained. Other reducible functionalities including carbonyls, nitriles, alkenes, alkynes and halogens all remained intact during the reaction. The broad substrate scope, high yield and excellent chemoselectivity has made it one of the most efficient systems for the reduction of nitroarenes into anilines. One major drawback of this method, however, is the high reaction temperature and high hydrogen pressure (Scheme 3.03).

**Scheme 3.03.** Carbon-supported iron catalyst for the hydrogenation of nitroarenes.

Beller’s group121 also reported an Fe(BF₄)₂-catalysed chemoselective hydrogenation of nitro compounds into the corresponding amines using a phosphine ligand. Excellent yields were obtained in most cases, however, the high temperature, high hydrogen pressure and the use of stoichiometric amounts of TFA may limit its further application in industry.
3.2.2 Hydrazine as the Reducing Agent

Hydrazine is another reducing agent that has been widely used in the reduction of nitro compounds. Due to the high toxicity of hydrazine, hydrazine hydrates are always used as hydrazine surrogates as they are much less toxic and easier to handle. In 2006, the research group of Lu\textsuperscript{122} demonstrated that polymer-supported hydrazine is also an excellent reductant for nitroarene reduction. The preparation of the polymer-supported hydrazine is straightforward: a macroporous acidic ion-exchange resin was washed with a 50% solution of hydrazine in methanol. The resin was subsequently washed with methanol and dried under vacuum. The resulting polymer was then used as a reducing agent for the chemoselective reduction of nitroarenes in the presence of iron oxide-hydroxide. The reaction proceeded smoothly in isopropanol at reflux and gave the aniline products in almost quantitative yields within 1 hour.

Iron phthalocyanine (FePc), together with iron sulfate, has been used by Singh and Kumar\textsuperscript{123} for the reduction of nitro compounds in a green solvent system using hydrazine hydrate as the reducing agent (Scheme 3.04). The reaction was highly chemoselective, tolerating other reducible functionalities such as amides, esters, nitriles, hydroxyls, heterocycles, ketones, carboxylic acids and halogens. Greater than 99% GC conversion was obtained in most cases.


Pyrolysis of a carbon-supported Fe(OAc)$_2$-phenanthroline complex gave a highly efficient heterogeneous catalyst for the chemoselective reduction of nitroarenes in excellent yields (90-99%). The catalyst can be reused at least 6 times without loss in either chemoselectivity or reactivity (Scheme 3.05).\textsuperscript{124}

Scheme 3.05. Carbon-supported iron catalyst for the reduction of nitroarenes with hydrazine.
The group of Kappe reported a nanocatalyst that exhibited unparalleled activity towards the reduction of nitroarenes. Under microwave irradiation, the active $\text{Fe}_3\text{O}_4$ nanoparticles were formed \textit{in situ} from an inexpensive iron precursor, which then catalysed the reduction of nitroarenes with high efficiency in just several minutes (Scheme 3.06).\textsuperscript{125}

\textbf{Scheme 3.06.} Microwave-facilitated reduction of nitro compounds.

A commercially available $\text{Fe}_3\text{O}_4$ nanoparticle ($< 50$ nm) was reported to be highly efficient for the reduction of nitro compounds in the presence of hydrazine hydrate. The magnetic properties of the catalyst allowed it to be easily separated from the reaction mixture and to be reused. Under optimal conditions, the catalyst can be reused up to 10 times without loss in activity. It should be noted that nitroalkanes were also reduced, although with lower yields (Scheme 3.07).\textsuperscript{126}

\textbf{Scheme 3.07.} $\text{Fe}_3\text{O}_4$-nanoparticle-catalysed reduction of nitroarenes with hydrazine hydrate.

Another highly active, magnetically separable heterogeneous catalyst was developed by Xu, Sun and Su.\textsuperscript{127} They successfully synthesised a sub-$10$ nm $\gamma$-$\text{Fe}_2\text{O}_3$-polymer composite without the use of a surfactant. The composites containing $3.5$ nm $\gamma$-$\text{Fe}_2\text{O}_3$ nanoparticles and porous polymer turned out to be highly active towards the reduction of nitrobenzene in the presence of hydrazine hydrate, when the reaction was carried out in ethanol at $85\,^\circ\text{C}$. The catalyst can be recycled $9$ times without significant loss in activity.

\textbf{3.2.3 Hydrosilane as the Reducing Agent}

As an alternative to the aforementioned reducing agents, hydrosilanes have attracted extensive attention in recent years as they are inexpensive, abundant and easy-to-handle. Although iron-catalysed hydrosilylation of other unsaturated compounds such as carbonyl compounds, alkenes and alkynes has been well explored, the reduction of nitro compounds using silanes as reducing agents is somewhat much less studied, with only a few examples having been reported so far.
The first example of iron-catalysed hydrosilylation of nitro compounds was reported by Nagashima’s group,\textsuperscript{128} when they were working on the iron-catalysed hydrosilylation of carboxamides. The authors established a highly efficient method for the reduction of carboxamides into their corresponding amines. Two iron complexes, Fe(CO)\textsubscript{5} and Fe\textsubscript{3}(CO)\textsubscript{12} were both active when tetramethyldisiloxane (TMDS) was used as the reducing agent. However, they found that in the case of \textit{N,N}-dimethyl-\textit{p}-nitrobenzamide, the nitro group was reduced chemoselectively to give \textit{N,N}-dimethyl-\textit{p}-aminobenzamide as the only product (Scheme 3.08). However, only four nitro substrates were investigated in this work, thus making the method not generally applicable.

**Scheme 3.08.** Chemoselectivity in iron-catalysed hydrosilylation of carboxamides.

\[
\begin{align*}
\text{R-} \text{CONMe}_2 & \xrightarrow{2.2 \text{ equiv TMDS}} \text{R-} \text{NHMe}_2 \\
& \xrightarrow{10 \text{ mol\% Fe(CO)}_\text{12}} \text{toluene, 110 °C} \\
& \text{R = 4-NO}_2 \\
& \text{5.0 equiv TMDS}
\end{align*}
\]

A combination of FeBr\textsubscript{2} and triphenylphosphine was used to catalyse the chemoselective reduction of nitroarenes using phenylsilane as the reducing agent, as reported by Beller and co-workers.\textsuperscript{129} A wider range of substrates was investigated in this study, and in most cases good yields of the aniline products were obtained (Scheme 3.09).

**Scheme 3.09.** General nitro hydrosilylation with phosphine-supported iron catalyst.

\[
\begin{align*}
\text{R-} \text{NO}_2 & \xrightarrow{10 \text{ mol\% FeBr}_2} \text{R-} \text{NH}_2 \\
& \xrightarrow{12 \text{ mol\% PPh}_3} \text{toluene, 16 h} \\
& \xrightarrow{2.5 \text{ equiv PhSiH}_3} 110 °C \\
& \text{27 examples} \\
& \text{25-99% yield}
\end{align*}
\]

Simple Fe(acac)\textsubscript{3} has also been reported to be a potent catalyst for the hydrosilylation of aromatic nitro compounds by Lemaire’s group, using tetramethyldisiloxane as the reducing agent (Scheme 3.10). Nitroarenes with substituents on the \textit{ortho}- position were not well tolerated however, giving the products in low yields.\textsuperscript{130-131}
Scheme 3.10. Fe(acac)$_3$-catalysed hydrosilylation of nitro compounds.

3.2.4 Other Reducing Agents

γ-Fe$_2$O$_3$ nanoparticles were successfully used for the transfer hydrogenation of nitroarenes using isopropanol as the hydride source and KOH as the base. Several other reducible groups such as esters, carbonyls and halogens were well tolerated, showing the good chemoselectivity of the catalyst. The heterogeneous nature of the catalyst allowed it to be reused at least 4 times without loss in activity.\textsuperscript{132}

Formic acid was used for the first time by Beller’s group for the transfer hydrogenation of nitroarenes in the presence of an iron/phosphine complex (Scheme 3.11).\textsuperscript{133}

Scheme 3.11. Iron-catalysed transfer hydrogenation of nitroarenes.

Our group has reported a Fe(OTf)$_3$-catalysed reduction of nitro compounds using sodium borohydride as the reducing agent.\textsuperscript{134} The reactions proceeded well in ethanol at room temperature to afford the aniline products in mostly high yields (Scheme 3.12).

Scheme 3.12. Simple iron salt as efficient catalyst for nitro reduction.
3.3 Results and Discussion

3.3.1 Project Aims

Although iron-catalysed reduction of nitro compounds using reducing agents such as hydrogen, hydrazine, or transfer hydrogenation conditions has been well established, iron-catalysed reduction of nitro compounds using hydrosilane is still largely underdeveloped. Encouraged by the success of amine-bis(phenolate) iron(III) complexes in the chemoselective reduction of carbonyl compounds, the major aim of this project is to explore if this simple yet stable iron complex can also be applied to the reduction of nitro compounds.

3.3.2 Condition Screening

In the previous chapter, a highly efficient method has been developed for the hydrosilylation of carbonyl compounds. We found that in the case of the hydrosilylation of \( p \)-nitroacetophenone 116, it is the nitro group that had been reduced and the carbonyl group remained intact during the reaction. The corresponding \( p \)-aminoacetophenone 117 was obtained in 80% \(^1\)H NMR yield together with 15% unreacted starting material using 1.0 mol% of catalyst 84 and 3.0 equivalents of triethoxysilane in MeCN at 80 °C for 4 hours (Table 3.01, entry 1).

The yield of \( p \)-aminoacetophenone 117 was improved to 95% by using 2.0 mol% of catalyst 84 and 4.0 equiv of hydrosilane under otherwise identical reaction conditions (entry 2). Both the yield and chemoselectivity dropped when amine-bis(phenolate) iron(III) complex 83 was used as the catalyst (entry 3).

The effects of solvent on the reactivity and chemoselectivity were then investigated. Both conversion and chemoselectivity dropped substantially when the reaction was conducted in toluene (entry 4). Using THF as solvent gave an even lower conversion and reduction of the carbonyl group was observed (entry 5). A significantly decreased chemoselectivity was observed when the reaction was carried out in ethyl acetate (entry 6).

\( \text{PhSiH}_3 \) gave a reduced conversion and chemoselectivity (entry 7). It was observed that the steric effects of the silanes influenced the reaction outcome significantly. \( \text{Ph}_2\text{SiH}_3 \), which is sterically more hindered than \( \text{PhSiH}_3 \), gave even lower conversions and chemoselectivities (entry 8). Sterically more hindered silanes such as \( \text{Ph}_2\text{MeSiH} \) and \( (\text{Me}_3\text{SiO})_2\text{MeSiH} \) showed no reactivity towards either the nitro or carbonyl groups, probably due to increased steric hindrance (entries 9 and 10).

A 5.0 mol% catalyst loading was needed in order to reach full conversion of the starting material when diethoxymethylsilane was used as the reducing agent in place of triethoxysilane.
The ketoamine 117 was obtained in 90% yield together with 5% of alcohol 118, suggesting a slight decrease in the chemoselectivity (entry 11).

Table 3.01. Condition optimisation of the iron-catalysed chemoselective hydrosilylation of 4-nitroacetophenone

<table>
<thead>
<tr>
<th>entry</th>
<th>cat</th>
<th>solvent</th>
<th>silane</th>
<th>116 (%)(^c)</th>
<th>117 (%)(^c)</th>
<th>118 (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>84</td>
<td>MeCN</td>
<td>HSi(OEt)(_3)</td>
<td>15</td>
<td>80</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>MeCN</td>
<td>HSi(OEt)(_3)</td>
<td>trace</td>
<td>&gt;95(91)(^d)</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>MeCN</td>
<td>HSi(OEt)(_3)</td>
<td>7</td>
<td>79</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>PhMe</td>
<td>HSi(OEt)(_3)</td>
<td>46</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>THF</td>
<td>HSi(OEt)(_3)</td>
<td>84</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>EtOAc</td>
<td>HSi(OEt)(_3)</td>
<td>51</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>MeCN</td>
<td>PhSiH(_3)</td>
<td>22</td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>84</td>
<td>MeCN</td>
<td>Ph(_2)SiH(_2)</td>
<td>55</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>84</td>
<td>MeCN</td>
<td>Ph(_2)MeSiH</td>
<td>&gt;95</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>84</td>
<td>MeCN</td>
<td>(Me(_3)SiO)(_2)MeSiH</td>
<td>&gt;95</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11(^c)</td>
<td>84</td>
<td>MeCN</td>
<td>HSiMe(OEt)(_2)</td>
<td>trace</td>
<td>90</td>
<td>5</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise noted, all reactions were carried out using 4.0 eq. of hydrosilane (1.20 mmol), 1.0 eq. of 4-nitroacetophenone (0.3 mmol), 0.02 eq. of catalyst (0.006 mmol) in 0.3 mL solvent at 80 °C for 4 h. \(^b\) 0.01 eq. of catalyst 84, 3.0 equiv. of triethoxysilane were used. \(^c\) Determined by \(^1\)H NMR using 1,3,5-trimethoxybenzene as internal standard. \(^d\) Isolated yield. \(^e\) 0.05 equiv. of catalyst 84 was used.

3.3.3 Substrate Scope and Limitations

With the optimal reaction conditions developed, functional group tolerance of this method was subsequently probed. The reduction of simple nitroarenes without other reducible
functionalities was first investigated (Scheme 3.13). Non-substituted nitrobenzene was easily reduced to give aniline 112 in 84% yield. Mono-methyl-substituted substrates gave the corresponding methylated aniline derivatives in 70-84% yields. 2,6-Dimethyl nitrobenzene, which had been proved difficult to be reduced due to steric hindrance,\textsuperscript{130-131} was also readily reduced to give the product 121 in 82% yield. Although at a lower reaction rate, \( p \)-(methylthio)aniline 122 was produced from the corresponding nitroarene in excellent yield.

Scheme 3.13. Substrate scope of the iron-catalysed nitroarene reduction\textsuperscript{a}

\[
\begin{array}{c}
\text{R}^1 \text{NO}_2 \quad \text{MeCN, 80 °C} \quad 84 \text{ (2.0 mol\%)} \quad 4.0 \text{ equiv HSi(OEt)}_3 \quad \text{R}^2 \text{NH}_2 \\
\text{112, 4 h, 84%}^b \quad \text{119, 6 h, 84%}^b \quad \text{120, 6 h, 70%}^b \quad \text{121, 6 h, 82%}^b \quad \text{122, 8 h, 93%}^b
\end{array}
\]

\textsuperscript{a} Unless otherwise noted, all reactions were carried out using 4.0 equiv. of hydrosilane (2.4 mmol), 1.0 equiv. of nitro substrate (0.6 mmol), 0.02 equiv. of catalyst 84 (0.012 mmol) in 0.6 mL MeCN at 80 °C.  
\textsuperscript{b} Isolated yield.

The reduction of substrates bearing more than one other reducible functionality was then investigated to test the chemoselectivity of this newly developed method (Scheme 3.14). In the reduction of nitroarenes bearing an ester functionality, the corresponding aniline derivatives 123-126 were isolated in excellent yields, suggesting the good chemoselectivity of the catalyst towards nitro groups over the ester functionalities.\textsuperscript{135-137} No protodehalogenation\textsuperscript{112} or homocoupling\textsuperscript{138} was observed in the reduction of halogenated nitroarenes, giving products 127-129 in good yields. Nitroarenes bearing strongly electron-withdrawing groups turned out to be more reactive as products 130 and 131 were isolated in 90% and 85% yields respectively, with shorter reaction times. No ring-opening side reactions\textsuperscript{134} were observed in the reaction of nitro-substituted benzoazole, and the product 132 was isolated in 88% yield at a higher catalyst loading. Amide functionality remained intact during the reaction to give product 133 in quantitative yield. Nitro substrates bearing a free hydroxyl functionality gave the corresponding product 134 in decreased yield. This can be attributed to the interaction between free alcohol and hydrosilane, which decreases the amount of hydrosilane available for the reduction.

\[
\text{Scheme 3.14. Iron-catalysed chemoselective reduction of nitroarenes}^a
\]

\[
\begin{align*}
\text{R} & \quad \text{NO}_2 \\
& \quad \text{MeCN, 80 °C} \\
& \quad 84 (2.0 \text{ mol%}) \\
& \quad 4.0 \text{ equiv HSi(OEt)}_3 \\
& \quad \text{R} \quad \text{NH}_2
\end{align*}
\]

Unles otherwise noted, all reactions were carried out using 4.0 equiv. of hydrosilane (2.4 mmol), 1.0 eq. of nitro substrate (0.6 mmol), 0.02 eq. of catalyst 84 (0.012 mmol) in 0.6 mL MeCN at 80 °C. \(^b\) Isolated yield. \(^c\) Yield determined by \(^1\)H NMR using 1,3,5-trimethoxybenzene as internal standard. \(^d\) 0.04 eq of catalyst was used.

Coordinating functionalities such as sulfonyl and cyano groups have an inhibitory effect on catalytic activity. In the reduction of 4-sulfonyl nitrobenzene, the aniline product 135 was isolated in 80% yield together with 15% of unreacted starting material. A cyano group substantially decreased the conversion, as product 136 was isolated in 65% yield, together with 30% of unreacted starting material (Scheme 3.15).

Scheme 3.15. Decreased reactivity of substrates with coordinating groups

\[
\text{Scheme 3.15. Decreased reactivity of substrates with coordinating groups}^a
\]

\[
\begin{align*}
\text{R} & \quad \text{NO}_2 \\
& \quad \text{MeCN, 80 °C} \\
& \quad 84 (2.0 \text{ mol%}) \\
& \quad 4.0 \text{ equiv HSi(OEt)}_3 \\
& \quad \text{R} \quad \text{NH}_2
\end{align*}
\]

Unles otherwise noted, all reactions were carried out using 4.0 equiv. of hydrosilane (2.4 mmol), 1.0 equiv. of nitro substrate (0.6 mmol), 0.02 equiv. of catalyst 84 (0.012 mmol) in 0.6 mL MeCN at 80 °C. \(^b\) Isolated yield. \(^c\) Starting material recovered.
This could be caused by the coordination of the cyano group to the catalyst, which is inhibitory to the activity. To test this hypothesis, a control reaction was carried out: 4-nitrobenzonitrile 137 was added to a standard reduction of ethyl 4-nitrobenzoate 138 and the yield of nitro reduction at ethyl 4-nitrobenzoate 138 dropped from 98% to 30%, suggesting that the coordination of the cyano group to the iron complex may contribute to the deactivation of the catalyst, by preventing the coordination of nitro group to the iron centre (Scheme 3.16).

**Scheme 3.16.** Inhibitory effect of the cyano group on the catalytic activity.

Inhibitory effect of the cyano group on the catalytic activity.

In the reduction of dinitro substrate 139, the corresponding bis(2-aminophenyl)amine 140 was isolated in 80% yield (Scheme 3.17, upper equation), a result that was comparable to the palladium-catalysed reduction of the same substrate with hydrogen.139 The product 140 is a key intermediate for the synthesis of N,N,N-type pincer139 or triamido140 ligands. Amine 142 was obtained in 90% isolated yield from the reduction of drug precursor 141 (Scheme 3.17, lower equation). This iron-catalysed late-stage chemical modification of a drug precursor was ideal for the preparation of molecules to be tested in vivo, as the low-toxicity of iron greatly simplifies the removal of trace metal.141 Simple derivatisation of 142 would give 4-(pyrazole-1-yl)carboxamides, a group of pharmaceuticals that modify the activity of canonical transient receptor potential channels (TRPC) and thus regulate the influx of calcium cations into various types of mammalian cell.142

**Scheme 3.17.** Selective nitro reduction in the synthesis of ‘real-world’ targets

Reactions were carried out using 0.6 mmol of nitro compounds. a Isolated yield.
4-Nitrophenol 143 and 4-nitrobenzoic acid 144 are not tolerated, probably due to the strong interaction between the substrate and hydrosilane, as the strong electron-withdrawing property of nitro group substantially increases the acidity of the substrates. Substrates 145 and 146 bearing an additional alkene functionality were also not suitable. This could be attributed to the competing formal hydroamination of the alkene, which will be discussed in detail later in this chapter. Nitroalkanes 147 and 148 were not tolerated, giving a complex mixture of products (Figure 3.01).

Figure 3.01. Unsuccessful substrates

![Unsuccessful substrates](image)

3.3.4 Application in Alkene Formal Hydroamination

Recently, Baran and co-workers\(^{63, 143}\) reported an iron-catalysed formal hydroamination of alkenes using nitroarenes for the construction of heavily substituted aniline derivatives. 96 examples of substrate were investigated under the optimal reaction condition, covering a wide range of functional groups (Scheme 3.18).


\[(\text{Het})\text{Ar-NO}_2 + \overset{R_1}{\overset{R_3}{\overset{R_5}{\overset{R_4}{\overset{\text{cat. Fe(acec)$_2$, PhSiH$_3$}}{\text{EtOH, 60 $^\circ$C, 1 h}}}}} + \overset{R_1}{\overset{R_3}{\overset{R_5}{\overset{R_4}{\text{Zn, HCl(aq)}}}}}}\text{EtOH, 60 $^\circ$C, 1 h}}\]

96 examples

A radical mechanism was proposed by the authors. In the presence of hydrosilane, an iron hydride was formed \textit{in situ} from the iron precatalyst. A hydrogen atom transfer from the iron hydride to the alkene 149 gave an alkyl radical, which could be added to the nitrosobenzene intermediate 150, which was formed \textit{in situ} from the partial reduction of nitrobenzene to give a mixture of the \textit{N,O}-dialkylated product 151 and the hydroxylamine product 152. The reduction of the hydroxylamine product 152 under the reaction conditions by hydrosilane and the reduction of 151 by the addition of an external reductant such as Zn/HCl gave the formal hydroamination product 153 (Scheme 3.19). Such a mechanism is supported by the fact that
all the reactions take place on the most substituted carbon of the alkene. The control reaction between nitrosoarenes and alkenes under the same reaction conditions also gave the hydroamination products, suggesting the feasibility of the proposed mechanism.

Scheme 3.19. Proposed mechanism of iron-catalysed formal hydroamination of alkene.

Although the reduction has broad substrate scope, and in most cases the hydroamination product was isolated in synthetically useful yields, high catalyst loadings (30 mol%) and reaction temperatures (60 °C) were required. In this reaction, the rate of the reaction is determined by the reduction of the nitro compounds, as the hydrogen atom transfer from the iron catalyst is a rapid process. We hypothesised that the high activity of the amine-bis(phenolate) iron(III) complex 84 in nitro reduction would accelerate the formation of nitrosoarenes and thus increase the reaction rate of the hydroamination, which would allow the reaction to proceed with a reduced catalyst loading and reaction temperature.

3.3.4.1 Condition Optimisation

We started with the reaction between 4-nitrothioanisole 154 and 2-methyl-2-butene 155 under Baran’s optimal conditions (EtOH at 60 °C with 2.0 equivalent of PhSiH3 and 3.0 equiv of alkene) (Scheme 3.20). 4-Nitrothioanisole was completely consumed within 1 hour, producing a mixture of N,O-dialkylated adduct 156, aniline 122 and the hydroamination product 157. Zinc and aqueous hydrochloric acid were subsequently added, converting intermediate 156 to the hydroamination product 157. The hydroamination product 157 was isolated in 40% yield.
after the Zn/HCl work up. As expected, 30% of aniline 122 was also isolated, which is derived from the competing reduction of 4-nitrothioanisole 154. It should be noted that the combined yield of products 157 and 122 is 70% based on the nitroarene. This could be caused by yield loss in the reduction of 156 by zinc. The loss of amine products during isolation by column chromatography also leads to the loss of yields.

**Scheme 3.20.** Formal hydroamination under Baran’s conditions using 84 as the catalyst.

As the reduction of nitroarene to aniline is generally a process that is kinetically not favoured and thus requires elevated temperatures, we hypothesised that the formation of the aniline by-product could be inhibited if the reaction is carried out at lower temperature. The yield of the hydroamination product 157 was slightly increased to 45% at room temperature and the yield of aniline 122 dropped to 25%. The formation of the aniline by-product was further inhibited by reducing the amount of PhSiH$_3$, to give a slightly higher yield of the desired hydroamination product (**Scheme 3.21**).

**Scheme 3.21.** Iron-catalysed hydroamination at room temperature.
It should be noted that when the reaction was carried out at room temperature, formation of the \( N,O \)-dialkylated product 156 was not observed. Instead, hydroxylamine 158 turned out to be the major product, which is probably formed from the addition of the alkyl radical to the nitrosobenzene followed by a hydrogen transfer. The hydroxylamine product was not reduced by the hydrosilane into the desired hydroamination product under these reaction conditions due to the decreased reaction temperature (Scheme 3.22). In the presence of zinc under acidic condition, hydroxylamine 158 was reduced to the desired hydroamination product 157.

**Scheme 3.22.** Proposed mechanism for the formation of 158 at room temperature.

In comparison with ethanol, other solvents such as toluene and acetonitrile gave low conversions of the starting nitroarene. This can be attributed to the electron-donating property of the oxygen atom in ethanol, which facilitates the hydride transfer from hydrosilane to the iron complex (Scheme 3.23).

**Scheme 3.23.** Solvent effects on the activation of hydrosilane.

As a direct comparison to the catalytic system developed by Baran, a reaction was carried out using Fe(acac)\(_3\) as the catalyst. Under otherwise identical reaction conditions, yield of the formal hydroamination product 157 dropped dramatically to 15% when Fe(acac)\(_3\) was used as the catalyst, while the yield of the aniline 122 by-product increased to 65% (Scheme 3.24).

**Scheme 3.24.** Fe(acac)\(_3\)-catalysed hydroamination at room temperature.
In summary, under optimal conditions, the hydroamination product 157 was isolated in 51% yield, which is comparable to the result obtained by Baran and co-workers, though with much lower catalyst loadings and reaction temperatures.

### 3.3.4.2 Substrate Scope and Limitations

To test the functional group tolerance of the current system, the formal hydroamination of alkene 155 with various nitroarenes was first investigated (Scheme 3.25). Non-substituted nitrobenzene gave the hydroamination product 160 in 58% yield. Both electron-donating and electron-withdrawing groups on the nitroarenes were well tolerated, to give products 161-163 in 43-60% yields. Once again, no protodehalogenation was observed in the reaction of halogenated substrates, and the hydroamination products 164-166 were isolated in up to 75% isolated yields. In the reaction to give product 167, the carbonyl group on the nitroarene remained unreacted during the reaction, once again illustrating the good chemoselectivity of the current system. All the reactions take place on the most substituted carbon of alkene 155, suggesting a radical intermediate is involved in the reaction.

**Scheme 3.25. Reaction of various nitroarenes and alkene 155**

\[
\begin{align*}
\text{Ar-NO}_2 & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{160, 58\%} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{161, 43\%} & \quad \text{OMe} \\
\text{162, 60\%} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{163, 45\%} & \quad \text{CF}_3 \\
\text{164, 75\%} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{165, 56\%} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{166, 68\%} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{167, 45\%} & \quad \text{CH}_3\text{C(O)Me} \\
\end{align*}
\]

\* Unless otherwise noted, all the reactions were conducted with 0.9 mmol of alkene (3.0 equiv), 0.6 mmol of PhSiH$_3$ (2.0 equiv), 0.3 mmol of nitroarene (1.0 equiv), 0.006 mmol of catalyst 84 (0.02 equiv) in 1.5 mL EtOH at room temperature for 2 h. Zinc dust (20.0 equiv) and HCl solution (2N, 3mL) were then added to the reaction and the mixture stirred for another 1 h at 60 °C. Yields are those of the isolated products; b 0.3 mmol of PhSiH$_3$ (1.0 equiv) was used, 1 h.
Alkene 168 bearing a free hydroxyl group was also well tolerated to give the hydroamination products 169-172 in synthetically useful yields, suggesting good functional group tolerance of the method (Scheme 3.26). Halogenated nitroarenes were suitable reaction partners for alkene 168 to give product 169 and 170 in good yields without any protodehalogenation. Both electron-withdrawing and electron-donating functional groups on the nitroarene were well tolerated. The presence of a hydroxyl group in the substrate may be beneficial to the formation of the radical intermediate due to the electron donating effect of the oxygen atom, as alkene 168 gave the products 169-172 in increased average yield.

Scheme 3.26. The formal hydroamination of alkene with a free hydroxyl functionality

![Scheme 3.26](image)

*Unless otherwise noted, all the reactions were conducted with 0.9 mmol of alkene (3.0 equiv), 0.6 mmol of PhSiH₃ (2.0 equiv), 0.3 mmol of nitroarene (1.0 equiv), 0.006 mmol of catalyst 84 (0.02 equiv) in 1.5 mL EtOH at room temperature for 2 h. Zinc dust (20.0 equiv) and HCl solution (2N, 3mL) were then added to the reaction and the mixture stirred for another 1 h at 60 °C. Yields are those of the isolated products; b 0.3 mmol of PhSiH₃ (1.0 equiv) was used;*

In the reaction between 4-bromonitrobenzene 173 and tetra-substituted alkene 174, only 26% yield of the product 175 was obtained (Scheme 3.27). The decreased yield in the reaction of alkene 174 can be attributed to the increased steric hindrance of the alkene, which was inhibitory to the hydrogen atom transfer from the iron hydride to the alkene.

Scheme 3.27. Steric effect of the alkenes on the reaction outcomes.

![Scheme 3.27](image)
As the radical is always formed in the most substituted carbon of an alkene, we envisaged that the reaction between alkene 176 and 4-bromonitrobenzene 173 is also expected to give product 175. Compared to the tetra-substituted alkene 174, alkene 176 is much less sterically hindered, meaning an increase in the yield of product 175 can be expected. Gratifyingly, in the reaction of 1,1-disubstituted alkene 176, the product 175 was isolated in 51% yield (Scheme 3.28).

**Scheme 3.28.** Alternative strategy for the synthesis of 175 with increased yield.

The hydroamination reaction can be used for the construction of N-arylpiperidine scaffold by the reaction of nitroarenes and alkene 177 which bears an additional carbonyl group (Scheme 3.29). A formal hydroamination/reductive carbonyl domino reaction pathway is probable. Products 178-180 were isolated in moderate yields (30-51%). Product 178 may find application in the synthesis of 2,2,6-trimethylpiperidine, which is a versatile reagent in the activation of carbonyl compounds, simply by the removal of the 4-methoxyphenyl protecting group.

**Scheme 3.29.** Application in the synthesis of N-arylpiperidine

An aliphatic nitro compound was not tolerated under the optimal reaction conditions, with most of the starting material being recovered (Scheme 3.30). We proposed this to be caused
by the increased difficulty in the reduction of aliphatic nitro compounds and the decreased stability of the radical intermediates formed in the reaction of aliphatic substrates.

**Scheme 3.30.** Reactivity of aliphatic nitro compound.

A (hetero)nitroarene 182 turned out to be less reactive, with the reaction being carried out at elevated temperatures to give product 183 in 45% yield (Scheme 3.31). No product 183 was observed when the reaction was carried out at room temperature and most of the starting nitro compound was recovered. One possible explanation of this could be the poor solubility of the starting material in ethanol at room temperature. The competing coordination of pyridine to the catalyst could also be inhibitory to the nitro reduction.

**Scheme 3.31.** The reaction of (hetero)nitroarene 182.

Mono-substituted alkenes such as 1-octene 184 gave much lower yields, irrespective of the nitroarenes used. This can be explained by the decreased stability of the secondary radical compared to the tertiary alkyl radical (Scheme 3.32).

**Scheme 3.32.** Formal hydroamination of 1-octene.
3.4 Conclusion

In conclusion, a highly chemoselective reduction of nitroarenes was developed using hydrosilane as the reducing agent. Amine-bis(phenolate) iron(III) complex 84, that has been used in the hydrosilylation of carbonyl compounds, is also an active catalyst for the chemoselective reduction of nitroarenes into the corresponding anilines. Triethoxysilane once again turned out to be the best reducing agent in terms of both yield and chemoselectivity. In most cases, the aniline derivatives were isolated in good to excellent yields. The current method also exhibited excellent chemoselectivity as other reducible functional groups such as halogens, esters, nitriles, sulfonyls, heterocycles all remained unreacted during the reaction (Scheme 3.33).

Scheme 3.33. Iron-catalysed chemoselective reduction of nitroarenes with hydrosilane.

This catalytic system was then successfully applied to the formal hydroamination of alkenes for the synthesis of heavily substituted aniline derivatives. Optimal results were obtained when the reactions were carried out in ethanol at room temperature using PhSiH₃ as the hydride source. The method tolerated a variety of functional groups on both the nitroarenes and the alkenes to give the formal hydroamination products in synthetically useful yields (Scheme 3.34). Initial studies, together with the fact that all the reactions take place at the more substituted carbon of the alkene suggest a radical pathway.
Scheme 3.34. Iron-catalysed formal hydroamination of alkenes.

[Chemical reaction and structures]

Olefins explored in the hydroamination:

- R = H, 58%
- R = 4-Br, 63%
- R = 2-Cl, 76%
- R = 4-CF₃, 61%

55
4. Iron-Catalysed Formal Heck Cross-Coupling between Alkyl Halides and Styrenes

4.1 Introduction

Since its discovery in 1972 by Richard F. Heck, the Heck reaction (also known as Mizoroki-Heck reaction) has become one of the most widely used methods for the construction of C-C bonds, and particularly for the substitution of sp²-hybridised carbon centres. In most cases, the Heck reaction uses unsaturated halides, such as vinyl or aryl halides, as coupling partners for alkenes. It is always highly challenging to extend the substrate scope to alkyl halides as: (1) it is much more difficult for sp³-hybridised alkyl halides to undergo the oxidative addition to the metal centre; (2) the existence of β-hydrogen atom can lead to β-hydride elimination products (Scheme 4.01).

Scheme 4.01. Challenges in the Heck reaction of alkyl halides.

Recently, an alternative reaction pathway to realise the cross-coupling between alkyl halides and alkenes has been proposed, which proceeds through a single-electron transfer pathway (Scheme 4.02). The donation of one electron from the metal complex to the alkyl halide generates the alkyl radical and metal in its higher oxidation state. This step is largely considered as the initiating step in transition-metal-catalysed atom transfer radical polymerisation (ATRP). The addition of the alkyl radical to monomers such as styrene can initiate the chain propagation of the monomer to give polystyrene as the product (Scheme 4.02, upper equation). Alternatively, the addition product of the alkyl radical can undergo an oxidation/elimination process to give the formal Heck cross-coupling product, regenerating the complex in its lower oxidation-state (Scheme 4.02, lower equation). Several catalytic systems based on transition metals such as cobalt, palladium, nickel, and copper have been developed for this reaction. Ruthenium and iridium complexes have also been proved to be active under photocatalytic conditions.
**Scheme 4.02.** Transition-metal-catalysed radical alkenylation of alkyl halides.

4.1.1 Cobalt-Catalysed Radical Heck-type Reaction

In 2002, the Oshima group\(^\text{156}\) realised the Heck-type reaction between alkyl halides and styrenes by using the cobalt complex CoCl\(_2\)(dpph) \([\text{dpph} = 1,6\text{-bis(diphenylphosphino)hexane}].\) Alkyl bromides, alkyl iodides and even alkyl chlorides were all tolerated to give the alkylated styrene products in good yield (Scheme 4.03). One drawback of this method is the use of highly reactive alkyl magnesium halide as the base.

**Scheme 4.03.** Cobalt-catalysed radical alkenylation of alkyl halides.

Mechanistically, this reaction was quite different from the palladium-catalysed variant. The reaction is supposed to proceed through a radical pathway: a single-electron transfer from the cobalt complex to the alkyl halide generated the alkyl radical, which was then added to the styrenes to give a benzyl radical intermediate. A benzylic cobalt complex was then formed, which underwent β-hydride elimination to give the formal Heck cross-coupling product (Scheme 4.04).\(^\text{156-157}\)

**Scheme 4.04.** Mechanism for the cobalt-catalysed radical alkenylation of alkyl halides.
In the reaction of cyclopropylmethyl bromide 187, the ring-opening product 188 was isolated as the only product, which is supportive of a radical mechanism (Scheme 4.05).

**Scheme 4.05.** Radical ring-opening in the reaction of cyclopropylmethyl bromide.

This method was then extended to the intramolecular Heck-type reaction of 6-iodo-1-hexene, for the synthesis of methylenecyclopentanes in good yields (Scheme 4.06).

**Scheme 4.06.** Cobalt-catalysed intramolecular Heck-type reaction of 6-iodo-1-hexene.

### 4.1.2 Palladium-Catalysed Radical Heck-type Reaction

More recently, Alexanian and co-workers have reported a Pd(PPh₃)₄-catalysed Heck-type reaction of alkyl iodides (Scheme 4.07). Isomerisation of alkenes was observed during the reaction, which can be inhibited by the introduction of CO. No carbonylative cyclisation product 192 was observed when the reaction was carried out in the presence of CO. Initial results showed that this palladium-based catalytic system was also applicable to the intermolecular Heck-type reaction between styrene and cyclohexyl iodide. The yields varied from 51-60%, depending on the substituents on the styrene. It should be noted that carbonyl groups and free alcohols were tolerated in the reaction.

**Scheme 4.07.** Palladium-catalysed Heck-type reaction of alkyl iodide.
The reaction proceeded through a Pd(0)/Pd(I)/Pd(II) catalytic cycle, which is quite similar to the mechanism proposed by Oshima for the cobalt-catalysed version of the reaction (Scheme 4.08).\textsuperscript{159}

**Scheme 4.08.** Plausible mechanism of the palladium-catalysed alkenylation of alkyl halides.

In 2014, the same group\textsuperscript{160} reported a general intermolecular Heck-type reaction of alkyl iodides. In this work, [PdCl\textsubscript{2}(dppf)] [dppf = 1,1’-bis(diphenylphosphino)ferrocene] was used as the catalyst instead of Pd(PPh\textsubscript{3})\textsubscript{4}. One significant feature of this work, is that the alkene substrates are not limited to styrenes: electron-deficient alkenes such as vinyl ketones and acrylonitriles were used as substrates for the first time in a radical alkenylation of alkyl halides (Scheme 4.09).

**Scheme 4.09.** Palladium-catalysed intermolecular Heck-type reaction between alkenes and alkyl halides.

Another significant advancement was made by Zhou and co-workers,\textsuperscript{161} as they expanded the scope of alkyl halide from alkyl iodide to alkyl bromide and alkyl chlorides by the addition of Li\textsubscript{i}. The *in situ* generated alkyl iodides from the reaction of alkyl bromides (or chlorides) and Li\textsubscript{i} were thought to be the actual active species. Both secondary and primary alkyl halides were tolerated, while tertiary alkyl halides were not included in this study.
Scheme 4.10. Radical styrene alkylation with alkyl bromide and alkyl chloride.

A radical trapping experiment was carried out using TEMPO [2,2,6,6-tetramethylpiperidin-1-yl]oxyl]. It should be noted that a constant 2:1 ratio of the alkylated TEMPO product and the catalyst was obtained (Scheme 4.11). This result suggested the palladium catalyst may undergo two consecutive single-electron processes during the reaction, which is in good accordance with the mechanism suggested by Alexanian.

Scheme 4.11. Radical trapping experiments in palladium-mediated intermolecular Heck-type reaction between alkene and alkyl halides.

Although those above-mentioned cobalt- or palladium-based catalysts have enabled the Heck-type reaction between alkyl halides and alkenes, which is generally difficult to achieve by classic Heck cross-coupling due to competing β-hydride elimination, there are still several limitations associated with these methods: 1) for the cobalt-catalysed reactions, highly reactive alkyl magnesium halide is used as base, which will limit its application in large-scale production. 2) the high cost and high toxicity of palladium catalyst. (3) for both systems, the alkyl halides are limited to non-functionalised alkyl halides.

4.1.3 Nickel-Catalysed Radical Heck-type Reaction

The first example of a Heck-type reaction between functionalised alkyl halides and styrenes was reported by Lei and co-workers, using a dppp-supported [dpp = 1,3-bis(diphenylphosphino)propane] nickel catalyst (Scheme 4.12). Both secondary and tertiary
carbonyl halides reacted smoothly with styrenes bearing electron-donating groups. In the case of styrenes bearing electron-neutral substituents, stoichiometric acetanilide was needed in order to obtain good yields. The exact role of acetanilide in the reaction and how it helped increase the yields was not explained by the authors.

**Scheme 4.12.** Nickel-catalysed secondary and tertiary alkylation of styrenes.

![Scheme 4.12](image)

Mechanistically, a Ni(0)/Ni(I)/Ni(II) catalytic cycle was suggested by the authors (Scheme 4.13). Firstly, the Ni(0) complex reacts with alkyl bromide through a single-electron transfer process to generate the Ni(I) complex, which can further react with the alkyl bromide to generate the Ni(II) species and an alkyl radical. The addition of the alkyl radical to styrene gave the benzyl radical, which was subsequently oxidised into the benzyl cation, regenerating the Ni(I) species. Base-mediated deprotonation of the benzyl cation gave the desired formal Heck cross-coupling product. Unlike the mechanism suggested by Oshima in the cobalt-catalysed reaction, no carbon-metal bond is supposed to be formed during this reaction, as excellent regioselectivity was obtained in the reaction.

**Scheme 4.13.** Nickel-catalysed secondary and tertiary alkylation of styrenes.
The same group then applied this catalytic system in the alkenylation of α-cyano alkyl bromide, for the synthesis of β,γ-unsaturated nitrile compounds (Scheme 4.14). Electron-poor styrenes could be tolerated at elevated temperatures.

**Scheme 4.14.** Radical alkenylation of α-cyano alkyl bromide.

4.1.4 Copper-Catalysed Radical Heck-type Reaction

As the most widely used transition metal catalyst in ATRP, copper should be a good choice for this type of reaction, as the ability of copper in generating alkyl radicals from the corresponding alkyl halide is very well known. However, it was not until 2013, when the group of Nishikata reported the first example of a copper-catalysed radical alkenylation of functionalised alkyl halides with styrene derivatives (Scheme 4.15). CuI together with PMDTA (PMDTA = N,N,N',N''-pentamethyldiethylenetriamine), a classic catalytic combination in copper-catalysed ATRP, catalysed the reaction with high efficiency under mild conditions. PMDTA was used both as base and ligand in this reaction. Lower yields were obtained in the absence of TBABr (TBABr = tetra-n-butylammonium bromide). One major drawback of this method is that the substrates are strictly limited to styrenes bearing strongly electron-donating groups. When styrenes with electron-withdrawing, or even electron-neutral groups, such as methyl, were used as substrates, the reactions gave either the polymerisation products or low conversions. However, the low cost of the catalyst and the mild reaction conditions still makes this method a good choice for the synthesis of tertiary-alkylated styrenes.

**Scheme 4.15.** Copper-catalysed tertiary alkylation of styrenes.

In the nickel-catalysed reaction, a cation intermediate was suggested by Lei and co-workers. However, in this study, the authors suggested that the benzyl radical, which is formed from the addition of the alkyl radical to styrene, reacted with the Cu(II) species to give a brominated...
intermediate, rather than forming a cationic intermediate. Base-mediated elimination from the brominated intermediate gave the desired alkenylated product (Scheme 4.16).^{164}

**Scheme 4.16.** Suggested mechanism of the copper-catalysed tertiary alkylation of styrenes.

The existence of the brominated intermediate was indirectly supported by the formation of cyclopropane product 205 in the reaction of secondary alkyl bromide 204. The cyclisation step was supposed to proceed through intermediate 207, which was generated from the deprotonation of brominated intermediate 206 (Scheme 4.17).^{164}

**Scheme 4.17.** Cyclopropanation and the plausible mechanism.

Lei and co-workers^{165} then extended the scope of the alkyl halide from tertiary alkyl halide to primary halide by using a combination of CuCl and 1,10-phenanthroline (Scheme 4.18). Radical trapping experiments together with EPR data suggested the reaction proceeded through the same mechanism as suggested by Nishikata and co-workers in previous work.

**Scheme 4.18** Copper-catalysed alkenylation of primary halides.
4.1.5 Other Catalytic Systems

In 2013, Lei and co-workers\textsuperscript{166} reported a photocatalytic radical alkenylation of secondary and tertiary alkyl halides using the ruthenium catalyst [Ru(bpy)\textsubscript{3}]Cl\textsubscript{2} (bpy = 2,2\textquotesingle-bipyridine). The initial Ru(II) complex was reduced by Et\textsubscript{3}N under photocatalytic conditions, to give a Ru(I) species. Alkyl halides were activated by 4-methoxypyridine \textsuperscript{211} through the formation of an electron-deficient pyridinium salt \textsuperscript{212}, before generation of the alkyl radical through a single-electron transfer process (Scheme 4.19).

\textbf{Scheme 4.19.} Photocatalytic radical alkenylation with ruthenium.

\begin{center}
\begin{center}
\begin{align*}
\text{Br} & \quad \text{OEt} \quad \text{Bu} \quad \text{Ph} \quad \text{Ph} \quad \text{CO} \quad \text{Et} \quad \text{208} \quad \text{209} \quad \text{210} \quad \text{90}\% \\
2.0 \text{ mol}\% \text{[Ru(bpy)\textsubscript{3}]Cl\textsubscript{2}} & \quad 40 \text{ mol}\% \text{4-Methoxypyridine} \text{211} & \quad 40 \text{ mol}\% \text{Et\textsubscript{3}N}, 1 \text{ equiv NaHCO\textsubscript{3}} & \quad \text{DMF, hv, } 36 \text{ h} \\
\text{[Ru(bpy)\textsubscript{3}]\textsuperscript{2+}} & \quad \text{visible light} & \quad \text{*[Ru(bpy)\textsubscript{3}]\textsuperscript{2+}} & \quad \text{Et\textsubscript{3}N} & \quad \text{[Ru(bpy)\textsubscript{3}]\textsuperscript{+}} \\
\text{OMe} & \quad \text{CO\textsubscript{2}Et} & \quad \text{OMe} & \quad \text{Br} & \quad \text{CO\textsubscript{2}Et} \\
\text{211} & \quad \text{212} & \quad \text{208} \\
\text{A more active iridium complex (fac-[Ir(ppy)\textsubscript{3}]) was used for the alkenylation of primary alkyl halides under photocatalytic condition as the ruthenium-based catalyst was not active towards this type of substrate, which are inherently less reactive due to the decreased stability of the corresponding alkyl radicals (Scheme 4.20).\textsuperscript{166}}
\end{align*}
\end{center}
\end{center}

\textbf{Scheme 4.20.} Photocatalytic radical alkenylation with iridium.

\begin{center}
\begin{center}
\begin{align*}
\text{Br} \quad \text{Br} & \quad \text{MeO} \quad \text{Ph} \quad \text{Ph} \quad \text{Br} \quad \text{213} \quad \text{203} \quad \text{214} \quad \text{76}\% \\
1.0 \text{ mol}\% \text{fac-[Ir(ppy)\textsubscript{3}]} & \quad 10.0 \text{ mol}\% \text{Et\textsubscript{3}N} & \quad 1 \text{ equiv Na\textsubscript{2}CO\textsubscript{3}} & \quad \text{DMF, hv, } 36 \text{ h} \\
\text{fac-[Ir(ppy)\textsubscript{3}]}: \\
\begin{array}{c}
\text{[}
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\end{array}
\end{align*}
\end{center}
\end{center}
4.2 Results and Discussions

4.2.1 Project Aims

Transition-metal-catalysed radical alkenylation of alkyl halides, especially functionalised alkyl halides, has emerged as an attractive method for the alkylation of alkenes. However, the iron-catalysed version of this type of reaction has not so far been reported. Although the ability of iron-based catalysts in generating alkyl radicals has found application in the Kumada-type reaction (Eq 1, Scheme 4.21) and iron-catalysed ATRP (Eq 2, Scheme 4.21), a synthetically useful iron-catalysed radical alkenylation of functionalised alkyl halide has never been reported. Thus, the aim of this project is to develop the first iron-based catalytic system for this reaction, preferably using stable, easy-to-access iron catalysts (Eq 3, Scheme 4.21).

Scheme 4.21. Alkyl halide as radical source in iron catalysis.

4.2.2 Condition Optimisation

Previous work on transition-metal-catalysed radical alkenylation of alkyl halides have revealed that, styrenes with electron-withdrawing groups favor the competitive ATRP and gives the cross-coupling products in low yields, while styrenes with electron-donating groups favor the formation of the cross-coupling products. This can be explained by the stability of the brominated intermediate. As shown in Scheme 4.22, the formation of the brominated intermediate is the key step of the reaction as the following base-mediated elimination gives the desired alkenylated product irreversibly. In the brominated intermediate, the carbon atom is partially positively charged, as halogen atom is more electronegative than carbon. Thus, an electron-donating group on R’ stabilises the charge and helps decreasing the energy of the
molecule, making it more stable. On the other hand, electron-withdrawing groups on $R'$ increases the energy of the molecule, making it less stable.

**Scheme 4.22.** Key step in transition-metal-catalysed radical alkylation of styrenes.

Thus, in order to inhibit the undesired polymerisation of styrene, our studies commenced with the reaction between electron-rich $p$-methoxystyrene 203 and ethyl $\alpha$-bromoisobutyrate 215 (Table 4.01). Different solvents were first screened using $\alpha$-diimine iron(II) complex 217 as the catalyst, which has previously been used as an efficient ATRP catalyst. Polystyrene was observed as the major product while only trace amounts of the desired alkenylation product 216 were detected when the reaction was carried out in THF and toluene (entries 1 and 2). However, product 216 was observed in 15% and 30% yields, respectively, when the reaction was carried out in strongly coordinating solvents such as MeCN and DMF (entries 3 and 4). We hypothesise that the coordination of solvents to the iron complex is crucial as it increases the steric hindrance of the complex, preventing the equilibrium as depicted in Scheme 4.22 from going left and favoring the formation of the brominated intermediate. $\alpha$-Diimine iron(II) complexes with dipp ($dipp = 2,6$-disisopropylphenyl) substituents gave the desired product in higher yields (entries 5 and 6). Simple FeCl$_2$ turned out to be even more active, giving the product 216 in 65% yield (entry 7). A DMF-coordinated FeCl$_2$ complex is highly likely to be the active catalyst as FeCl$_2$ is not active in weaker coordinating solvents such as THF and toluene. As the initial step of the reaction is supposed to be a single-electron transfer process from the iron catalyst to the alkyl halide, in which process the oxidation state of the iron catalyst increases, iron(III) catalyst is not supposed to be active as the oxidation of Fe(III) into Fe(IV) is not favored. As expected, iron in a higher oxidation state (FeCl$_3$) was not reactive (entry 8). Other iron(II) catalysts such as Fe(acac)$_2$ were not active catalysts as no desired product was observed (entry 9).

Other bases such as K$_2$CO$_3$ and K$_3$PO$_4$ gave much lower yields than Cs$_2$CO$_3$ (entries 10 and 11). However, as all the salts employed in this study were not dried before use, the decrease in the yields could simply be caused by the moisture as potassium salts are more hygroscopic, particularly K$_3$PO$_4$. Na$_2$CO$_3$, which is much cheaper than Cs$_2$CO$_3$, gave a lower yield when 2.0 equivalent of 215 was used (entry 12), though gave an almost identical result when 3.0 equivalent of 215 was used (entries 13 and 14). PMDTA, which is a commonly used ligand in
iron-catalysed ATRP, was not a suitable base, as polystyrene was observed as the predominant product, and only trace amounts of alkenylation product were obtained (entry 15). A PMDTA-ligated iron catalyst might be formed in this reaction, which then acted as an efficient ATRP catalyst to give the polystyrene as major product.

Table 4.01 Condition screening of the iron-catalysed radical alkenylation of α-halocarbonyl

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>base</th>
<th>yield%b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy,H[N,N]FeCl2</td>
<td>THF</td>
<td>Cs2CO3</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Cy,N,N]FeCl2</td>
<td>toluene</td>
<td>Cs2CO3</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Cy,N,N]FeCl2</td>
<td>MeCN</td>
<td>Cs2CO3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>Cy,N,N]FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Dipp,H[N,N]FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Dipp,Me[N,N]FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>Fe(acac)2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>FeCl2</td>
<td>DMF</td>
<td>K2CO3</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>FeCl2</td>
<td>DMF</td>
<td>K2PO4</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Na2CO3</td>
<td>55</td>
</tr>
<tr>
<td>13c</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>94d</td>
</tr>
<tr>
<td>14c</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Na2CO3</td>
<td>93d</td>
</tr>
<tr>
<td>15</td>
<td>FeCl2</td>
<td>DMF</td>
<td>PMDTA</td>
<td>trace</td>
</tr>
</tbody>
</table>

a Reaction conducted at 80 °C for 16 h with 10 mol % catalyst, 1.1 equiv of base, 203 (0.25 mmol, 1.0 equiv) and 215 (2.0 equiv). b Determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard. c 3.0 equiv of 215 was used. d Isolated yield.
4.2.3 Substrate Scope and Limitations

The substrate scope of this newly developed iron-catalysed radical alkenylation of alkyl halides was then probed using FeCl₂ (10 mol%) as the catalyst and Na₂CO₃ (1.1 equiv) as the base in DMF (0.25 M) at 80 °C. Styrene derivatives with electron-donating substituents were initially investigated as those substrates have relatively lower polymerisation rates. The reactions of various alkyl halides with p-methoxystyrene 203 were first tested (Scheme 4.23). A bromocyclic ester was well tolerated to give the product 220 in 76% yield. The high reactivity of the iron catalyst was demonstrated by the successful alkenylation of primary and secondary alkyl bromides, which are far less active than tertiary alkyl halide because of the decreased stability of the radical intermediates. In the reaction of 2-bromopropionate, the product 221 was isolated in 65% yield, at higher catalyst and alkyl bromide loadings. Ethyl α-bromophenylacetate gave the product 222 in a much higher yield than the reaction of methyl 2-bromopropionate, probably because of the enhanced stability of the radical brought about by the phenyl ring. However, in this reaction, the desired alkylated 4-methoxystyrene 222 cannot be separated from several unidentified by-products. Thus, the yield of 222 was determined by ¹H NMR using 1,3,5-trimethoxybenzene as the internal standard. In an effort to obtain characterisable product, hydrogenated product of 222 was isolated after treatment with H₂ under Pd/C catalysis, in 87% yield. Other secondary functionalised alkyl bromides such as 2-bromopropionitrile gave the product 223 in 61% yield. Compared to direct cyanation of allylic compounds using highly toxic cyanide salts, our system provides a more environmentally friendly method for the preparation of β,γ-unsaturated nitrile compounds, which are widely found in natural products and bioactive molecules. Compared to tertiary and secondary alkyl halides, primary alkyl halides are supposed to be much less reactive due to the decreased stability of the corresponding alkyl radicals. As expected, under the standard reaction condition, the yield of the formal cross-coupling product turned out to be very low, when 4-chlorobenzyl bromide was used as the radical source. As the C-X bond has a higher dissociation energy in primary alkyl halides, increasing the reaction temperature may help generating alkyl radicals from primary alkyl halides. Indeed, under otherwise identical conditions, the yield of product 224 was increased to 52% when the reaction was carried out at 100 °C, compared to 20% at 80 °C. The product is not able to be isolated by standard column chromatography as it has very close polarity with 4-chlorobenzyl bromide and the yield of the product is determined by ¹H NMR using 1,3,5-trimethoxybenzene as the internal standard.
Scheme 4.23. Reactions between 4-methoxystyrene 203 with various alkyl halides

As expected, 3,4-dimethoxystyrene was also well tolerated, giving the products 225 in good yield. Steric effect has a limited effect on the reaction outcome, as reactions of 2-methoxystyrene gave comparable yields to that of 4-methoxystyrene (Scheme 4.24).

Scheme 4.24. Reaction of 2-methoxy- and 3,4-dimethoxystyrene.

Strongly electron-donating dimethylamino substituent gave the alkylated 4-dimethylaminostyrene 229 in decreased yield (Scheme 4.25). As amines have been extensively used as ligand for efficient iron-catalysed ATRP of styrene, it is possible that the substrate coordinates to the iron to form an active catalyst for ATRP, which is accountable of the diminished yield of this substrate.
Scheme 4.25. Radical alkylation of 4-dimethylaminostyrene.

Surprisingly, methyl-substituted styrenes, which have been proved to be difficult substrates in previous work, also gave the products 202 and 230 in good yields without the need for additives. However, as a methyl group is less electron-donating than the methoxy group, the corresponding methylated styrenes exhibit decreased reactivity and higher reaction temperature was required. However, 2,4,6-trimethylstyrene was not reactive, with only trace amounts of product 231 being observed, probably because of steric hindrance (Scheme 4.26).


1,1-Diphenyl ethylene 192 exhibited decreased reactivity as higher catalyst and alkyl halide loadings were needed. The corresponding alkenylation product 232 was isolated in 73% yield (Scheme 4.27). The decreased reactivity of α-substituted styrene can be attributed to the increased steric hindrance of the radical addition product, which is detrimental to the formation of the brominated intermediate.

Scheme 4.27. Reaction of α-substituted styrene.

Non-substituted indene 233 was also tolerated, to give the alkylated indene product 234 in 52% isolated yield, with higher catalyst and alkyl halide loadings at higher reaction temperatures (Scheme 4.28). The bicyclic structure of indene gives a more rigid radical species, thus decreases its overlap with the benzene ring. The outcome of this effect is the decreased stability
of the radical that has caused the diminished reactivity of indene. This reaction will have potential applications in natural product synthesis, as substituted indenes and their reduced products (indanes) are widely found motifs in natural products\textsuperscript{175-177} and bioactive molecules.\textsuperscript{178-180}

**Scheme 4.28.** Radical alkylation of indene.

In the reaction of α-methyl styrene \textsuperscript{235}, the brominated intermediate has two sets of protons: \textsuperscript{181} H\textsubscript{a} and H\textsubscript{b} (*Scheme 4.29*). Deprotonation of H\textsubscript{a} would give trisubstituted alkene \textsuperscript{237}, while deprotonation of H\textsubscript{b} gives terminal alkene \textsuperscript{236}. Deprotonation of H\textsubscript{a} is sterically more favorable as it is less sterically hindered, though it is less acidic, while deprotonation of H\textsubscript{b} is electronically more favorable as it is more acidic due to the electron-withdrawing effect of the ester functionality. Under the optimal reaction conditions, a 9:1 ratio of alkenes \textsuperscript{236} and \textsuperscript{237} was obtained, suggesting that the reaction was controlled by steric effects. However, the two regioisomers were not able to be separated by column chromatography and were obtained as a mixture in 40% overall yield (*Scheme 4.29*). The decreased yield of the products can be attributed to the increased steric hindrance of the radical addition product brought about by the methyl group, which is detrimental to the formation of the brominated intermediate due to the bulkiness of bromine atom. The lack of a radical-stabilising substituent such as methoxy or dimethylamino group on the phenyl ring also leads to decreased stability of the radical intermediate, thus diminishing the yield of the products.

**Scheme 4.29.** Regioselectivity in the alkenylation of α-methylated styrene.

The reaction of 2-methoxystyrene \textsuperscript{238} and alkyl halide \textsuperscript{239} bearing an amide group was dominated by β-hydride elimination, to give the α, β-unsaturated amide \textsuperscript{240} in 62% yield, and only trace amounts of alkenylation products \textsuperscript{241} were observed (*Scheme 4.30*).
Scheme 4.30. β-Hydride elimination of α-amide alkyl halide 239.

Control reaction between alkyl halide 239 and Na₂CO₃ was carried out and the α, β-unsaturated amide 240 was isolated as the only major product. Thus, it is possible that product 240 is formed through a base-mediated elimination of alkyl halide 239. However, it is also possible that the alkyl radical generated from 239 coordinates to the iron center to form an iron-alkyl species, which then undergoes β-elimination to give α, β-unsaturated amide 240 (Scheme 4.31). In this substrate, the presence of an amide group may help stabilising the iron-alkyl intermediate, thus facilitate such a reaction pathway.


Interestingly, in the reaction of 4-methoxystyrene 203 and 1-bromo-1-phenyl ethane 242, the head-to-tail dimerisation of the styrene was found to be the main reaction, with the corresponding dimer 243 being isolated in 80% yield, while no desired Heck-type coupling product 244 was observed (Scheme 4.32).

Scheme 4.32. Unexpected head-to-tail dimerisation of 4-methoxystyrene.

Iron-catalysed dimerisation of styrenes has been reported previously by Corma and co-workers, in which a combination of FeCl₃ and AgOTf is used as the catalyst. Under the optimal reaction conditions, styrenes with electron-withdrawing substituents gave lower yields than
non-substituted styrenes, while 4-methoxystyrene gave polystyrenes as the major product (Scheme 4.33).

**Scheme 4.33.** Iron-catalysed dimerisation of styrenes reported by Corma and co-workers.

A benzylic cation mechanism is proposed by the authors. Firstly, the styrene substrate is activated by the iron(III) catalyst to form a benzylic cation, which was subsequently added to another equivalent of substrate. Deprotonation and dissociation of iron gave the dimerised styrene (Scheme 4.34). The proposed mechanism well explained the low yields observed in the reactions of styrene with electron-withdrawing substituents as the benzylic cation could be destabilised by electron-deficient functionalities. On the other hand, in the reaction of styrene with strongly electron-donating substituent such as methoxy group, the benzyl cation is stabilised enough to favour polymerisation.

**Scheme 4.34.** Proposed mechanism of iron-catalysed dimerisation of styrenes.

Based on this study, for the reaction in Scheme 4.32, it was initially hypothesised that the iron(III) species formed *in situ* during the reaction catalysed the dimerisation of styrene, as no
dimerization of styrene was observed when the reaction was carried out in the absence of 1-bromo-1-phenyl ethane 242. It is proposed that the alkyl radicals generated in situ from benzyl bromide 242 forms dimer 247, affording the iron(III) species irreversibly (Scheme 4.35). The iron(III) species then catalyses the dimerisation of styrene in the mechanism as suggested by Corma and co-workers. However, no dimerisation product 247 was detected in the reaction mixture. Furthermore, when an iron(III) salt such as FeCl₃ or FeBr₃ was used directly as the catalyst, no styrene dimerisation product 243 was obtained, suggesting such a hypothesis is not feasible.

Scheme 4.35. Proposed irreversible formation of iron(III) catalyst.

In their work on the organometallic intermediates in iron-catalysed ATRP of styrene, Gibson and co-workers⁶⁴ have demonstrated that the alkyl radical, generated in situ from the corresponding alkyl chloride 248 through single-electron transfer, can form an iron-alkyl complex with the iron catalyst. β-Hydride elimination of this iron-alkyl species gave an iron-hydride intermediate and styrene 9 (Scheme 4.36).

Scheme 4.36. Formation of iron-hydride complex in iron-catalysed ATRP.
Inspired by this work, an alternative mechanism for the 4-methoxystyrene dimerisation has been proposed, in which an iron-hydride intermediate is involved. Hydrogen atom transfer from the iron-hydride to 4-methoxystyrene gives a benzyl radical intermediate, which was trapped by another equivalent of 203. The radical trapping product then abstracted a bromine atom from the iron(III) species to give the brominated intermediate 249, which then undergoes a base-mediated elimination to give the styrene dimerisation product 243, regenerating the active iron(II) complex (Scheme 4.37). In such a mechanism, a styrene by-product, which is derived from the 3-hydride elimination of the iron-alkyl intermediate, should be detected as a major by-product. Indeed, in this reaction, styrene has been detected directly by $^1$H NMR as a major by-product. However, control reaction suggests that styrene can also be generated from the reaction between 1-bromo-1-phenyl ethane 242 and Na$_2$CO$_3$. At this moment, it is unclear if the styrene by-product is derived from the base-mediated elimination of 242 or from the 3-hydride elimination of the iron-hydride intermediate.

Scheme 4.37. Styrene dimerisation catalysed by iron-hydride complex.

Several types of substrate are currently not tolerated in this newly developed iron-catalysed alkyl halide alkenylation reaction (Figure 4.01). In the reaction of 3-methyl styrene 250, poly(3-methylstyrene) was formed as the major product and the desired alkenylated product was obtained in very low yield. Substrates 251 and 252 with electron-withdrawing groups
were not suitable, as polymerisation was more favoured in the reaction of these substrates. No product was obtained when 1,3-diene 253 was used as the substrate. Alkyl chloride 254 was not reactive due to the increased bond strength of the C-Cl bond, when compared to the C-Br bond, thus inhibiting the generation of alkyl radical.

**Figure. 4.01.** Unsuccessful substrates.

![Substrates](image)

In copper-catalysed radical alkenylation of alkyl halides, as reported by Nishikata and co-workers,\textsuperscript{164} the reaction of 4-methoxystyrene 203 and dimethyl bromomalonate 204 gave cyclopropane derivative 205. The reaction was proposed to proceed through a key intermediate 207, which was derived from the deprotonation of the brominated intermediate 206 (Scheme 4.38, a). However, in our system, dimethyl bromomalonate 204 failed to give either the formal Heck cross-coupling product 255 or cyclopropane derivative 205. We hypothesised that this was caused by the deprotonation of the acidic proton of dimethyl bromomalonate 204 by the base (Scheme 4.38, b).

**Scheme 4.38.** Iron vs copper in the reaction of dimethyl bromomalonate.

![Scheme 4.38](image)
Radical trapping experiments were then carried out to gain insight into the reaction mechanism, by using TEMPO as the radical scavenger. When TEMPO was added directly to the reaction between alkyl halide 215 and 4-methoxystyrene 203, no desired Heck-type cross-coupling product was detected (Scheme 4.39, Eq 1). The reaction between α-bromoisobutyrate 215 and TEMPO with stoichiometric amount of FeCl₂ gave the alkylated TEMPO product 255 in 15% yield (Scheme 4.39, Eq 2). These results suggest an alkyl radical might be generated from the alkyl halide in the presence of iron catalyst. However, it cannot be ruled out that TEMPO reacted with iron catalyst to form an iron(III) species,¹⁸³ which was not active for the radical alkenylation.

Scheme 4.39. Radical capture by TEMPO.

4.3 Conclusion

To conclude, an iron-catalysed radical alkenylation of functionalised alkyl bromide was successfully developed using FeCl₂ as catalyst and Na₂CO₃ as base (Scheme 4.40). The reactions proceeded well in DMF to give the formal Heck reaction products in good to excellent yields and tolerated styrenes with electron-donating groups and electron-neutral groups. Styrenes with electron-withdrawing groups were not suitable substrates. Tertiary, secondary and even primary alkyl halides were tolerated. Inferior results were obtained when the reaction was catalysed by α-diimine iron(II) complexes. Initial studies revealed that the reaction proceeded through a radical intermediate. Detailed study of the reaction mechanism, further condition screening for the reaction of styrenes with electron-withdrawing groups and the radical coupling of alkyl halides with other unsaturated compounds could be the focus of future work.
Scheme 4.40. Iron-catalysed Heck-type reaction between functionalised alkyl halide and styrenes.

\[
\begin{align*}
\text{FeCl}_2 & \quad \text{Br} \quad \text{FG} \\
\text{Na}_2\text{CO}_3, \text{DMF} & \quad \text{FG} \\
\text{R} & \quad \text{R'} \quad \text{R''} \\
\text{up to 93\% yield} & \\
\end{align*}
\]

- ligand free
- \(1^\circ, 2^\circ\) and \(3^\circ\) alkyl halide
- \(\text{FeCl}_2\) as catalyst
- non-electron-rich styrenes

\begin{align*}
\text{216, 93\%} & & \text{220, 76\%} & & \text{221, 65\%} \\
\text{222, 91\%} & & \text{223, 61\%} & & \text{224, 52\%} \\
\text{225, 85\%} & & \text{226, 82\%} & & \text{227, 81\%} \\
\text{229, 65\%} & & \text{202, 70\%} & & \text{230, 71\%} \\
\text{231, trace} & & \text{232, 73\%} & & \text{234, 52\%} \\
\end{align*}
5. General Conclusions and Future Work

To conclude, four reactions have been studied using either iron complexes or simple iron salts as catalysts: 1) iron-catalysed chemoselective hydrosilylation of carbonyl compounds; 2) iron-catalysed chemoselective reduction of nitroarenes into aniline derivatives; 3) iron-catalysed formal alkene hydroamination with nitroarenes; 4) iron-catalysed radical alkenylation of functionalised alkyl halides. The activity of two sets of iron complexes was tested during these studies: 1) amine-bis(phenolate) iron(III) complexes 83-86; 2) α-diimine iron(II) complex 217-219 (Scheme 5.01). The former set of iron complexes were used for the hydrosilylation of carbonyl compounds, the reduction of nitroarenes and the formal hydroamination of alkenes. α-Diimine iron(II) complexes were used as catalysts in the radical alkenylation of alkyl halides, and exhibited moderate activities. The activity of simple FeCl₂ salt was also investigated in the radical alkenylation reaction of functionalised alkyl halides, and turned out to be more active than the α-diimine iron(II) complexes.

Scheme 5.01 Iron complexes used in this thesis.

Carbonyl hydrosilylation, nitroarenes reduction, alkene formal hydroamination:

![Chemical structure](https://example.com/structure.png)

- 83: R₁ = R₂ = Me, D = (CH₂)₂NMe₂
- 84: R₁ = R₂ = Me, D = CH₂Fur
- 85: R₁ = R₂ = Cl, D = CH₂Py
- 86: R₁ = R₂ = Cl, D = (CH₂)₂NMe₂

Furf = tetrahydro-2-furanyl
Py = 2-pyridiny1

Radical alkenylation of alkyl halides:

![Chemical structure](https://example.com/structure.png)

- Cy, Hf(N, N)FeCl₂ 217: R₁ = Cy, R₂ = H
- Dipp, Hf(N, N)FeCl₂ 218: R₁ = Dipp, R₂ = H
- Dipp, Me(N, N)FeCl₂ 219: R₁ = Dipp, R₂ = Me

R¹, R²: (N, N)FeCl₂, 217-219

The hydrosilylation of carbonyl compounds was first investigated. A simple, easy-to-handle, air- and moisture stable iron(III) amine-bis(phenolate) complex 84 catalysed the hydrosilylation of carbonyl compounds efficiently using triethoxysilane as the reducing agent in MeCN. The reaction tolerated a wide range of substrates to give the corresponding alcohol products in good to excellent yields after a base-mediated hydrolysis of the hydrosilylated products (Scheme 5.02). Excitingly, this catalytic system also exhibited activity towards the hydrosilylation of carbon dioxide, although only 5% conversion was obtained at this stage. Future work in this area could involve the development of chiral iron complexes for the
asymmetric reduction of ketones to give enantiopure secondary alcohols. Further investigations into the mechanism of the reaction should also be the focus of future work.

**Scheme 5.02.** Iron-catalysed hydrosilylation of carbonyl compounds.

Attention was also paid to the chemoselective reduction of nitroarenes into aniline derivatives, which is a highly industry-relevant process. Amine-bis(phenolate) iron(III) complex 84, that had been used in the hydrosilylation of carbonyl compounds, was also an active catalyst for the chemoselective reduction of nitroarenes into the corresponding aniline derivatives. Triethoxysilane once again turned out to be the best reducing agent in terms of both yields and chemoselectivities. The method exhibited excellent chemoselectivity, as other reducible functional groups such as halogens, esters and nitriles all remained intact during the reaction (Scheme 5.03). However, nitroalkanes were not suitable substrates, leading to complex mixtures of products. The development of new iron complexes for the reduction of nitroalkanes would be an interesting topic for future research.

**Scheme 5.03.** Iron-catalysed chemoselective reduction of nitroarenes.
The same catalyst was then successfully applied in the formal hydroamination of alkenes with nitroarenes, for the synthesis of heavily substituted aniline derivatives (Scheme 5.04). Optimal results were obtained when the reactions were carried out in ethanol at room temperature using PhSiH₃ as the hydride source. Initial studies, together with the fact that all the reactions took place at the more substituted carbon of the alkene, suggest a radical pathway.

**Scheme 5.04.** Iron-catalysed formal hydroamination of alkenes.

Finally, the iron-catalysed formal Heck cross-coupling between alkyl halides and styrenes was investigated (Scheme 5.05). α-Diimine iron(II) complexes 217-219 were screened in the presence of a base, giving moderate yields of the desired alkenylated product 216. Simple FeCl₂ turned out to be the optimal catalyst and Na₂CO₃ to be the optimal base. The reaction tolerated both electron-rich and electron-neutral substrates, to give the products in moderate to excellent yields (up to 93%). Initial studies revealed that the reaction also proceeds through a radical intermediate as suggested by previous works. Styrenes with electron-withdrawing groups were found not to be suitable substrates. The screening of greener solvents, detailed study of the reaction mechanism, further condition screening for the reaction of styrenes with electron-withdrawing groups and the radical coupling of alkyl halides with other unsaturated compounds could be the focus of future work.
Scheme 5.05. Iron-catalysed radical alkenylation of functionalised alkyl halides.

a) effect of iron catalyst on the reaction outcome

\[
\begin{align*}
\text{203} & \quad \text{215} & \quad \text{cat (10 mol\%)} & \quad \text{Na}_2\text{CO}_3, \text{DMF} & \quad 80 \ ^\circ\text{C}, \ 16 \ \text{h} & \quad \text{216} \\
\text{217: } \ R_1 = \text{Cy, } R_2 = \text{H} & \quad \text{218: } \ R_1 = \text{Dipp, } R_2 = \text{H} & \quad \text{219: } \ R_1 = \text{Dipp, } R_2 = \text{Me} \\
\text{Cy = cyclohexyl, Dipp = 2,6-disisopropylphenyl} & \\
\end{align*}
\]

b) functional group tolerance

\[
\begin{align*}
\text{FG = ester, phenyl, nitrile} \\
- \text{1}^\circ, \text{2}^\circ \text{ and } \text{3}^\circ \text{ alkyl halide} \\
- \text{non-electron-rich styrenes} \\
\end{align*}
\]

up to 94\% yield 20 examples
6. Experimental

6.1 General Considerations

All air- and moisture-sensitive reactions were carried out either using standard Schlenk techniques or in a glovebox with a purified nitrogen atmosphere. Acetonitrile, acetonitrile-$d_3$ and chloroform-$d$ were dried over CaH$_2$ and distilled under N$_2$. Benzene-$d_6$ was dried over Na/benzophenone and distilled under N$_2$. All other solvents for air- and moisture-sensitive reactions were obtained from an anhydrous solvent system (Innovative Technology). All glassware was cleaned using base (NaOH/EtOH) and acid (HCl(aq)) baths, rinsed with acetone, and oven dried (180 °C) prior to use.

All $^1$H, $^{13}$C{$^1$H}, $^{19}$F spectra were obtained on Bruker Avance III 400 and 500 MHz spectrometers or on a Bruker Avance I 600 MHz spectrometer. $^{13}$C{$^1$H} denotes proton-decoupled $^{13}$C spectra. All spectra were obtained at ambient temperature. The chemical shifts (δ) and coupling constants (J) were recorded in parts per million (ppm) and Hertz (Hz) respectively. $^1$H and $^{13}$C{$^1$H} multiplicities and coupling constants are reported where applicable. Spectra were recorded relative to the residual solvent residual peak (CDCl$_3$, 7.27 ppm, 77.00 ppm; CD$_3$CN, 1.97 ppm; C$_6$D$_6$, 7.18 ppm).

Amine-bis(phenolate) iron(III) complexes 83-86 used in this work were synthesised according to established literature procedures. $^{138, 184}$ α-Diimine iron(II) complexes 217-219 were synthesised according to literature procedure. $^{173}$ p-Tolyl 2-bromo-2-methylpropanoate 257 and 2-bromo-2-methyl-1-(1-piperidinyl)-1-propanone 259 were prepared according to literature procedure. $^{185}$ 4-Dimethylaminostyrene 228 was prepared according to literature procedure. $^{186}$ Triethoxysilane was purchased from Alfa Aesar. PMHS was purchased from Acros Organics. Iron(III) chloride was purchased from Sigma-Aldrich. Ketones, aldehydes, nitro compounds, alkenes and styrenes were purchased from various commercial vendors. Carbon dioxide was purchased from BOC Ltd (UK) (C40-VB-Carbon dioxide cylinder, vapour, B-size 10).

Flash chromatography was performed on silica gel (Merck Geduran Si 60). Petroleum spirit refers to petroleum ether distillate obtained at 40-60 °C. Thin layer chromatography was performed on aluminium backed silica plates (Merck 60 F$_{254}$).

Infra-red spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.
6.2 Experimental for the Hydrosilylation of Carbonyl Compounds

6.2.1 General Procedure for the Hydrosilylation of Carbonyl Compounds

A mixture of catalyst 84 (0.006 mmol, 2.8 mg), ketone/aldehyde (0.6 mmol), triethoxysilane (1.8 mmol, 295 mg) and acetonitrile-d₃ (0.6 mL) were stirred in a preheated oil bath (80 °C) for a specified time. After full consumption of the starting material, as determined by ¹H NMR, methanol (1 mL) and 2 M aqueous sodium hydroxide (1 mL) were added to the stirred mixture before dilution with water (2 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL), the combined organic portions dried over anhydrous Na₂SO₄ and solvents removed in vacuo. 1,3,5-Trimethoxybenzene (16.8 mg, 0.1 mmol) was added to the crude residue as an internal standard and the product yield determined by ¹H NMR spectroscopy. Pure product was isolated by flash column chromatography using petroleum spirit/ethyl acetate.

1-Phenylbenzenemethanol 82:

Using benzophenone (0.6 mmol, 109 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD₃CN (0.6 mL) at 80 °C for 3 h. The alcohol 82 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless needle (103 mg, 93%). Melting point: 68-69 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.42-7.36 (m, 8H), 7.32-7.28 (m, 2H), 5.86 (s, 1H), 2.36 (br, 1H); ¹³C {¹H} NMR (CDCl₃, 125 MHz): δ 143.8, 128.5, 127.6, 126.6, 76.3.

Data obtained are in accordance with those previously reported.¹⁸⁷

1-Phenylethanol 14:

Using acetophenone (0.6 mmol, 72.0 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD₃CN (0.6 mL) at 80 °C for 3 h. The alcohol 14 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (66.6 mg,
91%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.42-7.36 (m, 4H), 7.32-7.28 (m, 1H), 4.92 (q, $J = 5.0$ Hz, 1H), 1.88 (br, 1H), 1.53 (d, $J = 10.0$ Hz, 3H); $^{13}$C($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 145.8, 128.5, 127.5, 125.4, 70.4, 25.2.

Data obtained are in accordance with those previously reported.$^{96}$

1-(4-Methoxyphenyl)ethanol 87:

![Structure of 1-(4-Methoxyphenyl)ethanol](image1)

Using 4'-methoxyacetophenone (0.6 mmol, 90.0 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 87 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a light yellow oil (82.1 mg, 90%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.33-7.30 (m, 2H), 6.92-6.89 (m, 2H), 4.86 (q, $J = 5.0$ Hz, 1H), 3.82 (s, 3H), 2.12 (br, 1H), 1.50 (d, $J = 5.0$ Hz, 3H); $^{13}$C($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 159.0, 138.1, 126.7, 113.8, 69.9, 55.3, 25.0.

Data obtained are in accordance with those previously reported.$^{96}$

1-(3-Methoxyphenyl)ethanol 88:

![Structure of 1-(3-Methoxyphenyl)ethanol](image2)

Using 3'-methoxyacetophenone (0.6 mmol, 90.0 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 88 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a light yellow oil (82.1 mg, 90%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.31-7.27 (m, 1H), 6.98-6.97 (m, 2H), 6.85-6.83 (m, 1H), 4.90 (q, $J = 5.0$ Hz, 1H), 3.84 (s, 3H), 1.98 (br, 1H), 1.52 (d, $J = 5.0$ Hz, 3H); $^{13}$C($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 159.8, 147.6, 129.6, 117.7, 112.9, 110.9, 70.3, 55.2, 25.2.

Data obtained are in accordance with those previously reported.$^{188}$

1-(3,4-Dimethoxyphenyl)ethanol 89:

![Structure of 1-(3,4-Dimethoxyphenyl)ethanol](image3)
Using 3',4'-dimethoxyacetophenone (0.6 mmol, 108 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 ml) at 80 °C for 3 h. The alcohol 89 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (102 mg, 93%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 6.97 (s, 1H), 6.93-6.91 (m, 1H), 6.87-6.85 (m, 1H), 4.88 (q, $J = 5.0$ Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 1.80 (br, 1H), 1.52 (d, $J = 5.0$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 149.1, 148.4, 138.6, 117.6, 111.1, 108.7, 70.2, 56.0, 55.9, 25.1.

Data obtained are in accordance with those previously reported.$^{189}$

1-(4-Trifluoromethylphenyl)ethanol 90:

Using 4'-(trifluoromethyl)acetophenone (0.6 mmol, 113 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 24 h. The alcohol 90 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (62.7 mg, 55%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.64-7.62 (m, 2H), 7.52-7.50 (m, 2H), 4.99 (q, $J = 5.0$ Hz, 1H), 1.97 (br, 1H), 1.53 (d, $J = 10.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 149.7, 129.7 (q, $J_{C-F} = 32.0$ Hz), 127.4, 125.6, 125.4 (q, $J_{C-F} = 4.0$ Hz), 122.0 (q, $J_{C-F} = 270.0$ Hz), 69.8, 25.4; $^{19}$F NMR (CDCl$_3$, 376 MHz): δ -62.5.

Data obtained are in accordance with those previously reported.$^{96}$

1-(4-Bromophenyl)ethanol 91:

Using 4'-bromoacetophenone (0.6 mmol, 119 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 4 h. The alcohol 91 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a light yellow oil (119 mg, 87%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.49-7.47 (m, 2H), 7.26-7.24 (m, 2H), 4.86 (q, $J = 5.0$ Hz, 1H), 2.11 (br, 1H), 1.48 (d, $J = 5.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 144.8, 131.6, 127.2, 121.2, 69.8, 25.2.

Data obtained are in accordance with those previously reported.$^{96}$
1-(4-Biphenyl)ethanol 30:

Using 4-acetylbiphenyl (0.6 mmol, 118 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 30 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a white solid (107 mg, 90%). Melting point: 95-96 °C. $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.65-7.62 (m, 4H), 7.50-7.47 (m, 4H), 7.41-7.38 (m, 1H), 5.00-4.96 (m, 1H), 2.11 (br, 1H), 1.58 (d, $J = 5.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 144.9, 140.9, 140.5, 128.8, 127.3, 127.2, 127.1, 125.9, 70.2, 25.2.

Data obtained are in accordance with those previously reported.$^{190}$

Benzyl alcohol 93:

Using benzaldehyde (0.6 mmol, 63.6 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 93 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (54.4 mg, 84%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.41-7.31 (m, 5H), 4.66 (s, 2H), 2.47 (br, 1H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 140.9, 128.6, 127.6, 127.0, 66.2.

Data obtained are in accordance with those previously reported.$^{96}$

3-Chlorobenzyl alcohol 94:

Using 3-chlorobenzaldehyde (0.6 mmol, 84.0 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 94 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a light yellow oil (78.4 mg, 92%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.38-7.37 (m, 1H), 7.32-7.27 (m, 2H), 7.25-7.22 (m, 1H), 4.67 (s, 2H), 2.17 (br, 1H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): 142.8, 134.4, 129.8, 127.7, 127.0, 124.9, 64.5.

Data obtained are in accordance with those previously reported.$^{191}$
2-Fluorobenzyl alcohol 95:

\[
\begin{array}{c}
\text{F} \\
\text{O} \\
\text{H}
\end{array}
\]

Using 2-fluorobenzaldehyde (0.6 mmol, 74.4 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 95 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a colourless oil (66.5 mg, 88%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.45-7.42 (m, 1H), 7.32-7.28 (m, 1H), 7.18-7.15 (m, 1H), 7.09-7.05 (m, 1H), 4.76 (s, 2H), 2.24 (br, 1H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 160.6 (d, $J_{C-F}$ = 245.0 Hz), 129.2 (merged with other signals), 129.3 (d, $J_{C-F}$ = 13.8 Hz), 127.8 (d, $J_{C-F}$ = 15.0 Hz), 124.2 (d, $J_{C-F}$ = 3.8 Hz), 115.2 (d, $J_{C-F}$ = 21.3 Hz), 59.3 (d, $J_{C-F}$ = 3.8 Hz); $^{19}$F NMR (CDCl$_3$, 470 MHz): $\delta$ -119.8.

Data obtained are in accordance with those previously reported.$^{93}$

4-(Hydromethyl)benzonitrile 96:

\[
\begin{array}{c}
\text{NC} \\
\text{OH}
\end{array}
\]

Using 4-formylbenzonitrile (0.6 mmol, 78.6 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 4 h. The alcohol 98 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:1 v/v) as a colourless oil (64.6 mg, 81%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.63-7.60 (m, 2H), 7.48-7.46 (m, 2H), 4.76 (d, $J$ = 5.0 Hz, 2H), 2.69 (br, 1H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): $\delta$ 146.5, 132.3, 127.0, 118.9, 110.9, 64.0. IR: $v$ = 3400 (s), 2240 (s), 1620 (s), 1440 (m), 1200 (m), 1080 (s), 1010 (s), 810 (s) cm$^{-1}$.

Data obtained are in accordance with those previously reported.$^{187}$

4-Methylbenzyl alcohol 97:

\[
\begin{array}{c}
\text{Me} \\
\text{OH}
\end{array}
\]

Using 4-methylbenzaldehyde (0.6 mmol, 72.0 mg), triethoxysilane (1.8 mmol, 295 mg) and 84 (2.8 mg, 0.006 mmol) in CD$_3$CN (0.6 mL) at 80 °C for 3 h. The alcohol 98 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless needle (65.9 mg, 90%). Melting point: 60-61 °C $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.29-7.27 (m,
2H), 7.21-7.19 (m, 2H), 4.66 (s, 2H), 2.39 (s, 3H), 1.83 (br, 1H); \(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\), 125 MHz): \(\delta\) 138.0, 137.4, 129.2, 127.1, 65.2, 21.1.

Data obtained are in accordance with those previously reported.\(^{96}\)

3-Methoxybenzyl alcohol 98:

\[
\begin{align*}
\text{OMe} & \quad \text{OH}
\end{align*}
\]

Using 3-methoxybenzaldehyde (0.6 mmol, 81.6 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD\(_2\)CN (0.6 mL) at 80 °C for 3 h. The alcohol 98 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (71.8 mg, 88%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.30-7.27 (m, 1H), 6.95-6.94 (m, 2H), 6.86-6.84 (m, 1H), 4.66 (d, \(J = 5.0\) Hz, 2H), 3.82 (s, 3H), 2.24 (br, 1H); \(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\), 125 MHz): \(\delta\) 159.8, 142.6, 129.6, 119.1, 113.2, 112.3, 65.1, 55.2.

Data obtained are in accordance with those previously reported.\(^{190}\)

4-(Trifluoromethoxy)benzyl alcohol 99:

\[
\begin{align*}
\text{F}_3\text{CO} & \quad \text{OH}
\end{align*}
\]

Using 4-(trifluoromethoxy)benzaldehyde (0.6 mmol, 114.0 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD\(_2\)CN (0.6 mL) at 80 °C for 6 h. The alcohol 99 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (102 mg, 89%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.42-7.39 (m, 2H), 7.24-7.22 (m, 2H), 4.71 (s, 2H), 1.99 (br, 1H); \(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\), 125 MHz): \(\delta\) 148.6, 139.5, 128.3, 121.05, 120.5 (q, \(J_{C,F} = 255.0\) Hz), 64.4; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \(\delta\) -57.9.

Data obtained are in accordance with those previously reported.\(^{192}\)

5-Ethyl-2-furanmethanol 100:

\[
\begin{align*}
\text{O} & \quad \text{OH}
\end{align*}
\]

Using 5-ethyl-2-furaldehyde (0.6 mmol, 74.4 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD\(_2\)CN (0.6 mL) at 80 °C for 6 h. The alcohol 100 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless
oil (65.0 mg, 86%). 1H NMR (CDCl₃, 500 MHz): δ 6.18 (d, J = 5.0 Hz, 1H), 5.94 (d, J = 5.0 Hz, 1H), 4.55 (s, 2H), 2.66 (q, J = 10.0 Hz, 2H), 2.11 (br, 1H), 1.24 (t, J = 10.0 Hz, 3H); 13C{¹H} NMR (CDCl₃, 125 MHz): δ 158.1, 152.2, 108.5, 104.6, 57.5, 21.4, 12.1.

Data obtained are in accordance with those previously reported.¹⁹³

(Hydroxymethyl)cyclohexane 101:

Using cyclohexylmethanol (0.6 mmol, 67.2 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD₃CN (0.6 mL) at 80 °C for 3 h. The alcohol 101 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (62.2 mg, 91%). 1H NMR (CDCl₃, 400 MHz): δ 3.44 (d, J = 4.0 Hz, 2H), 1.83-1.67 (m, 5H), 1.55-1.44 (m, 2H), 1.32-1.12 (m, 3H), 0.99-0.89 (m, 2H); 13C{¹H} NMR (CDCl₃, 100 MHz): δ 68.7, 40.5, 29.6, 26.6, 25.8.

Data obtained are in accordance with those previously reported.¹⁹¹

2-Cyclohexen-1-ol 106:

Using cyclohexenone (0.6 mmol, 57.6 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD₃CN (0.6 mL) at 80 °C for 3 h. The alcohol 106 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a light yellow oil (32.3 mg, 55%). 1H NMR (CDCl₃, 500 MHz): δ 5.85-5.83 (m, 1H), 5.76 (d, J = 10.0 Hz, 1H), 4.21-4.20 (m, 1H), 2.06-1.58 (m, 8H); 13C{¹H} NMR (CDCl₃, 125 MHz): δ 130.5, 129.9, 66.5, 32.0, 25.0, 19.0.

Data obtained are in accordance with those previously reported.¹⁹⁴

3-Phenyl-2-propen-1-ol 108:

Using cinnamaldehyde (0.6 mmol, 79.2 mg), triethoxysilane (1.8 mmol, 295.2 mg) and 84 (2.8 mg, 0.006 mmol) in CD₃CN (0.6 mL) at 80 °C for 3 h. The alcohol 108 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless oil (65.1
mg, 81%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.43-7.41 (m, 2H), 7.36-7.33 (m, 2H), 7.29-7.26 (m, 1H), 6.64 (d, $J = 15.0$ Hz, 1H), 6.42-6.37 (m, 1H), 4.36-4.34 (m, 2H); $^{13}$C $^1$H NMR (CDCl$_3$, 125 MHz): δ 136.7, 131.2, 128.6, 128.5, 127.7, 126.5, 63.7.

Data obtained are in accordance with those previously reported.

### 6.2.2 Procedure for the Hydrosilylation of CO$_2$

A mixture of catalyst 84 (0.012 mmol, 5.6 mg), triethoxysilane (1.0 mmol, 164 mg), benzene-$d_6$ (1 mL) were stirred under an atmosphere of CO$_2$ (1 atm) in a preheated oil bath (80 °C) for 12 h. The reaction mixture was analysed by $^1$H NMR and the signals characteristic of triethoxysilyl formate were found: $^1$H NMR (C$_6$D$_6$, 500 MHz): δ 7.72 (s, 1H), 3.82 (q, $J = 7.0$ Hz, 6H), 1.08 (t, $J = 7.0$ Hz, 9H), which is in accordance with the literature data.

### 6.2.3 Procedure for Gram-Scale Hydrosilylation of Benzophenone

A mixture of catalyst 84 (0.24 mmol, 110 mg), benzophenone 81 (12.0 mmol, 2.2 g), PMHS (36 mmol of Si-H, 2.2 g) and MeCN (12.0 mL) were stirred in a preheated oil bath (100 °C) for 4 h. After full consumption of the starting material, as determined by $^1$H NMR, methanol (20 mL) and 2M aqueous sodium hydroxide (20 mL) were added to the stirred mixture before dilution with water (40 mL). The aqueous phase was extracted with diethyl ether (3 x 100 mL), the combined organic portions dried (Na$_2$SO$_4$) and the solvent removed in vacuo. The alcohol 82 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a colourless needle (2.0 g, 90%).
6.3 Experimental for the Nitro Compound Reduction and Formal Hydroamination

6.3.1. General Procedure for the Reduction of Nitro Compounds:

A mixture of catalyst 84 (0.012 mmol, 5.5 mg), nitro compound (0.6 mmol), triethoxysilane (2.4 mmol, 393.6 mg) and acetonitrile (0.6 mL) were stirred in a preheated oil bath (80 °C) for a specified time. After full consumption of the starting material, as determined by TLC, the solvents were removed under vacuum. The crude product was then dissolved in a minimal amount of CH$_2$Cl$_2$ and purified by flash column chromatography using petroleum spirit/ethyl acetate.

4-Aminoacetophenone 117:

Using 4-nitroacetophenone (0.6 mmol, 99.0 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 4 h. The amine 117 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a pale yellow powder (73.7 mg, 91%). Melting point: 104-105 °C. (Petroleum Spirit/EtOAc); Lit. 105-106 °C (hexane/EtOAc). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.84-7.81 (m, 2H), 6.68-6.64 (m, 2H), 4.18 (br, 2H), 2.52 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): δ 196.5, 151.2, 130.8, 127.9, 113.7, 26.1.

Data obtained were in accordance with those previously reported.

Aniline 112:

Using nitrobenzene (0.6 mmol, 73.8 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 4 h. The amine 112 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a brown oil (46.9 mg, 84%).
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.22-7.17 (m, 2H), 6.82-6.77 (m, 1H), 6.74-6.70 (m, 2H), 3.66 (br, 2H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): $\delta$ 146.4, 129.3, 118.6, 115.1.

Data obtained are in accordance with those previously reported.$^{197}$

3-Aminotoluene $^{119}$:

![3-Aminotoluene](image)

Using 3-nitrotoluene (0.6 mmol, 82.2 mg), triethoxysilane (2.4 mmol, 394 mg) and $^{84}$ (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine $^{119}$ was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a pale yellow oil (53.9 mg, 84%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.10-7.07 (m, 1H), 6.64-6.62 (m, 2H), 6.56-6.53 (m, 1H), 3.62 (br, 2H), 2.31 (s, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 146.4, 139.1, 129.2, 119.5, 115.9, 112.3, 21.4.

Data obtained are in accordance with those previously reported.$^{197}$

2-Aminotoluene $^{120}$:

![2-Aminotoluene](image)

Using 2-nitrotoluene (0.6 mmol, 82.2 mg), triethoxysilane (2.4 mmol, 394 mg) and $^{84}$ (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine $^{120}$ was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a light yellow oil (45.0 mg, 70%). $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 7.08-7.05 (m, 2H), 6.75-6.72 (m, 1H), 6.70 (d, $J$ = 6.0 Hz, 1H), 3.61 (br, 2H), 2.20 (s, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): 144.6, 130.4, 127.0, 122.3, 118.6, 114.9, 17.3.

Data obtained are in accordance with those previously reported.$^{197}$

2,6-Dimethylaniline $^{121}$:

![2,6-Dimethylaniline](image)

Using 1, 3-dimethyl-2-nitrobenzene (0.6 mmol, 90.7 mg), triethoxysilane (2.4 mmol, 394 mg) and $^{84}$ (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine $^{121}$ was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1 v/v) as a pale yellow
oil (59.5 mg, 82%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 6.99 (d, $J = 10.0$ Hz, 2H), 6.71-6.68 (m, 1H), 3.61 (br, 2H), 2.23 (s, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 142.7, 128.3, 121.7, 118.0, 17.6.

Data obtained are in accordance with those previously reported.$^{198}$

4-(Methylthio)aniline 122:

\[
\begin{array}{c}
\text{S} \\
\text{NH}_2
\end{array}
\]

Using 4-nitrothioanisole (0.6 mmol, 101 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 8 h. The amine 122 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a pale yellow oil (77.6 mg, 93%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.22-7.19 (m, 2H), 6.67-6.63 (m, 2H), 3.68 (br, 2H), 2.44 (s, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): δ 145.2, 131.1, 125.8, 115.8, 18.8.

Data obtained are in accordance with those previously reported.$^{198}$

Ethyl 3-aminobenzoate 123:

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{NH}_2
\end{array}
\]

Using ethyl 4-nitrobenzoate (0.6 mmol, 117 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 5 h. The amine 123 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a pale yellow oil (90.1 mg, 91%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.46-7.44 (m, 1H), 7.38-7.37 (m, 1H), 7.22 (t, $J = 8.0$ Hz, 1H), 6.88-6.85 (m, 1H), 4.37 (q, $J = 8.0$ Hz, 2H), 3.81 (br, 2H), 1.40 (t, $J = 8.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 100 MHz): δ 166.8, 146.5, 131.5, 129.2, 119.7, 119.3, 115.8, 60.9, 14.3.

Data obtained are in accordance with those previously reported.$^{199}$

Ethyl 4-aminobenzoate 124:

\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{NH}_2
\end{array}
\]

Using ethyl 4-nitrobenzoate (0.6 mmol, 117 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 5 h. The amine 124 was isolated by
flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a white powder (97.1 mg, 98%). Melting point: 88-89 °C. (Petroleum Spirit/EtOAc); Lit.° 89-90 °C (hexane/EtOAc). 'H NMR (CDCl3, 500 MHz): δ 7.89-7.86 (m, 2H), 6.66-6.63 (m, 2H), 4.34 (q, J = 10.0 Hz, 2H), 4.14 (br, 2H), 1.38 (t, J = 10.0 Hz, 3H); 'C{H} NMR (CDCl3, 125 MHz): δ 166.8, 150.9, 131.6, 119.9, 113.8, 60.3, 14.4.

Data obtained are in accordance with those previously reported.°

Methyl 3-aminobenzoate 125:

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{NH}_2
\end{array}
\]

Using methyl 4-nitrobenzoate (0.6 mmol, 109 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 5 h. The amine 125 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a light yellow oil (85.2 mg, 94%). 'H NMR (CDCl3, 500 MHz): δ 7.45-7.43 (m, 1H), 7.37 (s, 1H), 7.24-7.21 (m, 1H), 6.88-6.86 (m, 1H), 3.90 (s, 3H), 3.83 (br, 2H); 'C{H} NMR (CDCl3, 125 MHz): δ 167.3, 146.6, 131.1, 129.3, 119.7, 119.4, 115.8, 52.0.

Data obtained are in accordance with those previously reported.°

Methyl 4-aminobenzoate 126:

\[
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{NH}_2
\end{array}
\]

Using methyl 4-nitrobenzoate (0.6 mmol, 109 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 5 h. The amine 126 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a white powder (84.2 mg, 93%). Melting point: 109-111 °C. (Petroleum Spirit/EtOAc); Lit.° 108 °C (hexanes/EtOAc). 'H NMR (CDCl3, 400 MHz): δ 7.89-7.85 (m, 2H), 6.67-6.64 (m, 2H), 4.08 (br, 2H), 3.87 (s, 3H); 'C{H} NMR (CDCl3, 100 MHz): δ 167.2, 150.8, 131.6, 119.8, 113.8, 51.6.

Data obtained are in accordance with those previously reported.°
4-Fluoroaniline 127:

\[
\begin{array}{c}
\text{F} \\
\text{NH}_2
\end{array}
\]

Using 1-fluoro-4-nitrobenzene (0.6 mmol, 84.6 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 5 h. The amine 127 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a colourless oil (54.6 mg, 82%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 6.90-6.85 (m, 2H), 6.66-6.62 (m, 2H), 3.55 (br, 2H); \(^13\)C\{\(^1\)H\} NMR (CDCl\(_3\), 125 MHz): \(\delta\) 156.5 (d, \(J_{C,F} = 235 \text{ Hz}\)) 142.4, 116.1 (d, \(J_{C,F} = 7.5 \text{ Hz}\)), 115.7 (d, \(J_{C,F} = 25.0 \text{ Hz}\)).

Data obtained are in accordance with those of an authentic sample (Aldrich Cat. No. F3800).

2-Chloroaniline 128:

\[
\begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\]

Using 1-chloro-2-nitrobenzene (0.6 mmol, 94.2 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 8 h. Solvents were removed under vacuum and the residue was purified isolated by flash column chromatography using petroleum spirit/ethyl acetate (6:1 v/v) to give an unisolable mixture of the starting material and the aniline product. The yield of amine 128 was determined by \(^1\)H NMR using 1,3,5-trimethoxybenzene as internal standard (87%).

Data obtained are in accordance with those of an authentic sample (Aldrich Cat. No. 23310).

4-Bromoaniline 129:

\[
\begin{array}{c}
\text{Br} \\
\text{NH}_2
\end{array}
\]

Using 1-bromo-4-nitrobenzene (0.6 mmol, 121 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 8 h. The amine 129 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (3:1 v/v) as a pale yellow powder (92.0 mg, 90%). Melting point: 58-60°C (Petroleum Spirit/EtOAc); Lit.\(^{196}\) 61-62 °C (hexane/EtOAc). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.27-7.24 (m, 2H), 6.59-6.56 (m, 2H), 3.68 (br, 2H); \(^13\)C\{\(^1\)H\} NMR (CDCl\(_3\), 125 MHz): \(\delta\) 145.5, 132.0, 116.7, 110.2.

Data obtained are in accordance with those previously reported.\(^{196}\)
3-(Trifluoromethyl)aniline 130:

Using 3-nitrobenzotrifluoride (0.6 mmol, 115 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 3 h. The amine 130 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (4:1 v/v) as a colourless oil (86.9 mg, 90%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.28-7.25 (m, 1H), 7.02-7.00 (m, 1H), 6.92 (s, 1H), 6.85-6.83 (m, 1H), 3.86 (s, 2H); $^{13}$C{${^1}$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 146.7, 131.6 (q, $J_{C-F} = 31.2 \text{ Hz}$), 129.7, 124.2 (q, $J_{C-F} = 271.2 \text{ Hz}$), 118.0, 115.0 (q, $J_{C-F} = 3.8 \text{ Hz}$), 111.3 (q, $J_{C-F} = 3.8 \text{ Hz}$). $^{19}$F NMR (CDCl$_3$, 471 MHz): $\delta$ -63.0.

Data obtained are in accordance with those previously reported.$^{134}$

4-(Trifluoromethyl)aniline 131:

Using 4-nitrobenzotrifluoride (0.6 mmol, 115 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 3 h. The amine 131 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (4:1 v/v) as a colourless oil (82.1 mg, 85%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41 (d, $J = 8.0, 2H$) 6.71 (d, $J = 8.0 \text{ Hz}, 2H$), 3.96 (br, 2H); $^{13}$C{${^1}$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 149.4, 126.7 (q, $J_{C-F} = 3.8 \text{ Hz}$), 124.8 (q, $J_{C-F} = 268.8 \text{ Hz}$), 120.2 (q, $J_{C-F} = 32.5 \text{ Hz}$), 114.2; $^{19}$F NMR (CDCl$_3$, 471 MHz): $\delta$ -61.2.

Data obtained are in accordance with those previously reported.$^{200}$

2-Ethyl-6-benzoxazolamine 132:

Using 2-ethyl-6-nitrobenzoxazole (0.6 mmol, 115 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine 132 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:1 v/v) as an orange powder (85.6 mg, 88%). Melting point: 57-58 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.42 (d, $J = 12.0 \text{ Hz}, 1H$), 6.78 (s, 1H), 6.64 (d, $J = 8.0 \text{ Hz}, 1H$), 3.79 (br, 2H), 2.89 (q, $J = 8.0 \text{ Hz}, 2H$),
1.42 (t, J = 8.0 Hz, 3H); \(^{13}\)C\({}^{1}\)H NMR (CDCl\(_3\), 100 MHz): δ 166.1, 152.0, 144.3, 133.8, 119.6, 112.5, 96.5, 22.0, 11.0.

Data obtained are in accordance with those previously reported.\(^{201}\)

4-(3-Aminobenzoyl)morpholine 133:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{NH}_2
\end{array}
\]

Using morpholin-4-yl(3-nitrophenyl)methanone (0.6 mmol, 142 mg), triethoxysilane (2.4 mmol, 394 mg) and \(84\) (11.0 mg, 0.024 mmol) in MeCN (0.6 mL) at 80 °C for 4 h. The amine 133 was isolated by flash column chromatography using ethyl acetate as a yellow oil (121 mg, 98%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.18-7.14 (m, 1H), 6.73-6.70 (m, 3H), 3.89-3.45 (m, 10H); \(^{13}\)C\({}^{1}\)H NMR (CDCl\(_3\), 125 MHz): δ 170.6, 146.8, 136.4, 129.4, 116.7, 116.3, 113.4, 66.9. HRMS (EI) Exact mass calcd for C\(_{11}\)H\(_{14}\)N\(_2\)O\(_2\) [M]+: 206.1055, found: 206.1061.

4-(Hydroxymethyl)aniline 134:

\[
\begin{array}{c}
\text{OH} \\
\text{NH}_2
\end{array}
\]

Using 4-nitrobenzyl alcohol (0.6 mmol, 91.8 mg), triethoxysilane (2.4 mmol, 394 mg) and \(84\) (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine 134 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as colourless solid (40.8 mg, 55%). Melting point: 60-61 °C. (Petroleum Spirit/EtOAc); Lit.\(^{202}\) 60-63 °C (EtOAc) \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.20-7.17 (m, 2H), 6.69-6.66 (m, 2H), 4.76 (s, 2H) 3.65 (br, 2H); \(^{13}\)C\({}^{1}\)H NMR (CDCl\(_3\), 125 MHz): δ 145.7, 130.3, 128.5, 114.9, 65.3.

Data obtained are in accordance with those previously reported.\(^{202}\)

4-(Methylsulfonyl)aniline 135:

\[
\begin{array}{c}
\text{MeO}_2\text{S} \\
\text{NH}_2
\end{array}
\]

Using 1-Methylsulfonyl-4-nitrobenzene (0.6 mmol, 121 mg), triethoxysilane (2.4 mmol, 394 mg) and \(84\) (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 4 h. The amine 135 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:2 v/v) as a pale yellow powder (82.1 mg, 80%). Melting point: 130-133 °C (Petroleum Spirit/EtOAc);
Lit.\textsuperscript{203} 134 °C (water). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 7.71-7.68 (m, 2H), 6.74-6.71 (m, 2H), 4.26 (br, 2H), 3.02 (s, 3H); \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (CDCl\textsubscript{3}, 125 MHz): δ 151.4, 129.4, 128.8, 114.1, 45.0.

NMR data obtained are in accordance with those previously reported.\textsuperscript{134}

4-Aminobenzonitrile 136:

\[
\text{\begin{tikzpicture}
  \node at (0,0) {\textbf{NC}};
  \node at (0.5,0) {\textbf{NH}_2};
\end{tikzpicture}}
\]

Using 4-nitrobenzonitrile (0.6 mmol, 88.8 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (0.6 mL) at 80 °C for 6 h. The amine 136 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as a pale yellow powder (46.0 mg, 65%). Melting point: 83-84°C (Petroleum Spirit/EtOAc); Lit.\textsuperscript{196} 85-86 °C (hexane/EtOAc). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 7.43-7.41 (m, 2H), 6.68-6.65 (m, 2H), 4.22 (br, 2H); \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (CDCl\textsubscript{3}, 125 MHz): δ 150.5, 133.8, 120.2, 114.5, 100.1.

Data obtained are in accordance with those previously reported.\textsuperscript{196}

Bis(2-aminophenyl)amine 140:

\[
\text{\begin{tikzpicture}
  \node at (0,0) {\textbf{NH}_2};
  \node at (0.5,0) {\textbf{NH}_2};
\end{tikzpicture}}
\]

Using 2-nitro-N-(2'-nitrophenyl)aniline (0.6 mmol, 155 mg), triethoxysilane (4.8 mmol, 787 mg) and 84 (5.5 mg, 0.012 mmol) in MeCN (1.2 mL) at 80 °C for 4 h. The amine 140 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1 v/v) as an orange powder (110 mg, 80%). Melting point: 100-102 °C. (Petroleum Spirit/EtOAc); Lit.\textsuperscript{204} 101 °C (petroleum). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 6.99-6.93 (m, 2H), 6.83-6.77 (m, 6H), 5.08 (br, 1H), 3.67 (br, 4H); \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (CDCl\textsubscript{3}, 125 MHz): δ 138.4, 131.2, 123.3, 120.3, 119.8, 116.5.

NMR data obtained are in accordance with those previously reported.\textsuperscript{140}

Ethyl 1-(4-aminophenyl)-5-(trifluoromethyl)-1\textit{H}-pyrazole-4-carboxylate 142:
Using ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (0.6 mmol, 197 mg), triethoxysilane (2.4 mmol, 394 mg) and 84 (8.2 mg, 0.018 mmol) in MeCN (0.6 mL) at 80 °C for 3 h. The amine 142 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:1 v/v) as a white powder (162 mg, 90%). Melting point: 107-108 °C. 1H NMR (CDCl3, 500 MHz): δ 8.08 (s, 1H), 7.20-7.18 (m, 2H), 6.74-6.71 (m, 2H), 4.38 (q, J = 10.0 Hz, 2H), 3.94 (br, 2H), 1.40 (t, J = 10.0 Hz, 3H); 13C{1H} NMR (CDCl3, 125 MHz): δ 161.2, 148.1, 142.0, 132.5 (q, JCF = 40.0 Hz), 130.0, 126.9, 119.2 (q, JCF = 270 Hz), 116.1, 114.6, 61.2, 14.0.

Data obtained are in accordance with those previously reported.142

6.3.2 Procedure for the Reduction of Mixed Substrates

A mixture of catalyst 84 (0.012 mmol, 5.5 mg), 4-nitrobenzonitrile 137 (0.3 mmol, 44.4 mg), ethyl 4-nitrobenzoate 138 (0.3 mmol, 58.5 mg), triethoxysilane (2.4 mmol, 394 mg) and acetonitrile (0.6 mL) were stirred in a preheated oil bath (80 °C) for 5 h. The solvents were removed under vacuum. The crude product was then dissolved in a minimal amount of CH2Cl2 and purified by flash column chromatography using petroleum spirit/ethyl acetate (4:1-2:1, v/v) to give a mixture of 136 and 124. The yield was analysed by 1H NMR using 1,3,5-trimethoxybenzene as internal standard.

6.3.3. General Procedure for Alkene Formal Hydroamination

To a solution of the nitro compound (0.3 mmol, 1.0 equiv) and catalyst 84 (2.8 mg, 0.006 mmol, 2.0 mol%) in EtOH (1.5 mL) was added donor olefin (0.9 mmol, 3.0 equiv), and PhSiH3 (1.0 or 2.0 equiv). The resulting mixture was stirred at room temperature until full consumption of the starting nitro compound was observed as indicated by TLC. Zinc (390 mg, 6.0 mmol, 20 equiv) and aqueous HCl (2 m, 3.0 mL) was added to the reaction mixture. After stirring at 60 °C for another 1h, the reaction mixture was cooled to room temperature and filtered through Celite and the filter cake washed with EtOAc. The filtrate was collected and
saturated aqueous NaHCO₃ solution added until strongly basic and then extracted with EtOAc three times. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product purified by flash column chromatography using petroleum spirit/ethyl acetate.

4-Methylthio-N-(tert-pentyl)aniline 157:

General procedure was followed by using 4-nitrothioanisole (0.3 mmol, 50.7 mg), phenylsilane (0.3 mmol, 32.4mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 157 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a colourless oil (32.3 mg, 51%). ¹H NMR (CDCl₃, 600 MHz): δ 7.18 (d, J = 6.0 Hz, 2H), 6.88 (d, J = 6.0 Hz, 2H), 2.44 (s, 3H), 1.68 (q, J = 7.4 Hz, 2H), 1.29 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H); ¹³C{¹H} NMR (CDCl₃, 150 MHz): δ 145.7, 130.8, 124.8, 117.3, 54.0, 33.9, 27.8, 18.8, 8.4. HRMS (EI) Exact mass calcd for C₁₂H₁₉NS+ [M]+: 209.1233, found: 209.1230.

N-(tert-pentyl)aniline 160:

General procedure was followed by using nitrobenzene (0.3 mmol, 36.9 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 160 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a colourless oil (28.7 mg, 58%). ¹H NMR (CDCl₃, 500 MHz): δ 7.19-7.15 (m, 2H), 6.77-6.74 (m, 3H), 1.70 (q, J = 7.5 Hz, 2H), 1.31 (s, 6H), 0.93 (t, J = 7.5 Hz, 3H); ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 147.0, 128.9, 117.9, 116.9, 53.9, 34.1, 27.8, 8.4.

Data obtained were in accordance with those previously reported.
**N-(tert-Pentyl)benzo[\textit{d}][1,3]dioxol-5-amine 161:**

General procedure was followed by using 1,2-(methylenedioxy)-4-nitrobenzene (0.3 mmol, 50.1 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 161 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1–30:1 v/v) as a colourless oil (27.0 mg, 43%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 6.66 (d, $J = 8.3$ Hz, 1H), 6.44 (d, $J = 2.3$ Hz, 1H); 6.26 (dd, $J = 8.3$, 2.3 Hz, 1H), 5.90 (s, 2H), 1.59 (q, $J = 7.5$ Hz, 2H), 1.22 (s, 6H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C ($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 147.8, 141.6, 141.3, 112.3, 108.1, 102.3, 100.7, 54.7, 34.4, 27.8, 8.5.

Data obtained were in accordance with those previously reported.$^{63}$

**4-Methoxy-N-(tert-pentyl)aniline 162:**

General procedure was followed by using 4-nitroanisole (0.3 mmol, 45.9 mg), phenylsilane (0.3 mmol, 32.4 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 162 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1–30:1 v/v) as a brown oil (34.8 mg, 60%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 6.71-6.77 (m, 4H), 6.44 (d, $J = 2.3$ Hz, 1H); 6.26 (dd, $J = 8.3$, 2.3 Hz, 1H), 5.90 (s, 2H), 1.59 (q, $J = 7.5$ Hz, 2H), 1.22 (s, 6H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C ($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 153.9, 140.0, 121.8, 114.2, 55.6, 54.6, 34.4, 27.7, 8.6.

Data obtained were in accordance with those previously reported.$^{63}$

**3-Trifluoromethyl-N-(tert-pentyl)aniline 163:**
General procedure was followed by using 3-nitrobenzotrifluoride (0.3 mmol, 57.3 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 163 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a colourless oil (31.5 mg, 45%). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.25-7.22 (m, 1H), 6.94-6.91 (m, 2H), 6.86-6.84 (m, 1H), 1.72 (q, $J = 7.5$ Hz, 2H), 1.34 (s, 6H), 0.92 (t, $J = 7.5$ Hz, 3H); $^{13}$C$\{^1$H$\}$ NMR (CDCl$_3$, 150 MHz): δ 147.2, 131.3 (q, $J = 31.4$ Hz), 129.3, 124.4 (q, $J = 270.0$ Hz) 118.6, 113.6 (q, $J = 3.9$ Hz), 112.0 (q, $J = 3.9$ Hz), 54.0, 33.8, 27.6, 8.4; $^{19}$F NMR (CDCl$_3$, 470 MHz): δ -62.9. HRMS (EI) Exact mass calcd for C$_{12}$H$_{16}$F$_3$N [M]$^+$: 231.1235, found: 231.1230.

4-Chloro-N-(tert-pentyl)aniline 164:

![4-Chloro-N-(tert-pentyl)aniline](image)

General procedure was followed by using 1-chloro-4-nitrobenzene (0.3 mmol, 47.1 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 164 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a colourless oil (44.3 mg, 75%). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.12-7.09 (m, 2H), 6.67-6.64 (m, 2H), 1.67 (q, $J = 7.5$ Hz, 2H), 1.29 (s, 6H), 0.91 (t, $J = 7.5$ Hz, 3H); $^{13}$C$\{^1$H$\}$ NMR (CDCl$_3$, 150 MHz): δ 145.6, 128.8, 122.6, 117.8, 54.0, 33.9, 27.8, 8.4. HRMS (EI) Exact mass calcd for C$_{11}$H$_{16}$ClN [M]$^+$: 197.0971, found: 197.0968.

4-Fluoro-N-(tert-pentyl)aniline 165:

![4-Fluoro-N-(tert-pentyl)aniline](image)

General procedure was followed by using 1-fluoro-4-nitrobenzene (0.3 mmol, 42.3 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 165 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a
colourless oil (30.8 mg, 56%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 6.90-6.87 (m, 2H), 6.74-6.72 (m, 2H), 1.62 (q, \(J = 7.5\) Hz, 2H), 1.24 (s, 6H), 0.93 (t, \(J = 7.5\) Hz, 3H); \(^1^3\)C \(\{^1\}H\) NMR (CDCl\(_3\), 125 MHz): 156.9 (d, \(J = 235.5\) Hz), 142.9, 119.5 (d, \(J = 7.4\) Hz). 115.2 (d, \(J = 21.9\) Hz), 54.4, 34.2, 27.7, 8.4; \(^1^9\)F NMR (CDCl\(_3\), 470 MHz): δ -126.0. HRMS (EI) Exact mass calcd for C\(_{11}\)H\(_{16}\)FN [M]: 181.1267, found: 181.1268.

4-Bromo-\(N\)-(tert-pentyl)aniline 166:

\[
\begin{align*}
\text{HN} & \\
\text{Me} & \\
\text{Me} & \\
\text{Br} & \\
\end{align*}
\]

General procedure was followed by using 1-bromo-4-nitrobenzene (0.3 mmol, 60.6 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 166 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~30:1 v/v) as a colourless oil (50.0 mg, 68%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): δ 7.25-7.22 (m, 2H), 6.62-6.59 (m, 2H), 1.67 (q, \(J = 7.5\) Hz, 2H), 1.29 (s, 6H), 0.90 (t, \(J = 7.5\) Hz, 3H); \(^1^3\)C \(\{^1\}H\) NMR (CDCl\(_3\), 125 MHz): δ 146.0, 131.7, 118.0, 109.5, 54.0, 33.8, 27.7, 8.4. HRMS (EI) Exact mass calcd for C\(_{11}\)H\(_{16}\)BrN [M]$: 241.046 0, found: 241.0460.

1-[4-(tert-Pentylamino)phenyl]propan-2-one 167:

\[
\begin{align*}
\text{HN} & \\
\text{Me} & \\
\text{Me} & \\
\text{CH}_2\text{(O)Me} & \\
\end{align*}
\]

General procedure was followed by using 1-(4-nitrophenyl)propan-2-one (0.3 mmol, 53.7 mg), phenylsilane (0.6 mmol, 64.8 mg), 2-methyl-2-butene 155 (0.9 mmol, 63.0 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 167 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (10:1~5:1 v/v) as a colourless oil (29.8 mg, 45%). \(^1\)H NMR (CDCl\(_3\), 600 MHz): δ 7.00 (d, \(J = 8.0\) Hz, 2H), 6.70 (d, \(J = 8.0\) Hz, 2H), 3.57 (s, 2H), 2.14 (s, 3H), 1.68 (q, \(J = 7.5\) Hz, 2H), 1.30 (s, 6H), 0.92 (t, \(J = 7.5\) Hz, 3H); \(^1^3\)C \(\{^1\}H\) NMR (CDCl\(_3\), 150 MHz): δ 207.5, 146.0, 129.9, 123.3, 117.0, 63.9, 50.3, 34.0, 29.0, 27.8, 8.5.

Data obtained were in accordance with those previously reported.\(^63\)
3-Methyl-3-[(2-chlorophenyl)amino]butan-1-ol 169:

![Chemical Structure](image)

General procedure was followed by using 1-chloro-2-nitrobenzene (0.3 mmol, 47.1 mg), phenylsilane (0.6 mmol, 64.8 mg), 3-methyl-2-buten-1-ol 168 (0.9 mmol, 77.4 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 169 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (10:1~5:1 v/v) as a colourless oil (48.9 mg, 76%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.32-7.30 (m, 1H), 7.16-7.11 (m, 2H), 6.77-6.74 (m, 1H), 3.89 (t, $J = 6.3$ Hz, 2H), 1.99 (t, $J = 6.3$ Hz, 2H), 1.39 (s, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 142.5, 129.4, 127.3, 122.9, 119.4, 117.6, 59.9, 54.5, 43.0, 28.4

Data obtained were in accordance with those previously reported.$^{63}$

3-Methyl-3-[(4-bromophenyl)amino]butan-1-ol 170:

![Chemical Structure](image)

General procedure was followed by using 1-bromo-4-nitrobenzene (0.3 mmol, 60.6 mg), phenylsilane (0.6 mmol, 64.8 mg), 3-methyl-2-buten-1-ol 168 (0.9 mmol, 77.4 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 170 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (2:1~1:1 v/v) as a colourless oil (48.8 mg, 63%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.31-7.27 (m, 2H), 6.76-6.72 (m, 2H), 3.90 (t, $J = 6.0$ Hz, 2H), 1.89 (t, $J = 6.0$ Hz, 2H), 1.31 (s, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 144.9, 131.8, 121.1, 112.5, 60.0, 54.7, 42.9, 28.2

Data obtained were in accordance with those previously reported.$^{63}$

3-Methyl-3-[(4-(trifluoromethyl)phenyl)amino]butan-1-ol 171:
General procedure was followed by using 4-nitrobenzotrifluoride (0.3 mmol, 57.3 mg), phenylsilane (0.6 mmol, 64.8 mg), 3-methyl-2-buten-1-ol 168 (0.9 mmol, 77.4 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 171 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:1~1:2 v/v) as a colourless oil (45.4 mg, 61%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.40 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 3.88 (t, $J = 6.3$ Hz, 2H), 1.99 (t, $J = 6.3$ Hz, 2H), 1.40 (s, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 149.2, 126.3 (q, $J = 3.8$ Hz), 124.9 (q, $J = 268.7$ Hz), 119.7 (q, $J = 32.5$ Hz), 115.7, 59.8, 53.8, 43.2, 28.2.

Data obtained were in accordance with those previously reported.63

3-Methyl-3-{(4-(methylthio)phenyl)amino}butan-1-ol 172:

General procedure was followed by using 4-nitrothioanisole (0.3 mmol, 50.7 mg), phenylsilane (0.3 mmol, 32.4 mg), 3-methyl-2-buten-1-ol 168 (0.9 mmol, 77.4 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 172 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (5:1~3:1 v/v) as a colourless oil (50.3 mg, 74%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.20-7.17 (m, 2H), 6.84-6.81 (m, 2H), 3.90 (t, $J = 6.0$ Hz, 2H), 2.45 (s, 3H), 1.88 (t, $J = 6.0$ Hz, 2H), 1.29 (s, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 143.9, 129.6, 128.6, 120.7, 60.1, 54.8, 42.9, 28.2, 17.9.

Data obtained were in accordance with those previously reported.63

4-Bromo-N-(2,3-dimethylbutan-2-yl)aniline 175:

General procedure was followed by using 1-bromo-4-nitrobenzene (0.3 mmol, 60.6 mg), phenylsilane (0.6 mmol, 64.8 mg), 2,3-dimethyl-1-butene 176 (0.9 mmol, 75.7 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 175 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (20:1~10:1 v/v) as a colourless oil (39.2 mg, 51%). When 2,3-dimethyl-2-butene 174 was used, (0.9 mmol,
75.7 mg) the same product was isolated in 26% yield (19.7 mg). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.24-7.21 (m, 2H), 6.62-6.59 (m, 2H), 2.11 (septet, $J = 6.8$ Hz, 1H), 1.26 (s, 6H), 0.94 (d, $J = 6.8$ Hz, 6H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 146.0, 131.7, 118.1, 109.3, 56.7, 35.4, 24.9, 17.5.

Data obtained were in accordance with those previously reported.$^{63}$

1-(4-Methoxyphenyl)-2,2,6-trimethylpiperidine 178:

General procedure was followed by using 4-nitroanisole (0.3 mmol, 45.9 mg), phenylsilane (0.3 mmol, 32.4 mg), 6-methyl-5-hepten-2-one 177 (0.9 mmol, 113.6 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 178 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~20:1 v/v) as a colourless oil (31.5 mg, 45%). $^1$H NMR (CDCl$_3$, 600 MHz): δ; 7.05 (d, $J = 8.2$ Hz, 2H), 6.80 (d, $J = 8.2$ Hz, 2H), 3.81 (s, 3H), 3.42-3.19 (m, 1H), 1.78-1.64 (m, 2H), 1.62-1.54 (m, 3H), 1.36-1.29 (m, 1H), 1.06 (s, 3H), 0.90 (s, 3H), 0.72 (d, $J = 6.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz): δ 156.7, 140.7, 131.0, 112.7, 55.3, 54.7, 50.2, 41.1, 36.2, 32.6, 22.9, 21.0, 17.5.

Data obtained were in accordance with those previously reported.$^{63}$

1-[4-(Methylthio)phenyl]-2,2,6-trimethylpiperidine 179:

General procedure was followed by using 4-nitrothioanisole (0.3 mmol, 50.7 mg), phenylsilane (0.3 mmol, 32.4 mg), 6-methyl-5-hepten-2-one 177 (0.9 mmol, 113.6 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 1 h. The amine 179 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1~20:1 v/v) as a colourless oil (38.0 mg, 51%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.19-7.16 (m, 2H), 7.08-7.05 (m, 2H), 3.36-3.29 (m, 1H), 2.50 (s, 3H), 1.79-1.63 (m, 2H), 1.63-1.54 (m, 3H), 1.34-1.31 (m, 1H), 1.05 (s, 3H), 0.92 (s, 3H), 0.74 (d, $J = 6.0$ Hz, 3H); $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 145.4, 134.0, 130.9, 126.1, 54.8, 50.0, 41.1, 36.1, 32.6, 22.9, 20.9, 17.5, 16.3. HRMS (EI) Exact mass calcd for C$_{13}$H$_{23}$NS [M]$^+$: 249.1546, found: 245.1540.
1-(4-Bromophenyl)-2,2,6-trimethylpiperidine 180:

![Chemical Structure](image)

General procedure was followed by using 1-bromo-4-nitrobenzene (0.3 mmol, 60.6 mg), phenylsilane (0.6 mmol, 64.8 mg), 6-methyl-5-hepten-2-one 177 (0.9 mmol, 113.6 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. The amine 180 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (50:1–20:1 v/v) as a colourless oil (25.6 mg, 30%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.40-7.36 (m, 2H), 7.03-6.99 (m, 2H), 3.34-3.26 (m, 1H), 1.80-1.66 (m, 2H), 1.64-1.53 (m, 3H), 1.34-1.29 (m, 1H), 1.09 (s, 3H), 0.90 (s, 3H), 0.72 (d, $J = 6.0$ Hz, 3H); $^{13}$C {$^1$H} NMR (CDCl$_3$, 150 MHz): δ 147.1, 132.2, 130.7, 118.2, 54.7, 49.9, 41.0, 36.1, 32.5, 22.8, 20.8, 17.4. HRMS (EI) Exact mass calcd for C$_{14}$H$_{20}$NBr [M]$^+$: 281.0774, found: 281.0758.

2-((6-Chloropyridin-3-yl)amino)-2-methylpropan-1-ol 183:

![Chemical Structure](image)

General procedure was followed by using 2-chloro-5-nitropyridine (0.3 mmol, 47.4 mg), phenylsilane (0.6 mmol, 64.8 mg), 3-methyl-2-buten-1-ol 168 (0.9 mmol, 77.4 mg) and 84 (2.8 mg, 0.006 mmol) in EtOH (1.5 mL) at 60 °C for 1 h. The amine 183 was isolated by flash column chromatography using petroleum spirit/ethyl acetate (1:1~1:2 v/v) as a colourless oil (28.8 mg, 45%). $^1$H NMR (acetone-$d_6$, 500 MHz): δ 7.87 (d, $J = 3.0$ Hz, 1H), 7.21 (dd, $J = 8.7, 3.1$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 5.21 (s, 1H), 3.75-3.72 (m, 2H), 3.65 (t, $J = 4.8$ Hz, 1H), 1.94 (t, $J = 6.9$ Hz, 2H), 1.37 (s, 6H); $^{13}$C {$^1$H} NMR (CDCl$_3$, 125 MHz): δ 143.2, 137.8, 137.1, 124.8, 123.4, 58.2, 52.9, 43.3, 27.3.

Data obtained were in accordance with those previously reported.$^{63}$
6.4 Experimental for Iron-Catalysed Formal Heck Cross-Coupling

6.4.1 Substrate Synthesis

Alkyl bromide 257 was synthesised according to literature procedure\textsuperscript{185}

\[
\begin{align*}
\text{Me-OH} & \quad \text{Br} \quad \text{O} \quad \text{Br} \quad \text{Et}_3\text{N} (3.0 \text{ eq}), \text{DCM} \\
\text{258} & \quad \text{DMAP (10 mol \%)} \quad 0 \degree \text{C to r.t.}, 24 \text{ h} \\
\text{259} & \quad \text{Br-O-} \quad \text{o-tolyl} \\
\text{257}
\end{align*}
\]

4-Methylphenol 258 (10 mmol, 1.0 equiv, 1.08 g), Et\textsubscript{3}N (30 mmol, 3.0 equiv, 3.03 g) and 4-(dimethylamino)pyridine (1.0 mmol, 0.1 equiv, 122 mg) were dissolved in 20 mL of dichloromethane in a 50 mL round-bottomed flask. The mixture was cooled down to 0 °C using an ice bath and kept in this temperature for 15 min. 2-Bromoisobutyryl bromide 259 (12 mmol, 1.2 equiv, 2.86 g) was added over 1 h by syringe pump. The resulting mixture was stirred at room temperature for 24 h, filtered to remove the triethylamine hydrobromide. The filtrate was washed with saturated Na\textsubscript{2}CO\textsubscript{3} solution (3 x 15 mL) and water (3 x 15 mL), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, solvents removed under vacuum. The crude product was purified by column chromatography using pentane/ethyl acetate as eluent (15:1, v/v) to give the product as a colourless solid (2.12 g, 83%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600 MHz): \(\delta\) 7.22 (d, \(J = 8.1\) Hz, 2H), 7.03 (d, \(J = 8.4\) Hz, 2H), 2.38 (s, 3H), 2.09 (s, 6H). \textsuperscript{13}C {\textsuperscript{1}H} NMR (CDCl\textsubscript{3}, 150 MHz): \(\delta\) 170.5, 148.6, 135.8, 130.0, 120.7, 55.5, 30.7, 20.9. HRMS (EI) Exact mass calcd for C\textsubscript{15}H\textsubscript{20}O\textsubscript{3} [M]: 256.0099, found: 256.0090.

Alkyl bromide 239 was synthesised according to literature procedure\textsuperscript{185}

\[
\begin{align*}
\text{N} & \quad \text{Br} \quad \text{O} \quad \text{Br} \quad \text{Et}_3\text{N} (3.0 \text{ eq}), \text{DCM} \\
\text{260} & \quad \text{DMAP (10 mol \%)} \quad 0 \degree \text{C to r.t.}, 24 \text{ h} \\
\text{259} & \quad \text{Br-N} \quad \text{O} \\
\text{230}
\end{align*}
\]

239 was synthesised in the same procedure with 257 but use piperidine 260 (10 mmol, 1.0 equiv, 850 mg) instead of 4-methylphenol. The product was purified by column chromatography using pentane/ethyl acetate as eluent (15:1, v/v) as a pale yellow oil (2.10 g, 90%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600 MHz): \(\delta\) 3.72 (br, 4H), 1.98 (s, 6H), 1.70-1.67 (m, 2H), 1.64-1.61 (m, 4H). \textsuperscript{13}C {\textsuperscript{1}H} NMR (CDCl\textsubscript{3}, 150 MHz): \(\delta\) 168.8, 57.1, 32.8, 25.9, 24.5. HRMS (EI) Exact mass calcd for C\textsubscript{15}H\textsubscript{20}O\textsubscript{3} [M]: 233.0415, found: 233.0416.
4-Dimethylaminostyrene 228 was synthesised according to literature procedure.\(^{186}\)

\[ \text{Ph} \text{Me} \overset{\text{OTf}}{\text{Br}} + \text{Ph}_{3}P \overset{nBuLi \ (1.0 \ \text{eq})}{\text{THF, r.t, 2 h}} \xrightarrow{\text{261}} \text{228} \]

\(nBuLi\) (1.6 M in hexanes) (6.0 ml, 1.6 eq) was added dropwise to a solution of methyltriphenylphosphonium bromide 262 (6.0 mmol, 1.0 equiv, 2.14 g) in THF (50 mL). The yellow solution was allowed to stir at room temperature for 15 min before a solution of 4-(dimethylamino)benzaldehyde 261 (6.0 mmol, 1.0 equiv, 900 mg) in THF (5 mL) was added. The mixture was stirred at room temperature for 3 hours, saturated \(\text{NH}_{4}\text{Cl}\) was added (15 mL) and the mixture was extracted by dichloromethane (15 mL x 2). The organic layers were collected, dried over anhydrous \(\text{Na}_{2}\text{SO}_{4}\) and concentrated under vacuum. The crude product was purified by column chromatography using pentane/ethyl acetate as eluent (30:1, v/v) to give the product 228 as a colourless oil (441 mg, 50%). \(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz): \(\delta\) 7.35 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.87 (dd, J = 17.6, 10.8 Hz, 1H), 5.58 (dd, J = 17.6, 1.0 Hz, 1H), 5.05 (dd, J = 10.8, 1.0 Hz, 1H), 2.99 (s, 6H). \(^{13}\text{C}\{^1\text{H}\}\) NMR (CDCl\(_3\), 125 MHz): \(\delta\) 150.3, 136.6, 127.2, 126.3, 112.4, 109.4, 40.5.

Data obtained were in accordance with those previously reported.\(^{186}\)

### 6.4.2 General Procedure for Iron-Catalysed Formal Heck Cross-Coupling

\[ \text{FeCl}_2 \text{ and Na}_2\text{CO}_3 \text{ were added under air to a 20 mL Schlenck tube. Dry DMF, styrene and alkyl bromide were consequently added by syringe. The flask was then vigorously stirred under N}_2 \text{ atmosphere at specified temperature for 16 h.} \]

\[ \text{After the completion of the reaction, 10 mL 0.5 M HCl solution were added and the mixture extracted with diethyl ether (3 x 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na}_2\text{SO}_4. \]

Solvents were removed under vacuum and the crude product purified by flash column chromatography on silica gel using pentane and ethyl acetate as eluent.

\((E)-\text{Ethyl 4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate 216:}\)
General procedure was followed by using 4-methoxystyrene (0.25 mmol, 33.5 mg), ethyl α-bromoisobutyrate (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16h. 216 was isolated by flash column chromatography using pentane/ethyl acetate (50:1~30:1, v/v) as a colourless oil (57.5 mg, 93%). ¹H NMR (CDCl₃, 500 MHz): δ 7.35-7.32 (m, 2H), 6.88-6.86 (m, 2H), 6.41 (d, J = 16.2 Hz, 1H), 6.29 (d, J = 16.2 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.42 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 176.4, 159.1, 132.4, 130.0, 127.5, 127.3, 114.0, 60.7, 55.3, 44.3, 25.2, 14.2.

Data obtained were in accordance with those previously reported.¹⁶⁴

Ethyl 1-[(1E)-2-(4-methoxyphenyl)ethenyl]cyclobutanecarboxylate 220:

General procedure was followed by using 4-methoxystyrene (0.25 mmol, 33.5 mg), ethyl 1-bromocyclobutanecarboxylate (0.75 mmol, 155 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. 3b was isolated by flash column chromatography using pentane/ethyl acetate (50:1~30:1, v/v) as a colourless oil (49.5 mg, 76%). ¹H NMR (CDCl₃, 500 MHz): δ 7.37-7.34 (m, 2H), 6.89-6.87 (m, 2H), 6.48 (d, J = 16.0 Hz, 1H), 6.34 (d, J = 16.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.64-2.59 (m, 2H), 2.30-2.24 (m, 2H), 2.01-1.90 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 175.8, 159.1, 129.8, 129.3, 128.3, 127.5, 114.0, 60.8, 55.3, 49.9, 31.0, 16.0, 14.2.

Data obtained were in accordance with those previously reported.¹⁶⁴

(E)-Methyl 4-(4-methoxyphenyl)-2-methylbut-3-enoate 221:

General procedure was followed by using 4-methoxystyrene (0.25 mmol, 33.5 mg), methyl 2-bromopropionate (1.00 mmol, 167 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 80 °C for 16 h. 3e was isolated by flash column chromatography using pentane/ethyl acetate (30:1~15:1, v/v) as a colourless oil (35.8 mg, 65%). ¹H NMR (CDCl₃, 600 MHz): δ 7.34-7.31 (m, 2H), 6.88-6.86 (m, 2H), 6.44 (d, J = 15.8 Hz, 1H), 6.15 (dd, J = 15.8, 8.0 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.34-3.29 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 150 MHz): δ 175.2, 159.2, 130.6, 129.7, 127.5,
126.5, 114.0, 55.3, 51.9, 43.2, 17.5. HRMS (EI) Exact mass calcd for C_{13}H_{16}O_{3}[M]^{+}: 220.1094, found: 220.1096.

(E)-4-(4-Methoxyphenyl)-2-methylbut-3-enenitrile 223:

General procedure was followed by using 4-methoxystyrene (0.25 mmol, 33.5 mg), 2-bromopropionitrile (1.00 mmol, 134 mg), Na$_2$CO$_3$ (0.275 mmol, 29.2 mg) and FeCl$_2$ (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 80 °C for 16 h. 233 was isolated by flash column chromatography using pentane/ethyl acetate (50:1~20:1, v/v) as a colourless oil (28.5 mg, 61%). $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.35-7.32 (m, 2H), 6.91-6.88 (m, 2H), 6.68 (d, $J$ = 15.8 Hz, 1H), 5.95 (dd, $J$ = 15.8, 6.1 Hz, 1H), 3.84 (s, 3H), 3.53-3.47 (m, 1H), 1.52 (d, $J$ = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): δ 159.7, 132.0, 128.5, 127.8, 122.1, 121.1, 114.1, 55.3, 28.4, 19.2.

Data obtained were in accordance with those previously reported.

(E)-1-(4-Methoxyphenyl)-3-(4-chlorophenyl)-propene 224:

General procedure was followed by using 4-methoxystyrene (0.25 mmol, 33.5 mg), 4-chlorobenzyl bromide (0.75 mmol, 154 mg), Na$_2$CO$_3$ (0.275 mmol, 29.2 mg) and FeCl$_2$ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 100 °C for 16 h. The product 224 was not isolated. Yield (52%) was determined by $^1$H NMR using 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol) as internal standard by comparison with the $^1$H NMR spectrum reported previously.

(E) Ethyl 4-(3,4-dimethoxyphenyl)-2,2-dimethylbut-3-enoate 225:

General procedure was followed by using 3,4-dimethoxystyrene (0.25 mmol, 41.0 mg), ethyl $\alpha$-bromoisobutyrate (0.75 mmol, 146 mg), Na$_2$CO$_3$ (0.275 mmol, 29.2 mg) and FeCl$_2$ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. 3h was isolated by flash column chromatography using pentane/ethyl acetate (15:1~5:1, v/v) as a colourless oil (59.2 mg, 85%).
1H NMR (CDCl₃, 600 MHz): δ 6.95-6.92 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 16.1 Hz, 1H), 6.28 (d, J = 16.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 1.42 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H).

13C{1H} NMR (CDCl₃, 150 MHz): δ 176.4, 149.0, 148.7, 132.6, 130.3, 127.6, 119.4, 111.2, 108.8, 60.8, 55.9, 55.8, 44.3, 25.2, 14.2. HRMS (EI) Exact mass calcd for C₁₆H₂₂O₄ [M⁺]: 278.1513, found: 278.1512.

(E) Ethyl 4-(2-methoxyphenyl)-2,2-dimethylbut-3-enoate 226:

General procedure was followed by using 2-methoxystyrene (0.25 mmol, 33.5 mg), ethyl α-bromoisobutyrate (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. 226 was isolated by flash column chromatography using pentane/ethyl acetate (100:1~50:1, v/v) as a colourless oil (50.9 mg, 82%). 1H NMR (CDCl₃, 600 MHz): δ 7.47 (dd, J = 7.6, 1.6 Hz, 1H), 7.25-7.22 (m, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 16.3 Hz, 1H), 6.42 (d, J = 16.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.44 (s, 6H), 1.29 (t, J = 7.1 Hz, 3H). 13C{1H} NMR (CDCl₃, 150 MHz): δ 176.5, 156.6, 134.9, 128.4, 126.5, 126.3, 122.5, 120.6, 110.9, 60.7, 55.5, 44.7, 25.2, 14.2. HRMS (EI) Exact mass calcd for C₁₅H₂₀O₃ [M⁺]: 248.1407, found: 248.1402.

(E)-p-Tolyl 4-(2-methoxyphenyl)-2,2-dimethylbut-3-enoate 227:

General procedure was followed by using 2-methoxystyrene (0.25 mmol, 33.5 mg), p-tolyl 2-bromo-2-methylpropanoate (0.75 mmol, 193 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. 227 was isolated by flash column chromatography using pentane/ethyl acetate (100:1~50:1, v/v) as a colourless oil (62.8 mg, 81%). 1H NMR (CDCl₃, 500 MHz): δ 7.51 (dd, J = 7.5, 1.6 Hz, 1H), 7.27-7.24 (m, 1H), 7.19-7.17 (m, 2H), 7.01-6.93 (m, 4H), 6.91-6.89 (m, 1H), 6.53 (d, J = 16.3 Hz, 1H), 3.88 (s, 3H), 2.36 (s, 3H), 1.59 (s, 6H). 13C{1H} NMR (CDCl₃, 125 MHz): δ 175.2, 156.7, 148.9, 135.2, 134.2, 129.8, 128.6, 126.6, 126.1, 123.4, 121.2, 120.7, 110.9, 55.5, 45.0, 25.2, 20.9. HRMS (EI) Exact mass calcd for C₂₀H₂₂O₃ [M⁺]: 310.1569, found: 310.1560.
(E) Ethyl 4-[4-(dimethylamino)phenyl]-2,2-dimethylbut-3-enoate 229:

General procedure was followed by using 4-(dimethylamino)styrene (0.25 mmol, 36.8 mg), ethyl α-bromoisobutyrate (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. 229 was isolated by flash column chromatography using pentane/ethyl acetate (50:1~30:1, v/v) as a colourless oil (42.4 mg, 65%). ¹H NMR (CDCl₃, 600 MHz): δ 7.29 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.38 (d, J = 16.1 Hz, 1H), 6.21 (d, J = 16.1 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.97 (s, 6H), 1.42 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 150 MHz): δ 176.7, 150.0, 130.3, 127.7, 127.2, 125.8, 112.5, 60.6, 44.2, 40.6, 25.2, 14.2.

Data obtained were in accordance with those previously reported.¹⁶²

(E) Ethyl 4-(4-methylphenyl)-2,2-dimethylbut-3-enoate 202:

General procedure was followed by using 4-methylstyrene (0.25 mmol, 29.5 mg), ethyl α-bromoisobutyrate (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 100 °C for 16 h. 202 was isolated by flash column chromatography using pentane/ethyl acetate (50:1, v/v) as a colourless oil (40.7 mg, 70%). ¹H NMR (CDCl₃, 500 MHz): δ 7.30 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.43 (d, J = 16.2 Hz, 1H), 6.37 (d, J = 16.2 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.43 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 176.4, 137.2, 134.4, 133.5, 129.2, 127.8, 126.2, 60.8, 44.3, 25.1, 21.2, 14.2.

Data obtained were in accordance with those previously reported.¹⁶²

(E) Ethyl 4-(2,4-dimethylphenyl)-2,2-dimethylbut-3-enoate 230:

General procedure was followed by using 2,4-dimethylstyrene (0.25 mmol, 33.0 mg), ethyl α-bromoisobutyrate (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025
mmol, 3.2 mg) in DMF (1.0 mL) at 100 °C for 16 h. **230** was isolated by flash column chromatography using pentane/ethyl acetate (100:1–50:1, v/v) as a colourless oil (43.7 mg, 71%). $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 7.34 (d, $J = 7.7$ Hz, 1H), 7.01-6.99 (m, 2H), 6.64 (d, $J = 16.1$ Hz, 1H), 6.25 (d, $J = 16.0$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.33 (s, 6H), 1.44 (s, 6H), 1.30 (t, $J = 7.1$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz): $\delta$ 176.4, 137.0, 135.2, 135.1, 133.6, 131.0, 126.8, 125.7, 125.6, 60.7, 44.6, 25.2, 21.0, 19.7, 14.2. HRMS (EI) Exact mass calcd for C$_{16}$H$_{22}$O$_2$[M]: 246.1614, found: 246.1609.

Ethyl 2,2-dimethyl-4,4-diphenylbut-3-enoate **232**:  

![Structure](image)

General procedure was followed by using 1,1-diphenylethylene **192** (0.25 mmol, 45 mg), ethyl $\alpha$-bromoisobutyrate **215** (1.0 mmol, 195 mg), Na$_2$CO$_3$ (0.275 mmol, 29.2 mg) and FeCl$_2$ (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 80 °C for 16 h. **232** was isolated by flash column chromatography using pentane/ethyl acetate (100:1–50:1, v/v) as a colourless oil (53.7 mg, 73%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.37-7.23 (m, 8H), 7.17-7.15 (m, 2H), 6.12 (s, 1H), 3.76 (q, $J = 7.1$ Hz, 2H), 1.32 (s, 6H), 1.16 (t, $J = 7.1$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 125 MHz): $\delta$ 176.4, 143.4, 141.5, 139.3, 134.2, 130.1, 128.0, 127.8, 127.4, 127.2, 127.1, 60.4, 44.0, 27.8, 13.9.

Data obtained were in accordance with those previously reported.$^{162}$

Ethyl 2-(1H-inden-2-yl)-2-methylpropionate **234**:  

![Structure](image)

General procedure was followed by using indene **233** (0.25 mmol, 29 mg), ethyl $\alpha$-bromoisobutyrate **215** (1.0 mmol, 195 mg), Na$_2$CO$_3$ (0.275 mmol, 29.2 mg) and FeCl$_2$ (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 100 °C for 16 h. **234** was isolated by flash column chromatography using pentane/ethyl acetate (100:1–50:1, v/v) as a colourless oil (30.0 mg, 52%). $^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ 7.42 (d, $J = 7.4$ Hz, 1H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.28-7.25 (m, 1H), 7.18-7.16 (m, 1H), 6.71 (s, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.45 (s, 2H), 1.57 (s, 6H) 1.26 (t, $J = 7.1$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz): $\delta$ 176.0, 152.6, 144.6, 143.2, 126.6, 126.4, 124.3, 123.5, 120.7, 60.9, 44.7, 38.7, 25.7, 14.2.

Data obtained were in accordance with those previously reported.$^{208}$
Reaction of α-methyl styrene 235 and ethyl α-bromoisoobutyrate 215:

\[
\begin{align*}
\text{235} & \quad \text{Br} \quad \text{OEt} \\
& \quad \text{FeCl}_2 (10 \text{ mol}) \quad \text{Na}_2\text{CO}_3, \text{DMF, } 80^\circ \text{C, } 16 \text{ h} \\
\text{236} & \quad + \quad \text{237}
\end{align*}
\]

General procedure was followed by using α-methyl styrene 235 (0.25 mmol, 29.5 mg), ethyl α-bromoisoobutyrate 215 (0.75 mmol, 146 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. The ratio between 236 and 237 was determined by ¹H NMR of the crude product to be 9:1. The crude products were purified by flash column chromatography using pentane/ethyl acetate (50:1~30:1, v/v) to give a mixture of 236 and 237 as a colourless oil (30.0 mg, 40%). ¹H NMR (CDCl₃, 400 MHz): δ 7.40-7.23 (m, 5H), 5.25 (d, J = 1.8 Hz, 1H) 5.07 (s, 1H), 3.76 (q, J = 7.2 Hz, 2H), 2.81 (s, 2H), 1.14 (s, 6H), 1.14 (t, J = 7.2 Hz, 3H). ¹³C {¹H} NMR (CDCl₃, 150 MHz): δ 177.2, 146.2, 142.4, 128.0, 127.2, 126.7, 117.0, 60.2, 45.8, 42.5, 25.5, 14.0.

Data obtained were in accordance with those previously reported.¹⁸¹

### 6.4.3 Hydrogenation of Cross-Coupling Product 222

\[
\begin{align*}
\text{MeO} \quad \text{Ph} \\
\text{203} & \quad \text{Br} \quad \text{CO}_2\text{Et} \\
& \quad \text{FeCl}_2 (20 \text{ mol %}) \quad \text{Na}_2\text{CO}_3, \text{DMF, } 80^\circ \text{C} \\
\text{MeO} \quad \text{Ph} \\
\text{263} & \quad \text{CO}_2\text{Et} \\
& \quad \text{H}_2 (1 \text{ atm}) \quad \text{Pd/C}, \text{r.t., } 16 \text{ h} \\
\text{MeO} \quad \text{Ph} \\
\text{264} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

Synthesis of 222: General procedure for iron-catalysed formal Heck cross-coupling was followed by using 4-methoxystyrene 203 (0.25 mmol, 33.5 mg), ethyl α-bromophenylacetate 263 (1.00 mmol, 243 mg), Na₂CO₃ (0.275 mmol, 29.2 mg) and FeCl₂ (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 80 °C for 16 h. The crude product was not isolated. The yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene (16.8 mg, 1.0 mmol) as internal standard (91%).

Hydrogenation of 222 to give 264: The crude product obtained in previous step was then dissolved in 0.5 mL ethanol. Pd/C (5.0 mg) was added and the mixture were stirred under 1.0 atm of H₂ at room temperature. After being stirred for 16 h, 5 mL ethanol was added and the mixture was filtered through a short pad of Celite to remove the catalyst. Wash the filter with
ethanol (3 x 5 mL). The filtrates were collected, solvents removed under vacuum and the crude product was purified by flash column chromatography using pentane/ethyl acetate (50:1~30:1, v/v) to give the product as a colourless oil (64.9 mg, 87% over 2 steps). \[\text{\textsuperscript{1}H NMR (CDCl}_3, 600 MHz): \delta 7.36-7.32 (m, 4H), 7.30-7.27 (m, 1H), 7.10-7.08 (m, 2H), 6.86-6.84 (m, 2H), 4.20-4.09 (m, 2H), 3.81 (s, 3H), 3.56 (t, \textit{J} = 7.6 Hz, 1H), 2.54 (t, \textit{J} = 7.7 Hz, 2H), 2.43-2.37 (m, 1H), 2.12-2.07 (m, 1H), 1.24 (t, \textit{J} = 7.2 Hz, 3H), \text{\textsuperscript{13}C\text{\textsuperscript{1}H} NMR (CDCl}_3, 150 MHz): \delta 173.9, 157.9, 139.1, 133.4, 129.4, 128.6, 128.0, 127.2, 113.8, 60.7, 55.3, 51.0, 35.2, 32.7, 14.2. \text{HRMS (EI) Exact mass calcd for C}_{19}H_{22}O_{3} [M]^+: 298.1564, found: 298.1562.]

### 6.4.4 Elimination of 2-Bromo-2-methyl-1-(1-piperidinyl)-1-propanone

General procedure for iron-catalysed formal Heck cross-coupling was followed by using 2-methoxystyrene 238 (0.25 mmol, 33.5 mg), 2-bromo-2-methyl-1-(1-piperidinyl)-1-propanone 239 (0.75 mmol, 176 mg), Na\textsubscript{2}CO\textsubscript{3} (0.275 mmol, 29.2 mg) and FeCl\textsubscript{2} (0.025 mmol, 3.2 mg) in DMF (1.0 mL) at 80 °C for 16 h. Product 240 was purified by flash column chromatography using pentane/ethyl acetate (5:1~2:1, v/v) as a colourless oil (71.1 mg, 62%). \[\text{\textsuperscript{1}H NMR (CDCl}_3, 600 MHz): \delta 5.12 (s, 1H), 5.00 (s, 1H), 3.56 (br, 2H), 3.46 (br, 2H), 1.95 (s, 3H), 1.68-1.64 (m, 2H), 1.55 (br, 4H) \text{\textsuperscript{13}C\text{\textsuperscript{1}H} NMR (CDCl}_3, 150 MHz): \delta 171.1, 141.0, 114.5, 47.9, 42.3, 25.7, 25.5, 24.6, 20.5. \text{Radical alkenylation product 241 was not observed.}

Data obtained were in accordance with those previously reported.\textsuperscript{209}

### 6.4.5 Styrene Dimerisation

General procedure for iron-catalysed formal Heck cross-coupling was followed by using 4-methoxystyrene 203 (0.25 mmol, 33.5 mg), 1-bromo-1-phenylethane 242 (1.00 mmol, 185 mg), Na\textsubscript{2}CO\textsubscript{3} (0.275 mmol, 29.2 mg) and FeCl\textsubscript{2} (0.050 mmol, 6.3 mg) in DMF (1.0 mL) at 80 °C for 16 h. Styrene dimerisation product 243 was purified by flash column chromatography on silica gel using pentane and ethyl acetate (50:1) as a colourless oil (26.9
mg, 80%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.31 (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.36 (d, $J = 16.0$ Hz, 1H), 6.24 (dd, $J = 15.9$, 6.7 Hz, 1H), 3.82 (s, 3H), 3.82(s, 3H), 3.63-3.57 (m, 1H), 1.45 (d, $J = 7.0$ Hz, 3H). $^{13}$C ($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 158.8, 158.0, 138.0, 133.6, 130.5, 128.2, 127.6, 127.2, 113.9, 113.8, 55.3, 41.7, 21.4.

Data obtained were in accordance with those previously reported.$^{210}$

### 6.4.6 Radical Trapping Experiment

TEMPO (46.8 mg, 0.30 mmol, 1.2 equiv), FeCl$_2$ (31.5 mg, 0.25 mmol, 1.0 equiv) was added to a 20 mL Schlenck tube. Dry DMF (1.0 mL) and 215 (48.8 mg, 0.25 mmol, 1.0 equiv) were then added by syringe. The flask was then vigorously stirred under N$_2$ atmosphere at 80 °C for 16 h. After the completion of the reaction, 20 mL diethyl ether were added and washed with water (2 x 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na$_2$SO$_4$. Solvents were removed under vacuum and the crude product purified by flash column chromatography on silica gel using pentane as eluent to give 256 as a colourless oil (10.2 mg, 15%). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.19 (q, $J = 7.1$ Hz, 2H), 1.65-1.23 (m, 6H), 1.49 (s, 6H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.17 (s, 6H), 1.02 (s, 6H). $^{13}$C ($^1$H) NMR (CDCl$_3$, 125 MHz): $\delta$ 176.1, 81.1, 60.6, 59.6, 40.6, 33.5, 24.5, 20.5, 17.1, 14.2.

Data obtained were in accordance with those previously reported.$^{211}$
Reference

Appendix: Publications


