Manganese-Catalyzed Carbonylation of Alkyl Iodides

By

Felix Alexander Westerhaus

Vordiplom (Chemistry), Philipps-Universität Marburg, 2006

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF SCIENCE MASTERS IN ORGANIC CHEMISTRY AT THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY AUGUST 2009

© 2009 Massachusetts Institute of Technology. All rights reserved.

Signature of Author: ..................................................

Department of Chemistry

August 27, 2008

Certified by: ..........................................................

Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry

Academic Advisor

Accepted by: ..................................................

Robert W. Field
Chairman, Department Committee on Graduate Students
Palladium Catalyzed Cross-Coupling of Aryl Halides with Zirconocene-Benzyne Complexes and Manganese Catalyzed Carbonylation of Alkyl Halides

By

Felix Alexander Westerhaus

Vordiplom (Chemistry), Phillips Universität Marburg, 2006

Submitted to the Department of Chemistry on August 28, 2009

in Partial Fulfillment for the Degree of Science Masters in Organic Chemistry

ABSTRACT

The palladium-catalyzed cross-coupling of aryl bromides with zirconocene-benzyne complexes has been investigated by S.L. Buchwald and coworkers. This method allows the formation of substituted biphenyls and terphenyls, however only two ortho-substituents are tolerated in this transformation. The studies reported herein aimed at the synthesis of tri- and tetra substituted biaryls, since they are important precursors to biaryl phosphine ligands. The project did not succeed due to stability problems of the formed substituted zirconium biaryl.

A general method for the manganese-catalyzed carbonylation of alkyl iodides while using a variety of nucleophiles was developed. The method concerns the alkoxy and amino carbonylation as well as the use of more unconventional nucleophiles such as thiols, azide and hydride. The method employs alkyl iodides although bromides are also feasible substrates through in situ Finkelstein reaction with catalytic to substoichiometric amounts of sodium iodide. The functional group tolerance is high and the conditions for the transformation are mild using only 40 psi of carbon monoxide pressure and temperatures between r.t. and 90 °C for more difficult cases.

Thesis Supervisor: Stephen L. Buchwald

Title: Camille Dreyfus Professor of Organic Chemistry
Acknowledgements

I would like to thank my academic advisor Stephen L. Buchwald for his guidance, patience and understanding during the last two years, my thesis chair Prof. Fu for helping me out. Special thanks to Ruben and Dr. Surry for their outstanding mentorship, Georgiy and Debrabra for the enlightening conversations, as well as Dima and Xiaoqiang, being great lab neighbors.

Of course I would like to thank my family for the unconditional support during the last two years.
Table of Contents

Chapter 1: Palladium-Catalyzed Cross-Coupling Reactions of Zirconocene-Benzyne Complexes with Aryl Bromides

A. Introduction
B. Results and Discussion
C. Conclusions
D. Experimental

Chapter 2: Manganese-Catalyzed Carbonylation of Iodoalkanes

A. Introduction
B. Results and discussion
C. Conclusions
D. Experimental

Appendix A: Analytical Data
Appendix B: References
Appendix C: Curriculum Vitae
Chapter 1:

Palladium-Catalyzed Cross-Coupling Reactions of Zirconocene-Benzyne Complexes with Aryl Bromides

A. Introduction

Arynes are highly strained and reactive species that undergo a range of synthetically useful transformations when generated and used *in situ*, hence a number of methods for their formation have been developed.\(^1\)\(^2\)

Although highly reactive in solution, arynes can be stabilized by electron rich metal fragments. This stabilization can be attributed to several factors: 1) the aryne is less strained due to the back bonding of the metal which decreases the order of the triple bond and thus the bond angle distortion; 2) electropositive metals release electron density into the aryne. This metallacyclopropane is less strained than all carbon cyclopropanes because the metal based orbitals can accommodate the small bond in a three-membered ring more easily.

Although there was some early evidence for metal-stabilized benzyne complexes\(^3\)-\(^7\) the first isolated complex was described by the Schrock group using a tantalum system (Figure 1 [1]).\(^8\) This was followed by Bennett who reported an isolated nickel-benzyne complex (Figure 1 [2])\(^9\) and by Buchwald and coworkers who reported the first zirconium stabilized benzyne complex as the zirconocene benzyne trimethylphosphine adduct (Figure 1 [3]).\(^10\)
Zirconocene-benzyne complexes were first generated in the laboratories of Erker by thermolysis of diaryl zirconocene complexes.\(^{11}\) His work was based on related studies using diaryl titanocene compounds, which also give benzyne complexes upon heating.\(^{12-13}\) Erker established that the mechanism of formation of these metallocenes must proceed via \(\beta\)-abstraction from the aryne compound (Scheme 1).

A more synthetically useful method of generating zirconocene-benzyne complexes was introduced by Buchwald.\(^{14}\) This method uses zirconocene (methyl) chloride and an aryllithium species to form the aryl (alkyl) zirconocene which then undergoes \(\beta\)-abstraction to form the zirconocene-benzyne complex (Scheme 1).
This protocol was further simplified into a one step procedure to synthesize the zirconocene-benzyne starting from zirconocene dichloride.\textsuperscript{15} A further advantage is that this method does not make use of zirconocene (methyl) chloride, which must first be prepared in a two step process.\textsuperscript{16} \textit{tert}-Butyllithium is added to zirconocene dichloride, which after rearrangement of the initial adduct gives zirconocene (isobutyl) chloride. This mixture is then treated with the aryllithium to produce the zirconocene-benzyne as described above (Scheme 3).
This method allows the functionalization of an aromatic ring in two positions through C-H activation starting from a monohaloarene. These zirconium complexes show reactivity towards a wide array of electrophiles and unsaturated molecules. Insertion is highly regioselective, reaction of unsaturated molecules occurring at the less hindered position. In particular the insertion of nitriles is of great significance since upon hydrolysis anti-Friedel-Crafts-acylation products are obtained (Scheme 4).\textsuperscript{14,17}

\[
\begin{align*}
\text{R}^1 \text{ZrCp}_2 & \xrightarrow{\text{R}^2 \text{CN}} \text{R}^1 \text{ZrCp}_2 \quad \text{ZnH(E)} \\
\text{R}^1 \text{ZrCp}_2 & \xrightarrow{\text{H}_2\text{O}} \text{R}^1 \text{H(E)} \\
\end{align*}
\]

\textbf{Scheme 4: meta-acylation of aromatic compounds}

Zirconocene-benzylne complexes have also been reported to react with a variety of other unsaturated systems, such as olefins and alkynes, as well as organometallic species including boron or gallium reagents, which form heterobimetallic compounds (Scheme 5).\textsuperscript{17-18}
Scheme 5: Various reactions zirconocene-benzyne can undergo

By quenching the intermediate cyclic-aryl zirconocene species with an electrophile other than water, such as iodine or sulfur dichloride, polysubstituted aromatic compounds, or heterocycles can be generated (Scheme 6).\textsuperscript{15,17}
Scheme 6: Different electrophiles for quenching aryl-zirconocene species

Vinyl zirconocene species are known to be viable partners in palladium or nickel catalyzed cross-coupling reactions. In this case the zirconocene complex can be easily made by hydrozirconation of alkynes and can subsequently be coupled with aryl halides (Scheme 7).19

Scheme 7: Hydrozirconation and subsequent cross-coupling of vinyl-zirconocene

The Buchwald group has investigated the feasibility of zirconocene-benzyne as a nucleophile in cross-coupling reactions.20 It was found that these complexes are viable partners for palladium-catalyzed cross-coupling reactions, producing a variety of useful biaryls.
The optimized conditions for the coupling reaction show high regioselectivity for the transmetalation step, resulting in a method that can produce substituted biaryls in which a single regioisomer is formed. For toluene-derived benzyne-complexes the best ligand was DPEPhos, whereas for anisole derived benzyne-complexes DPPF was the superior ligand (Scheme 8).  

Scheme 8: Cross-coupling of zirconocene-benzyne

The use of an appropriate phosphine ligand is crucial to ensure coupling takes place in a regioselective fashion and prevent the resulting aryl zirconocene species from undergoing a second transmetalation (Scheme 9).

Scheme 9: The catalytic system reported by Buchwald and coworkers prevents further cross-coupling of the aryl zirconium species
The proposed mechanism for this transformation consists of oxidative addition to the aryl bromide followed by transmetalation of the zirconocene-benzyne complex. After reductive elimination and iodine quench the final product, an ortho-iodo biaryl is formed (Scheme 10).

**Scheme 10**: Proposed catalytic cycle for zirconocene-benzyne cross-coupling

The scope of the reaction is broad, with numerous functional groups such as ethers and chlorides as well as protected aldehydes, amines and esters being tolerated (Figure 2). There are, however, no examples of tri-ortho substituted biaryls being made by this method.
Figure 2: Biaryl iodides synthesized by zirconocene-benzyne cross-coupling

Substituted biaryl iodides are important precursors to modern biaryl phosphine ligands, thus further developing the reaction to tolerate increased steric bulk in the coupling partners would be of value. Development of an enantioselective version of this chemistry would also be desirable to facilitate the synthesis of chiral ligands.\textsuperscript{21-26}

Figure 3: Biaryl- and binaphthyl based phosphine ligands
B. Results and discussion

The cross-coupling reaction of zirconocene-benzyne species with ortho-substituted aryl halides to form tri- or tetra ortho-substituted biaryls was first examined using the conditions previously reported by Buchwald and coworkers.\textsuperscript{20} Initial experiments showed that this system did not give any of the desired cross-coupling products, hence a number of different biaryl phosphine ligands were examined (Figure 4). Several of these ligands proved effective, with XPhos giving the highest yields and conversions.\textsuperscript{27-29}

![Figure 4: Selection of biaryl phosphine ligands examined](image)

Although the biaryl was formed with good regioselectivity, after the final electrophilic quench, using iodine only the protonated biaryl could be recovered. This was the case for several substrates having different steric and electronic properties (Figure 5). Quenching the reaction mixture with D\textsubscript{2}O, DCl (20% in D\textsubscript{2}O) in or MeOD did not result in any deuterium incorporation, showing the proton incorporation occurred before addition of the electrophile.
Isolated yields of up to 80% of the protonated biaryl could be obtained, however without the possibility of further functionalization the method is not useful. There are a number of possible explanations for the exclusive formation of the protonated compounds: 1) The reaction of iodine with the biaryl zirconocene species may be significantly slower than competing protonation. 2) It is possible that adventitious water in the solvent is providing the proton source, however this is not consistent with formation of the desired iodinated compound for less hindered substrates. In order to demonstrate that protonation was not a result of water in the reaction vessel, all solvents were carefully dried and tested for moisture with benzophenone ketal. The reaction was also performed inside the glovebox. Despite these precautions, protonated material remained the only product. 3) Alternatively iodine may be too sterically demanding to react with the aryl zirconocene species, thus a number of other electrophiles were examined. Amongst these were very reactive reagents such as bromine, iodine or iodine monochloride as well as milder electrophiles such as NCS, NBS, NIS or dibromoethane. All of these attempts failed to yield any of the desired halogenated product.
Since THF is used as a reaction medium for the transformation, there is a possibility that the proton found in the final product derives from the solvent. A number of alternative solvents were examined, most of which give poor conversion and yield of the biaryl. When reaction was carried out in those solvents that gave successful coupling reactions, for example diethyl ether, the same undesired product was observed. Performing the reaction in deuterated THF, provided further evidence that the solvent is not acting as a proton source, as no incorporation of deuterium into the final biaryl product was observed. Using zirconocene (methyl) chloride instead of in situ generation of the zirconocene iso-butyl chloride gave the same outcome. Even using the isolated aryl lithium species with zirconocene (methyl) chloride to generate the benzyne-complex resulted in the same undesired product. Although tri- and tetra-ortho-susbtituted biaryl iodides proved elusive, compounds bearing only two ortho-substituents could be successfully synthesized using these reaction conditions (Scheme 11). From these biaryl iodides some novel ligands could be synthesized by simple lithiation and subsequent addition of a chlorophosphine. These ligands are especially interesting due to their resemblance to the new BrettPhos series which are highly effective in palladium-catalyzed cross-coupling reactions (Figure 6), where the methoxy group ortho to the phosphine seems be of great significance.

![BrettPhos and t-Bu-BrettPhos ligands](image)

**Figure 6:** BrettPhos type ligands
Scheme 11: Biaryl phosphine ligands synthesized over two steps starting with zirconocene-benzyne cross-coupling.
C. Conclusions

The synthesis of tri- and tetrasubstituted biaryl iodides via palladium-catalyzed zirconocene-benzyne cross-coupling reaction could not be achieved. Although the initial palladium-catalyzed coupling was successful, further functionalization of the aryl-zirconocene species using a variety of electrophiles was unsuccessful. The source of the proton found in the biaryl could not be identified. It is possible that the proton originates from cyclopentadienyl rings on the zirconium since other options have been eliminated (Scheme 12).

**Scheme 12**: Unknown protonation step in catalytic cycle
D. Experimental

General Considerations

All reactions were carried out in flame-dried or oven dried (150 °C) glassware under argon using Schlenk techniques. THF was either distilled or vacuum transferred from sodium benzophenone ketyl, the solvents were stored in Schlenk flasks with Teflon screw caps. Alternatively solvents were stored in a glovebox and tested for moisture with sodium benzophenone ketyl. All anhydrous solvents were purchased from Aldrich Chemical Company. Tris(dibenzylideneacetone)dipalladium was purchased from Strem Chemicals Inc. and stored either in the glovebox or in a desiccator. Zirconocene dichloride was a gift from Boulder Scientific and stored in a glovebox. Iodine was purchased from Mallinckrodt and stored in a desiccator. All liquid aryl bromides or iodides were distilled from calcium hydride, stored in the glovebox and filtered through alumina prior to use. Solid substrates were stored either in the glovebox or in desiccators. Products were generally purified by flash chromatography on silica gel using the Biotage SP4 system. $^1$H NMR spectra were recorded on a Bruker DRX 400 spectrometer in deuterochloroform operating at 400 MHz. $^{13}$C NMR spectra were recorded on a Bruker DRX 400 spectrometer operating at 100 MHz. Chemical shifts are quoted relative to residual solvent (7.26 ppm for CHCl$_3$) and coupling constant are given in Hz to the nearest 0.5 Hz. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s singlet, d doublet, t triplet, q quartet, m multiplet or br broad. NMR spectra were acquired at 300 K. Infrared spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer as thin films on KBr plates. Selected absorption maxima ($v_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$). GC analysis were performed on an
Agilent 6890 equipped with an FID detector and a Hewlett Packard 10 m \( \cdot \) 0.2 mm HP-1 capillary column using tetradecane as an internal standard.

**Scheme 12:** General procedure A and B

**General procedure A** for the synthesis of biaryl iodides using zirconocene (methyl) chloride:

Three oven dried Schlenk flasks with Teflon screw caps were introduced to the glove box. Schlenk flask A was charged with zirconocene (methyl) chloride (1.4 equiv) and THF (0.28 M), Schlenk flask B was charged with the aryl halide A (1.5 equiv) and THF (0.22 M), Schlenk flask C was charged with Pd\(_2\)(dba)\(_3\) (2 mol%), the phosphine ligand (XPhos, 5 mol%), the second aryl halide B (1 equiv) and THF (0.5 M). All Schlenk flasks were then removed from the glovebox. To Schlenk flask B containing aryl halide A, \( n \)-BuLi (1.5 equiv) was added dropwise at -78 °C via syringe. The resulting mixture was stirred for 30 min at -78 °C and then allowed to warm to -50 °C. The solution of zirconocene (methyl) chloride in Schlenk flask A was then added via cannula at -50 °C, the resulting solution was stirred at -50 °C for 30 min. The cold bath was then removed and the mixture was stirred for 1 h, before it was transferred into Schlenk flask C via cannula. Schenk flask C was then sealed.
and heated to 60 °C for 16-18 h. The reaction mixture was then cooled to -50 °C and a solution of iodine (3 equiv) in dry THF (1.5 M) and methylene chloride (0.4 M) was added via cannula. The resulting solution was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for another 10 h. The reaction mixture was poured into a saturated solution of sodium thiosulfite and extracted with three portions of diethyl ether. The combined organic layers were washed with brine and then dried over anhydrous magnesium sulfate. The resulting solution was filtered through celite and then concentrated under reduced pressure. The crude product was taken up in methylene chloride and added onto a biotage sample. Purification was then performed by flash chromatography on silica gel using the Biotage SP4 system.

**General procedure B** for the synthesis of biaryl iodides using zirconocene dichloride:

Three oven-dried Schlenk flasks with teflon screw caps were introduced into the glove box. Schlenk flask A was charged with zirconocene dichloride (1.5 equiv) and THF (0.22 M), Schlenk flask B was charged with aryl halide A (1.5 equiv) and THF (0.3 M), Schlenk flask C was charged with Pd$_2$(dba)$_3$ (2 mol%) and the phosphine ligand (5 mol%) and aryl halide B (1 equiv) in THF (0.5 M). All Schlenk flasks were sealed and removed from the glove box. To Schlenk flask A containing zirconocene dichloride was added $t$-BuLi (1.5 equiv) via syringe at -78 °C, the resulting mixture was stirred for 15 min, then the cold bath was removed and the reaction mixture was stirred for 75 min. The reaction mixture was then cooled to -78 °C. To Schlenk flask B containing aryl halide A was added $n$-BuLi via syringe under argon flow at -78 °C, the reaction mixture was stirred for 15 min and then
added to Schlenk flask A at -78 °C via cannula. The reaction was stirred at -78 °C for 15 min, then at -50 °C for 30 min, after which the cold bath was removed and the reaction mixture was stirred for another 40 min. The reaction was then transferred to Schlenk flask C containing the catalyst and aryl halide B via cannula. The resulting mixture was then heated to 60 °C for 16-18 h. After this period of time the reaction vessel was cooled down to -50 °C and a solution of iodine (3 equiv) in dry THF (1.5 M) and methylene chloride (0.4 M) was added via cannula. The resulting solution was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for another 10 h. The reaction mixture was then poured into an aqueous saturated solution of sodium thiosulfite. The resulting biphasic mixture was extracted with diethyl ether three times. The combined organic layers were washed with brine once and then dried over anhydrous magnesium sulfate. The resulting solution was filtered through celite and then concentrated in under reduced pressure. The crude product was taken up in methylene chloride and added onto a biotage samplet. Purification was then performed on the Biotage system using a gradient of ethyl acetate in hexanes as an eluant.

Procedure for isolation of aryllithium species

An oven dried Schlenk flask was evacuated and filled with argon (this sequence was repeated three times). To this was added 2-bromoanisole (1 equiv, 40 mmol) and dry pentane (2.7 M, 15 mL) via syringe. Then n-BuLi (1 equiv, 13.3 mL) was added dropwise via syringe at room temperature. After the 2-lithioanisole precipitates out of solution, the Schlenk flask was moved into the glovebox. The solid was washed out of the reaction vessel with pentane, and isolated by filtration. Excess pentane was then removed under reduced pressure in the
glovebox to give quantitative yield of the desired product. The final product was stored in the glovebox. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$: 7.61 (m, 1 H), 7.19 (m, 1 H), 7.17 (m, 1 H), 6.75 (m, 1 H), 3.65 (s, 3 H)

**Procedure D** for the synthesis of biaryl diphenyl and dicyclohexyl biaryl phoshine ligands:

The biaryliodide (1 equiv) was added to a Schlenk flask which was equipped with a teflon screw cap, the vessel was evacuated and purged with argon three times. THF (0.1 M) was added and the reaction cooled to $-78 \, ^\circ\text{C}$. $n$-BuLi (1.1 equiv, 2.5 M in hexanes) was added via syringe, the reaction was stirred at $-78 \, ^\circ\text{C}$ for 30 min. Then the chloro phosphine (1.2 equiv) was added to the reaction mixture and stirred for 30 min at $-78 \, ^\circ\text{C}$. The reaction was then allowed to warm to room temperature and was stirred for a further 10 h. The reaction vessel was then opened and the resulting crude was washed with brine and back extracted with ethyl acetate three times. The combined organic layers were dried over magnesium sulfate and filtered through a pad of silica layered on top of celite eluting with ethyl acetate. The resulting mixture was then concentrated in vacuo and recrystallized from methanol with addition of methylene chloride.

**Dicyclohexyl[2-methoxy-6-(2-methoxy)phenyl]phosphane:**

The general procedure D was used, 1.03 mmol (350 mg) of the starting iodide was employed to yield the desired biaryl in 75% yield (315 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.15-7.05 (m, 2 H), 6.90 (m, 2 H), 6.6 (m, 1 H), 6.4 (m, 2 H), 3.4 (s, 3 H), 3.3 (s, 3 H), 2.5 (m, 2 H), 1.95-0.95 (m, 20 H), $^{31}$P NMR (170 MHz, CDCl$_3$) $\delta$: 0.003
Diphenyl[2- methoxy-6-(2- dimethylamino)phenyl]phosphane:

The general procedure D was used, 2.1 mmol (750 mg) of the crude iodide was employed to yield the desired biaryl in 14% yield (115 mg) over 2 steps. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.6-7.0 (m, 15 H), 6.9 (m, 1 H), 6.5 (m, 1 H), 2.9 (s, 3 H), 2.2 (s, 6 H)

3-(2,6-dimethoxy)anisole:

General procedure B was employed to yield the biaryl compound in 78%. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.28 (m, 2 H), 7.14 (m, 1 H), 6.98 (m, 2 H), 6.61 (m, 2 H), 3.72 (s, 3 H), 3.70 (s, 6 H)
A. Introduction

Transition metal-catalyzed reactions have revolutionized organic synthesis in the last 40 years. Increasing interest has focused on reactions of alkyl halides which have previously proved challenging due to their facility in undergoing undesired β-hydride elimination and difficulty in undergoing oxidative addition. By the choice of an appropriate ligand, elegant studies by Fu and coworkers have demonstrated that alkyl halides can participate in a range of transition-metal catalyzed reactions such as Suzuki, Hiyama and Nehishi couplings which were until recently limited to aryl electrophiles. Although the transition metal-catalyzed carbonylation of aryl halides has been the subject of intensive research due to its industrial significance. The carbonylation of alkyl halides is far less developed. The conversion of an alkyl halide to a homologated carbonyl compound, however, is of great utility in the synthesis of natural products and pharmaceuticals. Present methods for this homologation rely on the transformation of an alkyl halide to an organometallic compound such as a Grignard reagent or organolithium, followed by quenching with carbon dioxide and subsequent interconversion of the resulting carboxylic acid in a separate step. Alternatively, the alkyl halide may undergo $S_N2$ reaction with cyanide to give the homologated nitrile followed by hydrolysis to the carboxylic acid, a method which, potentially offers much great functional group tolerance of electrophilic functional groups. Furthermore if the reaction is
performed in the presence of a suitable nucleophile such as an amine or alcohol the amide or ester may be accessed in a single synthetic operation.

The carbonylation of an alkyl halide was first reported by Chiusoli using a nickel catalyst (Scheme 13). The nickel catalyst can perform a carbonylation reaction of an allyl chloride in presence of an alcohol to produce a $\beta$-$\gamma$ unsaturated ester.

$$\text{Ni(CO)}_4 \quad \text{R}_1^\text{Cl} \quad \text{R}_2^\text{OH} \quad \text{CO} \quad \text{R}_2^\text{\textbf{R}} \quad \text{R}_1^\text{\textbf{R}}$$

$R_1 = \text{Alkyl},$

$R_2 = \text{Et, n-Bu}$

**Scheme 13:** Nickel-catalyzed carbonylation of allyl chlorides

The reaction is believed to proceed via a radical mechanism. The reaction is run at room temperature under one atmosphere of carbon monoxide with substoichiometric amounts of nickel carbonyl.

Carboxyalkylation by cobalt was subsequently reported by Heck and Breslow (Scheme 14). By using a cobalt carbonylate ion in the presence of either sodium methoxide or dicyclohexylethyl amine as base a variety of alkyl halides can be carbonylated. The reaction can occur over a range of temperatures from 0 °C for methyl iodide and 100 °C for more difficult substrates such as chlorooctane.
The reaction requires a high pressure of carbon monoxide (70 atm) and substoichiometric to stoichiometric amounts of the cobalt catalyst.

\[
\begin{align*}
R^1-X & \quad R^2-OH & \quad \text{0.2 - 1 equiv } & \text{NaCo(CO)}_4 & \quad \text{N(Et)Cy}_2 \text{ or NaOMe} \quad 70 \text{ atm CO} \quad 0-100 \ ^\circ\text{C} \\
& & & & \quad R^1 = \text{Benzyl, Allyl, Alkyl} \\
& & & & \quad R^2 = \text{Me, Et}
\end{align*}
\]

**Scheme 14:** Breslow’s method for carboxylation

Primary and secondary alkyl halides as well as benzylic and allylic halides and α-halo acetates could be carbonylated giving the corresponding methyl and ethyl esters in poor to good yields. The first example of an amino carboxylation of an alkyl halide was also reported (Table 1).
The carbonylation of alkyl halides came more into focus in the 1980s and 1990 when several methods for this transformation were developed using a variety of transition metal catalysts.

Table 1: Substrate scope of Breslow’s method
In the mid-1980s Alper and coworkers investigated carbonylation reactions of a range of substrates using several different catalysts.\textsuperscript{39-42} In the course of this work a catalyst for the carbonylation of alkyl halides was found. The system described by Alper employs a bimetallic catalyst composed of palladium and rhodium (Scheme 15). The source of the nucleophile are either titanium or zirconium alkoxides as well as borates. The reaction proceeds under one atmosphere of carbon monoxide at 75 or 150 °C. This method gives moderate yields for alkyl bromides, but is most efficient for aromatic halides.

\[
\text{Me}_5\text{C}^+\text{Br} \quad \text{B(On-Bu)}_3 \quad \begin{array}{c} 5.5\% \text{Pd(PPh}_3)_4 \\ 8.5\% \text{[Rh(HD)Cl]}_2 \end{array} \quad 1 \text{ atm CO} \\ 150 \, ^\circ\text{C, 12h} \quad \text{Me}_5\text{C}^+\text{On-Bu} \quad 57\% 
\]

\textbf{Scheme 15:} Combined palladium-rhodium catalyst for carbonylation of alkyl bromides

The Urata group also examined the carbonylation of carbon electrophiles.\textsuperscript{43-48} Although most of the studies were focused on aryl iodides and benzylic halides, some alkyl iodides and perfluoroalkyl iodides were also used as substrates. Urata mainly exploited a cobalt or palladium catalyst to perform the transformation, although other metals were also examined. The reaction occurs at 100 °C under 30 - 50 atmospheres of carbon monoxide.

Initially only perfluorinated alkyl iodides were examined for this transformation,\textsuperscript{45-47} these are much easier substrates due to the reduced potential to undergo \(\beta\)-hydride elimination. Although the desired acids and esters can be synthesized from the starting iodides in modest yields several side products are also formed in significant amounts. The base used for the alkoxy carbonylation is triethylamine and the catalyst loading is relatively high at 20 mol\% of cobalt (Scheme 16).
Scheme 16: Cobalt-catalyzed carboxylation of perfluoro alkyl iodides

The palladium system yields less of the isomerized product, but also requires high pressure and temperature to give good yields (Scheme 17). Double carboxylation is observed as a side product, and seems to be base dependent for this catalytic system, potassium fluoride giving the best results for the carboxylation reaction. For the alkoxy carboxylation triethylamine remains the base of choice.

Scheme 17: Palladium-catalyzed carboxylation of perfluoro alkyl iodides

Subsequently, Urata studied the carboxylation reaction of non-perfluorinated alkyl iodides. The procedure could be successfully employed for primary alkyl iodides using a cobalt catalyst. For secondary iodides the palladium catalyst gave the best results. Instead of using an inorganic or amine base, molecular sieves are used in this system.43-44
The reaction conditions remain harsh, requiring high temperature and pressure of carbon monoxide (Scheme 18). For the palladium system only 2 mol% catalyst is required, for the cobalt system 20 mol% is used.

Scheme 18: Palladium- and cobalt-catalyzed carbonylation of non-activated alkyl iodides

These authors later showed that by using tetraalkyl urea solvents the reactions could be performed in slightly higher yields and without the need for added base (Scheme 19).43,48 It also proved possible to perform the carbonylation of alkyl sulfonates under these conditions by carrying out an in situ Finkelstein reaction (Scheme 20).43
Scheme 19: Palladium- and cobalt-catalyzed carbonylation of non-activated alkyl iodides in tetramethyl ureas as solvents replacing the base

Scheme 20: Carbonylation of alkyl tosylates and mesylates via in situ Finkelstein reaction

Watanabe undertook several studies of carbonylation with platinum catalysts (Scheme 21), and a range of other metal carbonyls. Platinum catalysts were competent to convert alkyl iodides to the homologated esters under high pressures and temperatures. The reaction is run in 1,4-dioxane and the base of choice is potassium carbonate.
The same reaction could be also performed at room temperature and atmospheric carbon monoxide pressure under UV-irradiation (Scheme 22).\textsuperscript{51} The reactions are run in THF, potassium carbonate is the optimal base.

Although the main focus of Watanabe’s work was platinum-catalyzed carbonylation, various transition other metal complexes were also examined for this transformation (Table 2).\textsuperscript{51-52}
These authors performed thermal, photochemical and electrochemical investigations of the mechanism of the carbonylation reaction using manganese carbonyl. For the thermal variant they discovered that by using sodium tetracarbonyl manganate, alkyl iodides could be carbonylated at room temperature under only one atmosphere of carbon monoxide. Cyclohexyl iodide gave the best yields, consistent with other methods. The manganate catalyst is made from the manganese carbonyl dimer by reaction with sodium amalgam (Scheme 23).
Scheme 23: Watanabe’s studies on manganese-catalyzed carbonylation of alkyl iodides

The rationale behind using the manganate anion comes from the belief that in photochemical and electrochemical carbonylation reactions this species is formed from the manganese carbonyl dimer in situ, generating the active catalyst (Scheme 24). Several pentacarbonyl manganates were investigated and showed better activity than their neutral analogues.

Scheme 24: Watanabe’s theory on generation of active catalyst for carbonylation reaction

[35]
The reaction is thought to proceed via a radical mechanism based on ESR studies of the catalytic system (Scheme 25). The fact that no alkyl dimers are formed suggests the intervention of a tight radical pair. Further evidence for a radical process comes from the observation that the carbonylation reaction is inhibited by the addition of radical scavengers.

Scheme 25: Proposed catalytic cycle for pentacarbonyl manganate-catalyzed carbonylation reaction

A few alternative methods have also been published, for example Dragojlovic and coworkers have reported a cobalt-catalyzed methoxycarbonylation of bromoalkanes in the presence of Lewis acids (Scheme 26). Secondary and tertiary iodides and bromides can be
converted to the corresponding methyl esters in good yields. Aryl bromides are also viable substrates.

![Chemical structures and yields](image-url)

**Conditions:**
- 30-50% Co(acac)$_2$
- 1-2 equiv InCl$_3$
- MeOH:Acetone 1:3
- 1 atm CO, 18-48 h
- 5.5 W low pressure Hg-lamp

**Scheme 26:** Cobalt-catalyzed carbylation of alkyl bromides under UV-irradiation in the presence of a Lewis acid

A molybdenum-based system has been reported by Rolando and coworkers (Scheme 27). By using stoichiometric molybdenum carbonyl both as a catalyst and as the source of carbon monoxide primary iodides can be converted into the dimerized esters, while diiodides lactonize under the aqueous reaction conditions. One of the alkyl iodides is apparently selectively hydrolyzed while the other is carbonylated. The reaction is conducted at reflux in THF for 20 h, with a fluoride source being essential to activate the system. The transformation can also be run with catalytic amounts of metal by using one atmosphere
pressure of carbon monoxide. Yields are higher when molybdenum is used
stoichiometrically.

![Scheme 27](Image)

**Scheme 27:** Molybdenum-promoted carbonylation of alkyl iodides with fluoride activation

The photochemical carbonylation of iodides can also be achieved in the absence of a metal. The reaction presumably proceeds directly through the alkyl radical species. The method is almost exclusively applicable towards secondary iodides and a variety of alcohol nucleophiles can be used. For the reaction to proceed, carbon monoxide pressures of between 20 and 55 atmospheres and UV irradiation from a xenon lamp are required (Scheme 28).

![Scheme 28](Image)

**Scheme 28:** Photochemical carbonylation of alkyl iodides
A palladium-catalyzed oxidative carbonylation of indium reagents has been recently reported (Table 3). Primary and secondary alkyl indium species as well as aryl indium reagents can be carbonylated in the presence of a palladium SynPhos catalyst and a stoichiometric oxidant. The reaction is run at 60 °C and 50 psi carbon monoxide. The functional group tolerance is excellent and the yields are high. The drawback of this method, however, are the sensitive reagents which must be used in the glovebox.

\[
R_3\text{In} + \text{3-5\% PdCl}_2(\text{CH}_3\text{CN})_2 + 4\% \text{Synphos} + 0.83 \text{ equiv Desyl Chloride} \rightarrow \text{ROn-Bu}
\]

\[
\begin{array}{c}
60^\circ\text{C in n-BuOH} \\
50\text{ psi CO, 24-36 h}
\end{array}
\]

<table>
<thead>
<tr>
<th>Alkyl Indium Reagent</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{ClC}<em>{2}H</em>{4})_3\text{In})</td>
<td>((\text{ClC}<em>{2}H</em>{4})_3\text{On-Bu})</td>
<td>66%</td>
</tr>
<tr>
<td>((\text{C}<em>{6}H</em>{5})_3\text{In})</td>
<td>((\text{C}<em>{6}H</em>{5})_3\text{On-Bu})</td>
<td>90%</td>
</tr>
<tr>
<td>((\text{MeO}<em>{2}C</em>{2}H_{4})_3\text{In})</td>
<td>((\text{MeO}<em>{2}C</em>{2}H_{4})_3\text{On-Bu})</td>
<td>83%</td>
</tr>
</tbody>
</table>

**Table 3:** Oxidative carbonylation reaction of alkyl indium reagents
Despite the attention that the carbonylation of alkyl halides has received over the previous 40 years, none of these methods has received widespread use in synthetic chemistry. This is because all of these methods have poor functional group tolerance or require the use of specialized high-pressure equipment. The goal of this project was to develop a transition metal catalyst capable of bringing about the carbonylation of alkyl halides using a cheap, readily handled catalyst in standard laboratory glassware and in the presence of a range of functional groups, allowing application in complex molecule synthesis.
B. Results and Discussion

During initial screening the catalytic activity of a number of transition metal complexes was examined (Figure 7). Several manganese complexes gave promising results, manganese carbonyl dimer being superior to the other complexes examined.

Manganese Carbonyl Dimer  Cyclopentadienyl Mangenese  Tricarbonyl  MMT  Potassium Pentacarbonyl Manganate

\[ \text{Mn} \left( \text{HCO}_2 \right)_2 \quad \text{Mn} \left( \text{OAc} \right)_2 \quad \text{MnCl}_2 \quad \text{MnI}_2 \]

**Figure 7:** Manganese complexes and salts examined for carbonylation reaction

Iododecane was chosen as a model substrate to optimize and investigate the reactivity of manganese carbonyl dimer. It was found that the conversion to the homologated ethyl ester of iododecane with ethanol can be carried out at room temperature under only 20-40 psi of carbon monoxide pressure (Scheme 29).

**Scheme 29:** Model system for the investigation of manganese-catalyzed carbonylation reaction
After examining several bases, potassium carbonate and potassium bicarbonate were found to be optimal for the transformation. The bases do not have to be stored in a rigorously dry environment (desiccator or glove box).

![Chemical reaction diagram]

Table 4: Base screen for manganese-catalyzed carbonylation reaction

The use of excess base slightly lowered the yield. The best conditions were found to be one equivalent of potassium bicarbonate or half an equivalent of potassium carbonate (Table 4). Various solvents were screened for the reaction, cyclohexane giving both high yields and low amounts of reduction of the alkyl electrophile (Table 5).
**Table 5**: Solvent screen for manganese-catalyzed carbonylation reaction

A catalyst loading of 3 mol% manganese carbonyl dimer was found to be optimal (Table 6).

[43]
Higher temperatures were found to increase the rate of the reaction, but also to increase the amount of dehalogenated product formed. Reduction of the iodoalkane to the alkane is the main side product of the reaction, which presumably comes about through radical abstraction of a hydrogen atom from the solvent. As a very minor side product, <1%, of the branched ester was detected by GC-MS.
The optimized conditions for the reaction were found to be a catalyst loading of 3 mol% of the manganese dimer in cyclohexane under 40 psi of carbon monoxide, with one equivalent of potassium bicarbonate (Scheme 30). Five equivalents of the nucleophile ethanol were present, although when using more valuable nucleophiles this number could be lowered to between 1.2 and 1.5 equivalents with little reduction in yield.

\[
\text{Me}\begin{array}{c}
\text{OEt}\
\text{5 equiv}
\end{array}
\xrightarrow{3\%\text{ M}_{2}(\text{CO})_{10}}\text{Me}\begin{array}{c}
\text{OEt}\
96\% \text{GC-Yield}
\end{array}
\]

**Scheme 30:** Optimized system for manganese-catalyzed carbonylation reaction

It was found that the reaction had to be constantly exposed to ambient light in order to proceed (Scheme 31). Using light of higher intensity or shorter wavelengths (UV) had no effect on rate or yield of the reaction.

\[
\text{Me}\begin{array}{c}
\text{OEt}
\end{array}
\xrightarrow{\text{Isolation from any Light}}\text{Me}\begin{array}{c}
\text{I}\
\text{7}
\end{array}
\]

**Scheme 31:** Effects of light on manganese-catalyzed carbonylation reaction

Trace Yield
2% Conversion

\[
\text{Me}\begin{array}{c}
\text{OEt}
\end{array}
\xrightarrow{\text{Ambient Light}}\text{Me}\begin{array}{c}
\text{OEt}
\end{array}
\]

96% GC-Yield
100% Conversion
Having mild conditions in hand, the scope of the reaction with a range of electrophiles and nucleophiles was explored. It was found that primary, secondary or tertiary alkyl iodides were viable substrates, reacting with a wide variety of alcohols as the nucleophilic component. Several functional groups were tolerated in the transformation including, alkyl bromides and chlorides, aryl chlorides, bromides and iodides as well as nitriles and carbonyl groups (Table 7).

\[
\begin{array}{ccc}
\text{R}^1\text{I} & \text{R}^2\text{OH} & 3\% \text{Mn}_2(\text{CO})_{10} \\
1 \text{ equiv} & 1.2 \text{ equiv} & \text{R}^1\text{OR}^2 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Alkyl Iodide</th>
<th>Alcohol Nucleophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Ir})</td>
<td>(\text{Ph-Br})</td>
<td>(\text{O-Ph-Br})</td>
<td>64%</td>
</tr>
<tr>
<td>(\text{Ir})</td>
<td>(\text{Ph-I})</td>
<td>(\text{O-Ph-I})</td>
<td>63%</td>
</tr>
<tr>
<td>(\text{Ir})</td>
<td>(\text{CYCLO-CH})</td>
<td>(\text{O-CYCLO-CH})</td>
<td>67%</td>
</tr>
<tr>
<td>(\text{Ir})</td>
<td>(\text{Ph-OCH})</td>
<td>(\text{O-Ph-OCH})</td>
<td>68%</td>
</tr>
</tbody>
</table>
\[
\begin{align*}
\text{R}^1\text{I} & \quad \text{R}^2\text{OH} & \quad 3\% \text{Mn}_2(\text{CO})_{10} & \quad \text{Product} \\
1 \text{ equiv} & \quad 1.2 \text{ equiv} & \quad 40 \text{ psi CO} & \quad 0.5 \text{ equiv K}_2\text{CO}_3 \\
& & \quad \text{Cyclohexane} & \quad \text{r.t., 12-24 h}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Alkyl Iodide</th>
<th>Alcohol Nucleophile</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{C}<em>6\text{H}</em>{11}\text{I})</td>
<td>(\text{HO}\text{-}\text{O}\text{-}\text{C}<em>6\text{H}</em>{11})</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{-O}\text{-C}<em>6\text{H}</em>{11})</td>
<td>86%</td>
</tr>
<tr>
<td>(\text{C}<em>6\text{H}</em>{11}\text{I})</td>
<td>(\text{HO}\text{-}\text{C}<em>6\text{H}</em>{11}\text{-I})</td>
<td>(\text{C}<em>6\text{H}</em>{11}\text{-O}\text{-C}<em>6\text{H}</em>{11}\text{-I})</td>
<td>83%</td>
</tr>
<tr>
<td>(\text{C}<em>5\text{H}</em>{11}\text{I})</td>
<td>(\text{HO}\text{-}\text{O}\text{-}\text{C}<em>6\text{H}</em>{11})</td>
<td>(\text{C}<em>5\text{H}</em>{11}\text{-O}\text{-C}<em>6\text{H}</em>{11})</td>
<td>85%</td>
</tr>
<tr>
<td>(\text{C}<em>5\text{H}</em>{11}\text{I})</td>
<td>(\text{HO}\text{-}\text{N}\text{-}\text{C}<em>6\text{H}</em>{11})</td>
<td>(\text{C}<em>5\text{H}</em>{11}\text{-O}\text{-C}<em>6\text{H}</em>{11}\text{-N}\text{-C}<em>6\text{H}</em>{11})</td>
<td>83%</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_5\text{I})</td>
<td>(\text{HO}\text{-}\text{O}\text{-}\text{C}<em>6\text{H}</em>{11})</td>
<td>(\text{C}_2\text{H}_5\text{-O}\text{-C}<em>6\text{H}</em>{11})</td>
<td>62%</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_5\text{I})</td>
<td>(\text{HO}\text{-}\text{O}\text{-}\text{Cl})</td>
<td>(\text{C}_2\text{H}_5\text{-O}\text{-C}_2\text{H}_5\text{-Cl})</td>
<td>73%</td>
</tr>
</tbody>
</table>

**Table 7:** Esters generated by manganese-catalyzed carbonylation reaction
No product resulting from the carbonylation of aryl iodides was observed, the reaction was completely chemoselective. Tertiary iodides gave lower yields, presumably due to facile elimination of HI to generate the alkene under basic conditions. Substrates bearing heterocyclic rings containing nitrogen or sulfur require elevated temperatures. Neopentyl iodide was a very difficult case, requiring prolonged reaction times to reach full conversion.

For the synthesis of methyl and ethyl esters, the alcohol was used as solvent, giving very high yields of the corresponding esters (Table 8).
Table 8: Methyl- and ethyl esters generated using manganese-catalyzed carbonylation reaction in alcoholic solvents
Heterocyclic substrates were more difficult and required heating in order for reaction to occur. Diiodides could be converted to the diester in good yields. Adamantyl iodide was an easier case, probably because no elimination of HI can take place, in contrast to tert-butyl iodide. Reaction in ethanol was quite fast, the alkyl iodide was fully converted in less than eight hours at room temperature. Using alcohols as solvents also had advantages for the solubility of some compounds.

In addition to alcohols, the use of amines as nucleophiles was also examined, and found to be successful for the synthesis of primary and secondary amides. Although a temperature of 70 °C was required to achieve high yields, a variety of amines bearing either alkyl or aryl substituents could be employed (Table 9).
R¹-I
1 equiv
H-N(R²)R³
3% Mn₂(CO)₁₀
40 psi CO
2 equiv K₂CO₃
70 °C, 24 h

<table>
<thead>
<tr>
<th>Akyl Iodide</th>
<th>Amine</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₇I</td>
<td>H-N(n-Bu)₂</td>
<td>Me₇N(n-Bu)₂</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>H-N-Me</td>
<td>H-N-Me</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>H₂N-Me₆</td>
<td>H₂N-Me₆</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>H-N-Cl</td>
<td>H-N-Cl</td>
<td>93%</td>
</tr>
<tr>
<td>Me₇I</td>
<td>H₂N-Cl₂</td>
<td>Me₇N-Cl₂</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>H₂N-CN</td>
<td>H₂N-CN</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>H-N(n-Bu)₂</td>
<td>H-N(n-Bu)₂</td>
<td>74%</td>
</tr>
</tbody>
</table>

Table 9: Amides generated by manganese-catalyzed carbonylation reaction
The carbonylation reaction was significantly faster than the $S_N2$ reaction of the amine with the iodide, thus the amide was formed almost exclusively. The $S_N2$ reaction was only found to be a significant issue when primary iodides were reacted with primary amines. Although some of the amines were visibly insoluble in cyclohexane, the reaction still proceeded within 24 hours in excellent yield.

A number of more exotic nucleophiles were also examined. Thiols gave reasonable yields of the homologated thioesters, although higher temperatures were required (Scheme 32).

![Scheme 32: Generation of thioesters by manganese-catalyzed carbonylation reaction](image)

Preliminary results showed that free amino acids could be used as nucleophiles. An excess of base was required to deprotonate the free acid. The reaction proceeded in cyclohexane at elevated temperatures (Scheme 33).

![Scheme 32: Generation of thioesters by manganese-catalyzed carbonylation reaction](image)
**Scheme 33**: Amino Acids as Nucleophiles for Manganese-Catalyzed Carbonylation Reaction

This process has not been fully explored, the results are based on mass spectrometry data, however, conversion of the amino acid was good. An excess of cyclohexyl iodide was used since the amino acid is of greater value.

Azide was also examined as a potential nucleophile for the reaction. By using sodium azide at temperatures of 70 °C the intermediate acyl azide underwent Hofmann rearrangement to form the isocyanate. This isocyanate could then be reacted with another nucleophile such as an alcohol to give the corresponding carbamate (Scheme 34).

**Scheme 34**: Azides as nucleophiles for manganese-catalyzed carbonylation reaction to yield carbamates
Preliminary results show that aldehydes could be accessed by adding a hydride source to the reaction mixture. Silanes proved to give some reactivity in this transformation, the best was found to be polymethylhydrosiloxane (PMHS) (Scheme 35).

Scheme 35: Generation of aldehydes via manganese-catalyzed carbonylation reaction

It was found that bromides cannot be directly carbonylated using the manganese catalyst. To circumvent this problem an *in situ* Finkelstein-reaction was considered. This method does not only open the possibility of using bromides and chlorides, but could also be applied to sulfonate leaving groups such as mesylates or tosylates. Interestingly, the Finkelstein reaction took place in ethanol or methanol under the catalytic conditions (Scheme 36). A temperature of 70 °C was required for the initial Finkelstein reaction to occur. Under these conditions the manganese-catalyzed carbonylation was faster than the Finkelstein reaction thus no alkyl iodide was observed when the reaction is quenched at 50% conversion.

Scheme 36: Carbonylation reaction of alkyl bromides via *in situ* Finkelstein reaction
The yield of the ester was, however, slightly lower than from the direct carbonylation of iodides, probably because at the higher temperatures employed, more of the reduction side product is being produced. The iodide was regenerated after the carbonylation reaction and could be used catalytically (Table 10).

Preliminary results show that mesylates also undergo Finkelstein reaction under these conditions in ethanol, subsequent carbonylation provided the corresponding ester.

![Chemical reaction diagram]

**Table 10:** Screen of iodide sources and loadings for manganese-catalyzed carbonylation reaction in combination with *in situ* Finkelstein reaction
It was found that the in situ Finkelstein reaction of secondary bromides or primary chlorides required even higher temperatures, further reducing the yield of the ester. However, by forming the alkyl iodide prior to the carbonylation in a one flask, two step process using one equivalent of sodium iodide, reduction of the alkyl halide could be minimized. The Finkelstein was carried out in acetone with the starting bromide, sodium iodide and potassium carbonate all present in the reaction mixture. The reaction was then heated to 70 °C for 12 hours, after which the acetone was removed on the Schlenk line, since it is not a suitable solvent for the carbonylation reaction. Manganese catalyst as a solution in ethanol was then added to the reaction, and after application of the standard conditions for carbonylation the final product was isolated in high yield (Scheme 37).

![Scheme 37: Two step one pot carbonylation reaction of alkyl bromides](image)

This two step process also allowed for the use of different nucleophiles which could be added in cyclohexane solution, as opposed to the one step method which only provided methyl- and ethyl esters.

The mechanism of this reaction has not been explored; Watanabe and coworkers have proposed a radical mechanism for the pentacarbonyl manganate anion-catalyzed reaction. It is likely that the manganese carbonyl dimer-catalyzed carbonylation also proceeds via a radical mechanism. Light is known to dissociate the manganese carbonyl dimer; or to
labialize carbon monoxide ligands. Studies on methyl manganese pentacarbonyl reveal that carbon monoxide is inserted via an alkyl migration. Consistent with previous data a catalytic cycle can be proposed (Scheme 38).

**Scheme 38**: Proposed catalytic cycle
C. Conclusions

A general protocol for the carbonylation of alkyl iodides has been developed. The method may also be applied to alkyl bromides, chlorides or mesylates by generating the iodide \textit{in situ} via a Finkelstein reaction. Esters, amides, thioesters, aldehydes and carbamates could be accessed through this transformation. The reaction conditions are very mild, with reactions proceeding at room temperature for most substrates, and using a relatively low carbon monoxide pressure of only 40 psi, which does not require specialized high-pressure equipment. For methyl and ethyl esters the alcohol itself can serve as the solvent, whilst other substrates are run in environmentally friendly cyclohexane. Although the catalyst is not sensitive to moisture, air tends to oxidize the complex over the course of several weeks. In particular the solvents have to be degassed due to the higher sensitivity of the catalyst towards oxygen in solution. Overall, both the functional group tolerance and substrate scope of the method is excellent, with primary, secondary or tertiary alkyl halides producing good yields in the transformation.

The method is synthetically valuable to due to its ability to convert alkyl iodides into a variety of the corresponding homologated carbonyl compounds under very mild conditions.
D. Experimental

General Considerations:

All reactions were carried out in oven-dried glassware using standard Schlenk techniques. All commercial iodides were filtered through a plug of alumina prior to use. The solvents, cyclohexane, ethanol and methanol were degassed prior to use. Degassing consisted of freezing the solvent in liquid nitrogen under vacuum, then thawing the solution while keeping the vessel closed. This process was repeated once. Liquid reagents were degassed the same way. Manganese carbonyl was purchased from Strem Chemical and stored in the glove box. Flash chromatography was performed using the Biotage SP4 system. $^1$H NMR spectra were recorded on a Bruker DRX 400 spectrometer in deuterochloroform operating at 400 MHz. $^{13}$C NMR spectra were recorded on a Bruker DRX 400 spectrometer operating at 100 MHz. Chemical shifts are quoted relative to residual solvent (7.26 ppm for CHCl$_3$) and coupling constant are given in Hz to the nearest 0.5 Hz. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s singlet, d doublet, t triplet, q quartet, m multiplet or br broad. NMR spectra were acquired at 300 K. Infrared spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer as thin films on KBr plates. Selected absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$). GC analysis were performed on an Agilent 6890 equipped with an FID detector and a Hewlett Packard 10 m · 0.2 mm HP-1 capillary column using tetradecane as an internal standard.
General procedure C for the carbonylation reaction of alkyl iodides:

Into an oven-dried Schlenk flask with Teflon screw cap was added the manganese carbonyl dimer (3mol%), potassium carbonate (1 equiv) and the alkyl iodide (1 equiv) or nucleophile (1.2 equiv) if solid. The flask was then sealed, evacuated and charged with argon three times. Cyclohexane (0.13 M), methanol or ethanol was added via syringe followed by alkyl iodides (1 equiv) or nucleophiles (1.2 equiv). The vessel was then charged with carbon monoxide (40 psi) through a three way stop cock. The vessel was pressurized and released into the argon line three times before the final charge. The reaction vessel was then stirred at the specified temperature until full conversion was achieved as determined by GC analysis. After the reaction was completed, the reaction was allowed to cool to room temperature and the pressure carefully released. The reaction mixture was then poured into brine and extracted with ethyl acetate (3 times). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was dissolved in methylene chloride and purified via flash chromatography on silica gel using the Biotage SP4.

Procedure for carbonylation combined with in situ Finkelstein

Into an oven dried Schlenk flask with Teflon screw cap were added the reagents according to general procedure C. In addition sodium iodide (0.5 equiv) was added to the reaction mixture. The vessel was then sealed and heated to 70 °C until full conversion was achieved as determined by GC. The product was worked up and purified according to general procedure C.
Procedure for one pot two step Finkelstein followed by carbonylation:

Into an oven dried Schlenk flask with Teflon screw cap were added the alkyl electrophile (alkyl chloride, alkyl bromide or alkyl mesylate, 1 equiv), sodium iodide (1.05 equiv) and potassium carbonate (1 equiv). Acetone (0.2 M) was added and the reaction mixture was stirred until full conversion was achieved. The solvent was then removed on the Schlenk line and the vessel was evacuated and purged with argon three times. A solution of the manganese carbonyl (3 mol%) in degassed methanol or ethanol (0.2 M) was added. The vessel was then charged with carbon monoxide according to general procedure C and the reaction was then stirred at room temperature for 12 h. The workup and isolation of the final product was performed according to general procedure C.

Procedure for converting alcohols into iodides:

The alkyl alcohol (primary or secondary, 1 equiv) was dissolved in anhydrous methylene chloride (0.1 M), then triphenylphosphine (1.2 equiv) and imidazole (2 equiv) were added to the solution. The reaction was then cooled to 0 °C and iodine (3 equiv) was added slowly. The cold bath was removed and the reaction mixture was stirred for 1 h. After this period of time n-propanol (20 equiv) was added and stirring continued for 30 min. The excess iodine was then slowly quenched with saturated sodium thiosulfate solution. The reaction mixture was poured into brine and extracted with ethyl acetate (3 times). The combined organic layers were dried over magnesium sulfate, and filtered through alumina and concentrated in vacuo. Pentane was added and the resulting suspension filtered through
alumina, then concentrated and purified via flash chromatography on the Biotage SP4 system using a gradient of ethyl acetate in hexanes.

**Individual Procedures:**

**N-(3-cyanophenyl)cyclohexanecarboxamide:**

General Procedure C was employed using cyclohexyl iodide (2 mmol, 260 μL), 3-aminobenzenitrile (2.6 mmol, 307 mg) and potassium carbonate (4 mmol, 552 mg) with following exceptions: The reaction was heated to 70 °C in cyclohexane (15 mL) for 24 h, in addition to the work up reported in general procedure C the organic phase was washed in 1 M HCl. After Concentration of the combined organic layers the crude was taken up into methylene chloride and purified via flash chromatography using ethyl acetate in hexanes as an eluent to yield 411.0 mg (90%) of the desired amide. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.95 (s, 1H), 7.71 (d, 7.3 Hz, 1 H), 7.39 (m, 2H), 2.25 (m, 1 H), 1.97-1.29 (m, 10 H) $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 175.6, 139.3, 129.8, 127.4, 124.2, 123.1, 112.5, 46.3, 29.6, 25.6, 25.5; $\nu_{max}$ (film) / cm$^{-1}$ 3447, 1664

**N-(4-chlorophenyl)-N-methylcyclopentanecarboxamide:**

General Procedure C was employed using cyclopentyl iodide (2 mmol, 231 μL), 3-aminobenzenitrile (4 mmol, 660 μL) and potassium carbonate (4 mmol, 552 mg) with following exceptions: The reaction was heated to 70 °C in cyclohexane (15 mL) for 24 h, In addition to the work up reported in general procedure C the organic phase was washed in 1
M HCl. After concentration of the combined organic layers the crude was taken up in methylene chloride and purified via flash chromatography using ethyl acetate in hexanes as an eluent to yield 441.0 mg (93%) of the desired amide. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.24 (m, 2 H), 7.02 (m, 2 H), 3.96 (m, 1 H), 3.08 (m, 3 H), 2.38 (m, 1 H), 1.91 (m, 2 H), 1.63-1.09 (m, 10 H), $^{13}$C NMR (130 MHz, CDCl$_3$) $\delta$: 176.8, 142.8, 133.4, 129.9, 128.9, 41.9, 37.6, 31.1, 26.2; $\nu_{max}$ (film) / cm$^{-1}$ 2955, 1655, 1490, 1092, 1014, 840

3-iodobenzyl cyclohexanecarboxylate:

General Procedure C was employed using cyclohexyl iodide (2 mmol, 260 $\mu$L), (3-iodophenyl)methanol (2.6 mmol, 340 $\mu$L) and potassium bicarbonate (2.6 mmol, 260 mg), the reaction was run at room temperature in cyclohexane (15 mL) for 24 h, giving the desired ester in 83% Yield (571 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.65 (m, 2 H), 7.27 (m, 1 H), 7.04 (m, 1 H), 4.99 (s, 2 H), 2.32 (m, 1 H), 2.00-1.22 (m, 10 H), $^{13}$C NMR (130 MHz, CDCl$_3$) $\delta$: 175.5, 138.6, 137.1, 136.8, 130.3, 127.1, 94.4, 64.8, 43.1, 29.0, 25.8, 25.5; $\nu_{max}$ (film) / cm$^{-1}$ 2932, 1732, 1567, 1164

ethyl adamantane-1-carboxylate:

General procedure C was employed using 1-adamantyl iodide (2 mmol, 525 mg) and potassium bicarbonate (2 mmol, 200 mg) in ethanol (15 mL). The reaction was run at room temperature for 12 h yielding the desired ester in 84% (349 mg). $^1$H NMR (400 MHz, CDCl$_3$)
δ: 4.00 (m, 2 H), 1.91 (m, 3 H), 1.78 (m, 6 H), 1.61 (m, 6 H), 1.14 (m, 3 H), 13C NMR (130 MHz, CDCl₃) δ: 177.6, 59.9, 40.5, 38.8, 36.5, 27.9, 14.2; νmax (film) / cm⁻¹ 2907, 1729, 1453, 1235, 1078

2-(pyridin-2-yl)ethyl cyclopentanecarboxylate:

General procedure C was employed using cyclopentyl iodide (2 mmol, 231 ηL), 3-(pyridin-2-yl)propan-1-ol (2.6 mmol, 347 ηL) and potassium carbonate (2.6 mmol, 552 mg), the reaction was run at 70 °C in cyclohexane (15 mL) for 24 h yielding the desired ester in 83% (363 mg). ¹H NMR (400 MHz, CDCl₃) δ: 8.37 (m, 1 H), 7.44 (m, 1 H), 7.00 (m 2 H), 4.29 (m, 2 H), 2.95 (m, 2 H), 2.51 (m, 1 H), 1.65-1.37 (m, 8 H), 13C NMR (130 MHz, CDCl₃) δ: 175.9, 157.5, 148.8, 135.7, 122.8, 120.9, 62.7, 43.1, 36.8, 29.3, 25.2; νmax (film) / cm⁻¹ 2959, 1730, 1592, 1437, 1182, 756

6-chlorohexyl 3,3-dimethylbutanoate:

General Procedure C was employed using neopentyl iodide (2 mmol, 265 ηL), 6-chlorohexan-1-ol (2.6 mmol, 347 ηL) potassium carbonate (2.6 mmol, 552 mg). The reaction was run at 70 °C in cyclohexane for 24 h, yielding the desired ester in 73% yield (341 mg). ¹H NMR (400 MHz, CDCl₃) δ: 4.00 (m, 2 H), 3.47 (m, 2 H), 2.13 (s, 2 H), 2.13-1.33 (m, 8 H), 0.97 (s, 9 H), 13C NMR (130 MHz, CDCl₃) δ: 171.8, 63.3, 47.5, 44.3, 31.9, 30.1, 29.1, 28.0, 25.9, 24.8; νmax (film) / cm⁻¹ 2956, 1732, 1466, 1229, 1131
N-hexylcyclohexanecarboxamide:

General procedure C was employed cyclohexyl iodide (2 mmol, 260 μL), octylamine (4 mmol, 660 μL) and potassium carbonate (4 mmol, 552 mg). The reaction was run at 70 °C in cyclohexane for 24 h yielding the desired amide in 92% (388 mg). In addition to the standard workup the product was washed with 1 M HCl. $^1$H NMR (400 MHz, CDCl$_3$) δ: 5.99 (m, 1 H), 3.16 (m, 2 H), 2.02 (m, 3 H), 1.76-1.21 (m, 23 H), 0.81 (m, 3 H). $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 176.1, 45.0, 38.9, 31.2, 29.1, 29.0, 28.7, 28.6, 26.3, 25.2, 22.1, 20.4, 13.5; $\nu_{\text{max}}$ (film) / cm$^{-1}$ 3300, 1950, 1630

N,N-dibutylundecanamide:

General procedure C was employed with following additions: the crude reaction mixture was washed with 1 M HCl. The reaction was setup using iodo decane (2 mmol, 427 μL), dibutylamine (4 mmol, 676 μL) and potassium carbonate (4 mmol, 552 mg). The reaction was run at 70 °C in cyclohexane for 24 h yielding the desired amide in 88% (522 mg). $^1$H NMR (400 MHz, CDCl$_3$) δ: 3.15 (m, 2 H), 3.07 (m, 2 H), 2.13 (m, 2 H), 1.38-1.13 (m, 24 H), 0.80 (m, 9 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 176.1, 45.0, 38.9, 31.2, 29.1, 29.0, 28.7, 28.6, 26.3, 25.2, 22.1, 20.4, 13.2, 13.0, 12.9; $\nu_{\text{max}}$ (film) / cm$^{-1}$ 2929, 1645, 1465

Methyl undecanoate:

General procedure C was employed using iododecane (2mmol, 427 μL), potassium bicarbonate (2mmol, 200 mg) in methanol (15 mL) as a solvent and nucleophile. The
reaction was stirred at room temperature for 8 hours to yield the desired ester in 87% (348 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.59 (s, 3 H), 2.23 (t, 2 H), 1.55 (m, 2 H), 1.20 (m, 15 H), 0.81 (m, 3 H), $^{13}$C NMR (130 MHz, CDCl$_3$) $\delta$: 173.6, 50.7, 33.5, 31.3, 29.0, 28.9, 28.8, 28.7, 28.6, 24.4, 22.1, 13.5; $\nu_{\text{max}}$ (film) / cm$^{-1}$ 3461, 2926, 1743, 1436, 1170

**Ethyl undecanoate:**

General procedure C was employed using iododecane (2mmol, 427 $\mu$L), potassium bicarbonate (2mmol, 200 mg) in methanol (15 mL) as a solvent and nucleophile. The reaction was stirred at room temperature for 8 hours to yield the desired ester in 93% (398 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 4.08 (q, 2 H), 2.23 (t, 2 H), 1.56 (m, 2 H), 1.21 (m, 17 H), 0.82 (m, 3 H), $^{13}$C NMR (130 MHz, CDCl$_3$) $\delta$: 173.6, 59.8, 34.1, 29.3, 29.2, 29.1, 29.0, 28.9, 24.8, 22.5, 14.0, 13.8; $\nu_{\text{max}}$ (film) / cm$^{-1}$ 2929, 1739, 1178

**N-(tert-butyl)undecanamide:**

General procedure C was employed using iododecane (2mmol, 427 $\mu$L), potassium carbonate (4 mmol, 552 mg) in cyclohexane (15 mL). The reaction was heated to 70 °C for 24 h, in addition to the general workup, the crude solution was also washed with 1 M HCl, to yield the desired amide in 84% (405 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.39 (m, 1 H), 1.98 (q, 2 H), 1.51 (m, 2 H), 1.26-1.17 (m, 22 H), 0.79 (t, 3 H), $^{13}$C NMR (130 MHz, CDCl$_3$) $\delta$: 172.4, 50.8, 37.5, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.6, 25.6, 22.5, 13.9; $\nu_{\text{max}}$ (film) / cm$^{-1}$ 3306, 2933, 1700, 1600, 1450, 1350
2-phenoxyethyl cyclohexanecarboxylate:

General procedure C was employed using iodocyclohexane (2 mmol, 260 μL), 2-phenoxyethanol (2.4 mmol, 299 μL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 86% (427 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.27 (m, 2 H), 6.90 (m, 3 H), 4.39 (m, 2 H), 4.13 (m, 2 H), 2.33 (m, 1 H), 1.88-1.24 (m, 10 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 175.9, 158.4, 129.4, 121.0, 114.5, 65.8, 62.4, 42.9, 28.9, 25.6, 25.3

2-phenoxyethyl cyclopentanecarboxylate:

General procedure C was employed using iodocyclopentane (2 mmol, 231 μL), 2-phenoxyethanol (2.4 mmol, 299 μL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 85% (398 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.27 (m, 2 H), 6.91 (m, 3 H), 4.40 (m, 2 H), 4.13 (m, 2 H), 2.75 (m, 1 H), 1.82 (m, 8 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 176.2, 158.0, 129.0, 120.6, 114.1, 65.4, 62.1, 43.2, 29.5, 25.3

2-phenoxyethyl pivalate:

General procedure C was employed using tert-butyl iodide (2 mmol, 238 μL), 2-phenoxyethanol (2.4 mmol, 299 μL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 68% (302 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.27 (m, 2 H), 6.91 (m, 3 H), 4.40 (m, 2 H), 4.14 (m, 2 H), 1.21 (s, 9 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 178.3, 158.1, 129.0, 120.6, 114.2, 65.4, 62.2, 38.3, 26.7
3-bromobenzyl pivalate:

![Structure of 3-bromobenzyl pivalate](image)

General procedure C was employed using tert-butyl iodide (2mmol, 238 μL), 2-(3-bromophenyl)methanol (2.6 mmol, 312 μL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 64% (364 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.44 (m, 2 H), 7.21 (m, 2 H), 5.02 (s, 2 H), 1.19 (s, 9 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 177.7, 138.3, 130.6, 130.1, 129.6, 125.7, 122.1, 64.6, 38.3, 26.7; $\nu_{\text{max}}$ (film) / cm$^{-1}$: 2973, 1732, 1572, 1479, 1144, 779, 669

Ethyl 3-(thiophen-2-yl)propanoate:

![Structure of Ethyl 3-(thiophen-2-yl)propanoate](image)

General procedure C was employed using 2-(2-iodoethyl)thiophene (2mmol, 476 mg), ethanol as solvent and nucleophile, and potassium carbonate (4 mmol, 552 mg) in cyclohexane (15 mL). The reaction was heated to 70 °C for 36 h to give the desired ester in 59% (217 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.21 (m, 1 H), 6.95 (m, 2 H), 4.11 (m, 1 H), 2.94 (m, 2 H), 2.59 (m, 2 H), 1.21 (m, 3 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 172.4, 140.4, 127.5, 125.1, 120.1, 60.0, 34.7, 25.0, 13.8

3-iodobenzyl pivalate:

![Structure of 3-iodobenzyl pivalate](image)

General procedure C was employed using tert-butyl iodide (2mmol, 238 μL), 2-(3-iodophenyl)methanol (2.6 mmol, 340 μL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 63% (401 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.64 (m, 2 H), 7.59 (m, 1 H), 7.26 (m, 1 H), 4.99 (s, 2 H), 1.19 (s, 9 H), $^{13}$C NMR
(130 MHz, CDCl₃) δ: 177.5, 138.3, 136.5, 136.0, 129.8, 126.3, 93.9, 64.4, 38.3, 26.7; ν_max (film) / cm⁻¹ 3439, 1642

N,N-dibutyl-3,3-dimethylbutanamide:

General procedure C was employed using neopentyl iodide (2 mmol, 265 µL), potassium carbonate (XX mmol, XX mg) and dibutylamine (4 mmol, 676 µL) in cyclohexane (15 mL). The reaction was heated to 70 °C for 24 h, in addition to the general workup, the crude solution was also washed with 1 M HCl, to yield the desired amide in XX% (XX mg) yield.

¹H NMR (400 MHz, CDCl₃) δ: 3.13 (m, 4 H), 2.06 (s, 2 H), 1.37 (m, 4 H), 1.17 (m, 4 H), 0.91 (s, 9 H), 0.79 (m, 6 H), ¹³C NMR (130 MHz, CDCl₃) δ: 171.1, 48.2, 45.4, 44.4, 31.2, 31.0, 29.8, 20.1, 19.8, 13.7, 13.6; ν_max (film) / cm⁻¹ 2957, 1641, 1466, 1364

Ethyl 7-chloroheptanoate:

General procedure C was employed using 1-chloro-6-iodohexane (2 mmol, 308 µL), ethanol as solvent and nucleophile and potassium carbonate (2.6 mmol, 360 mg). The reaction was heated to 70 °C for 24 h to give the desired ester in 81% (311 mg) yield. ¹H NMR (400 MHz, CDCl₃) δ: 4.03 (m, 2 H), 3.44 (m, 3 H), 3.11 (m, 1 H), 2.21 (m, 2 H), 1.69-1.16 (m, 14 H), ¹³C NMR (130 MHz, CDCl₃) δ: 173.4, 60.0, 44.8, 44.7, 44.0, 33.1, 32.2, 29.6, 28.2, 26.3, 25.6, 24.6, 14.1, 6.6

[69]
(tetrahydro-2H-pyran-2-yl)methyl pivalate:

General procedure C was employed using tert-butyl iodide (2mmol, 238 µL), (tetrahydro-2H-pyran-2-yl)methanol (2.6 mmol, 294 µL) and potassium carbonate (2.6 mmol, 360 mg) in cyclohexane (15 mL) to give the desired ester in 67% (268 mg) yield. $^1$H NMR (400 MHz, CDCl$_3$) δ: 3.93 (m, 4 H), 3.44 (m, 3 H), 1.78 (m, 2 H), 1.47 (m, 9 H), 1.11 (s, 9 H), $^{13}$C NMR (130 MHz, CDCl$_3$) δ: 177.9, 75.0, 67.8, 66.6, 38.2, 27.5, 26.6, 25.3, 22.4; $\nu$$_{max}$ (film) / cm$^{-1}$ 3360, 2940, 1732, 1481, 1285, 1167
Appendix A:

Analytical Data
Current Data Parameters
NAME  Ie-1-181
FWNO  1
FHLA BU  1

F2 - Acquisition Parameters
Date_  20200512
Time  11:41
INSTRUM  spect
PRCBRD  5 nm QNP 1H/13
PCL-PROC  70:0
MT  65536
SOLVENT  CE56
NS  7
NS  2
AH  8278.166 Hz
VIDRES  0.1264 Hz
AQ  3.958223 sec
FZ  60.400 usec
JN  6.00 usec
TE  30.0 Hz
DF  0.00 sec
TCC

-------- CHANNEL F1 --------
MUC1
PS  14.00 usec
M1  0.00 dB
SP01  600.1324710 MHz

F2 - Processing parameters
C1  65536
SP  400.130122 MHz
AXR  EM
SR  0
LB  0.10 Hz
BB  0
PC  1.00
Appendix B:

References


(2) The Use of Arynes in Organic Synthesis

(3) A Transition-Metal Complex of Benzyne

(4) Oxidative Addition-Reactions of Triphenylphosphine with Dodecacarbonyl-Triosmium(0) - Benzene-Complexes, Phenyl-Complexes and Related Complexes of Osmium

(5) Fluxional Behavior of Some Cluster Complexes of Osmium Containing C₆H₄ as Ligands

(6) Some Benzyne Complexes of Osmium Derived from Dimethylphenylphosphine or Dimethylphenylarsine

(7) Metal-Complexes of Small Cycloalkynes and Arynes

(8) Synthesis of Monomeric Niobium-Benzyne and Tantalum-Benzyne Complexes and the Molecular-Structure of Ta(η-5-C₅Me₅)(C₆H₄)Me₂

(9) Synthesis and Single-Crystal X-Ray Study of the Mononuclear η -2-Benzyne (Dehydrobenzene) Nickel(0) Complex Ni(η -2-C₆H₄)((C₆H₁₁)₂PCH₂CH₂P(C₆H₁₁))₂ - Insertion Reactions with Simple Molecules and X-Ray Crystal-Structure of the Nickelaindan Complex Ni(CH₂CH₂C₆H₂-O)((C₆H₁₁)₂PCH₂CH₂P(C₆H₁₁))₂

(10) The Trimethylphosphine Adduct of the Zirconocene Benzyne Complex - Synthesis, Reactions, and X-Ray Crystal-Structure
(11) Reaction of Intermediate Zirconocene - Aryne Complexes with C-H Bonds in Thermolysis of Diarylzirconocenes

(12) Thermal-Decomposition of Dicyclopentadienyltitanium(Iv) Diaryl and Dibenzyl Compounds

(13) Mechanistic Aspects of Thermal-Decomposition of Dicyclopentadienyltitanium(Iv)Diaryl Compounds


(15) Zirconocene(Iso-Butyl) Chloride – In situ Generation of a Zirconocene(Methyl) Chloride Equivalent for Use in Organic-Synthesis

(16) Sulphur Dioxide Insertion Reactions with Dicyclopentadienyltitanium and Dicyclopenta-Zirconium Alkyl and Aryl Compounds

(17) Group-4 Metal-Complexes of Benzynes, Cycloalkynes, Acyclic Alkynes, and Alkenes

(18) Synthesis and Structure of Zirconium Group-13 Heterobimetallic Compounds
Derege, F. M. G.; Davis, W. M.; Buchwald, S. L. *Organometallics* 1995, 14, 4799.

(19) Novel-Approach to Cross-Coupling Exemplified by Ni-Catalyzed Reaction of Alkenyl-Zirconium Derivatives with Aryl Halides

(20) A Combined Zirconocene Benzyne-Palladium Cross-Coupling Route to Substituted Biphenyls and Terphenyls

(21) Negishi Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides

(22) A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides

(23) Catalytic Asymmetric Vinylation of Ketone Enolates
A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds

Chiral Monodentate Phosphine Ligand Mop for Transition Metal-Catalyzed Asymmetric Reactions

Novel Electron-Rich Bulky Phosphine Ligands Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers

Expanding Pd-Catalyzed C-N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions

A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides

A Rationally Designed Universal Catalyst for Suzuki-Miyaura Coupling Processes

Intramolecular Heck Reactions of Unactivated Alkyl Halides

Room-Temperature Hiyama Cross-Couplings of Arylsilanes with Alkyl Bromides and Iodides

Room-Temperature Alkyl-Alkyl Suzuki Cross-Coupling of Alkyl Bromides That Possess Beta Hydrogens

Suzuki Cross-Couplings of Alkyl Tosylates That Possess Beta Hydrogen Atoms: Synthetic and Mechanistic Studies

Nickel-Catalyzed Cross-Couplings of Organosilicon Reagents with Unactivated Secondary Alkyl Bromides

Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides

(37) Reazioni dell’ossido di carbonio: La funzione dem nickelcarbonile in alcune nuove sintesi.

(38) Carboxyalkylation Reactions Catalyzed by Cobalt Carbylate Ion

(39) Rhodium(I) Catalyzed Carboxylation Reactions of Halides and Ethers

(40) Palladium(O) and Rhodium(I) Catalysis of the Carboxylation of Unactivated Bromides

(41) Synthesis of Esters by Rhodium(I) Catalyzed Borate Ester Benzylic Bromide Carboxylation Reactions

(42) Rhodium and Palladium Catalyzed Carboxylation Reactions with Titanium and Zirconium Alkoxides

(43) Carboxylation of Alkyl Sulfonates Catalyzed by Cobalt Complexes

(44) Transition-Metal Complex Catalyzed Carboxylation of Organic Halides in the Presence of Molecular-Sieves Instead of Base

(45) Palladium-Catalyzed Double Carboxylation of Alkyl Iodides Bearing Perfluoroalkyl Group

(46) A Facile Synthesis of Alpha, Omega-Dicarboxylic Acids Containing Perfluoroalkylene Groups

(47) Carboxylation of 1-Perfluoroalkyl-Substituted 2-Iodoalkanes Catalyzed by Transition-Metal Complexes

(48) Transition-Metal Complex Catalyzed Carboxylation of Organic Halides in N,N,N',N'-Tetraalkylurea Solution in the Absence of Added Base

(49) Platinum Complex-Catalyzed Carboxylations of Organic Iodides Having Beta-Hydrogens Attached to sp<sup>2</sup>-Carbons

[124]
(50) Platinum Complex Catalyzed Carbonylation of Organic Iodides - Effective Carbonylation of Organic Iodides Having Beta-Hydrogens on Saturated sp³ Carbons

(51) Photochemical Carbonylation of Alkyl Iodides in the Presence of Various Metal-Carbonyls

(52) Photo Electro and Thermal Carbonylation of Alkyl Iodides in the Presence of Group-7 and 8-10 Metal-Carbonyl Catalysts

(53) Cobalt-Catalyzed Photolytic Methoxycarbonylation of Bromoalkanes in the Presence of a Lewis Acid

(54) Fluoride-Induced Activation of Molybdenum Hexacarbonyl - Formation of Esters and Lactones from Alkyl Iodides

(55) Radical Carboxylation: Ester Synthesis from Alkyl Iodides, Carbon Monoxide, and Alcohols under Irradiation Conditions

(56) Palladium-Catalyzed Oxidative Carbonylation of Alkyl and Aryl Indium Reagents with CO under Mild Conditions

Appendix C:

Curriculum Vitae

Education


Research Advisor: Professor Stephen L. Buchwald.

Thesis: “Palladium Catalyzed Cross-Coupling of Aryl Halides with Zirconocene-Benzyne Complexes and Manganese Catalyzed Carbonylation of Alkyl Halides”.

Vordiplom Chemie, 2006. Philipps-Universität Marburg

Professional Experience

Graduate Research with Professor Stephen L. Buchwald

*Massachusetts Institute of Technology,* January 2008 – September 2009

Investigation of Transition Metal-Catalyzed Cross-Coupling and Carbonylation Reactions.

Undergraduate Research with Professor Stephen L. Buchwald

*Massachusetts Institute of Technology,* April 2007 – September 2008

Investigation of Transition Palladium-Catalyzed Carbon-Nitrogen Cross-Coupling Reactions and Ligand Development.

Teachin experience

*Massachusetts Institute of Technology,* September 2007 – May 2008

Taught intermediate organic chemistry and advanced organic laboratory.