Aldehydes and Ketones Influence Reactivity and Selectivity in Nickel-Catalyzed Suzuki-Miyaura Reactions

Alasdair Cooper, David Leonard, Sonia Bajo, Paul Burton, David Nelson

Submitted date: 18/02/2019 • Posted date: 19/02/2019
Licence: CC BY-NC-ND 4.0

Citation information: Cooper, Alasdair; Leonard, David; Bajo, Sonia; Burton, Paul; Nelson, David (2019): Aldehydes and Ketones Influence Reactivity and Selectivity in Nickel-Catalyzed Suzuki-Miyaura Reactions. ChemRxiv. Preprint.

We show that the energetically-favorable coordination of aldehydes and ketones – but not esters – to nickel(0) during Suzuki-Miyaura reactions can lead either to exquisite selectivity and enhanced reactivity, or to the inhibition of the reaction. Aryl halides where the C-X bond is connected to the same π-system as an aldehyde or ketone functional group undergo unexpectedly rapid oxidative addition, and are selectively cross-coupled during inter- and intramolecular competition reactions. When aldehydes and ketones are present elsewhere, such as in the form of exogenous additives, the cross-coupling reaction is inhibited depending on how strongly the pendant carbonyl group can coordinate to nickel(0). This work advances our understanding of how common functional groups interact with nickel(0) catalysts, and presents synthetic chemists with a tool that can be used to achieve site-selectivity in functionalized molecules.
Aldehydes and Ketones Influence Reactivity and Selectivity in Nickel-Catalyzed Suzuki-Miyaura Reactions

Alasdair K. Cooper,†,‡ David K. Leonard,†,§ Sonia Bajo,†,† Paul Burton,‡ and David J. Nelson*†

† WestCHEM Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK, G1 1XL. ‡ Syngenta, Jealott’s Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK.

KEYWORDS: nickel, catalysis, density functional theory, reaction selectivity, organic synthesis

ABSTRACT: We show that the energetically-favorable coordination of aldehydes and ketones – but not esters – to nickel(0) during Suzuki-Miyaura reactions can lead either to exquisite selectivity and enhanced reactivity, or to the inhibition of the reaction. Aryl halides where the C-X bond is connected to the same π-system as an aldehyde or ketone functional group undergo unexpectedly rapid oxidative addition, and are selectively cross-coupled during inter- and intramolecular competition reactions. When aldehydes and ketones are present elsewhere, such as in the form of exogenous additives, the cross-coupling reaction is inhibited depending on how strongly the pendant carbonyl group can coordinate to nickel(0). This work advances our understanding of how common functional groups interact with nickel(0) catalysts, and presents synthetic chemists with a tool that can be used to achieve site-selectivity in functionalized molecules.

1. INTRODUCTION

The field of nickel catalysis is currently under intense study due to the potential for nickel to both replace palladium in some reactions and to enable new reactivity that can be exploited in organic synthesis.° These reactions include tandem photocatalysis/cross-coupling,† reductive cross-electrophile coupling,‡ and the cross-coupling of less reactive substrates such as phenol derivatives,‴ aryl fluorides,⁴ and amides.⁵ Several issues remain to be resolved before the full potential and impact of nickel catalysis can be realized. We must understand how nickel interacts with different functional groups so that we can understand the scope and limitations of existing methods, and opportunities and challenges to consider when developing new ones; target molecules in the pharmaceuticals, agrochemicals, and fine chemicals industries are typically rich in functionality. The underlying reaction mechanisms in nickel catalysis, and how these depend on substrate and ligand structure, remain relatively poorly understood compared to the analogous issues in palladium catalysis, and so these reactions are often treated as a ‘black box’. Correspondingly, reaction design and optimization often relies heavily on empirical observations.

Our research programme focusses on developing a fuller understanding of reaction mechanisms and structure/reactivity relationships in nickel catalysis. This has primarily concerned the oxidative addition event so far, establishing the order of reactivity of a series of aryl (pseudo)halides with model complex [Ni(COD)(dppf)] (I).⁷ Complex I reacts with aryl halides via oxidative addition followed by comproportionation (Figure 1 (a)), while [Ni(NHC)₃] and [Ni(PR₃)₃] (PR₃ = PMePh₃, PPh₃, PMePh,}

![Figure 1.](image)
2. RESULTS AND DISCUSSION

2.1 Kinetic Studies of Oxidative Addition

Aldehyde- and ketone-substituted aryl chlorides undergo oxidative addition much more rapidly than other aryl chlorides (Figure 2). Substrates 2-Cl to 4-Cl undergo oxidative addition more rapidly than electron-deficient aryl chloride 5-Cl. This rate enhancement is sufficiently high that 2(a-e)-Cl, 3-Cl, and 4-Cl all undergo oxidative addition more rapidly than aryl bromide 5-Br. These large differences in oxidative addition rate cannot be attributed simply to inductive or mesomeric electronic effects, as the Hammett substituent constant $\sigma_0$ has a similar value for ketones, aldehydes and esters ($ca. 0.4 - 0.5$) and for trifluoromethyl ($0.54$).

The measured $K_{eq}$ for the displacement of COD from 1 using benzaldehyde, benzophenone, and acetonitrile are sufficiently large that under catalytic conditions – i.e. in the presence of ca. 10 – 100 equiv. of each cross-coupling partner – this coordination would be expected to occur to the extent that 2 – 100% of the Ni° present would be coordinated to a carbonyl group (Scheme 1). These data are consistent with coordination of the nickel center to the aldehyde or ketone moiety prior to oxidative addition. The lack of a similar effect for esters can be attributed to $n \rightarrow \pi^*$ resonance effects, between the oxygen lone pair and the ester carbonyl group.

Scheme 1. Equilibrium constants for the displacement of COD from 1 by aldehydes and ketones.

2.3 Selective Catalysis

The coordination of aldehydes and ketones to the Ni° catalyst can be leveraged to achieve site selective cross-coupling reactions, as demonstrated through a series of competition experiments. Optimized cross-coupling reaction conditions were developed using a factorial experimental design approach and the prototypical cross-coupling of 2a-Br with p-tolylboronic acid (see the Supporting Information) (Scheme 2). Well-defined precatalyst 7 was employed for these reactions, as this generates a dpf-Ni° complex in situ but is an easy-to-handle air stable pre-catalyst.

Scheme 2. Optimized conditions for nickel-catalyzed Suzuki-Miyaura cross-coupling reactions.

To dissect the contributions of electronic and coordination effects, competition experiments were performed in which bromobenzene and a functionalized aryl bromide competed for a limiting amount of boronic acid (Figure 3 (a)). The data were interpreted by quantifying selectivity using equation (i) (Figure 3 (b)); this has a value of 1 where only the functionalized aryl bromide undergoes cross-coupling, or a value of -1 where only bromobenzene undergoes cross-coupling. The reactions in toluene (Figure 3 (c)) and THF/water (Figure 3 (d)) show the same
chloride achieved the selective cross-coupling of reaction conditions in Figure 3 (a) (THF/water), where functionalized aryl halides was extended to examples and less electron-rich Ni coordination occurs to Ni these species (see the Supporting Information); coordinationboronic acids did not lead to selective cross-coupling of halides. Control experiments with ketone-functionalized coupling of ketone- and aldehyde-functionalized aryl halides and aldehydes. The highly selective cross-coupling of ketone-containing aryl halides (Figure 4 (b)), and show that a directing effect is only observed if the carbonyl site that is in conjugation with the ketone functional group of the aryl halide can significantly change the expected order of reactivity, opening up new avenues for creative organic synthesis. Additional competition experiments establish the relative ‘directing power’ of aldehyde- and ketone-containing aryl halides (Figure 4 (b)), and show that a directing effect is only observed if the carbonyl group is in conjugation with the aryl halide π-system; benzophenone and benzaldehyde both undergo cross-coupling selectively in the presence of 8.

Finally, intramolecular competition experiments establish that carbonyl groups can be used to ensure site-selectivity within molecules that have two aryl halide sites; compound 9 undergoes selective cross-coupling at the site that is in conjugation with the ketone functional group (Figure 4 (c)).

These studies show that the coordination of ketones and aldehydes to Ni° can be used to achieve site-selective catalytic cross-coupling reactions.

Figure 3. Competition experiments: (a) reaction conditions; (b) quantification of selectivity; (c) reactions in toluene with 10 equiv. water; and (d) reactions in 4:1 v/v THF/water. 4-bromo-2,2,2-trifluoroacetophenone could not be studied in a THF/water solvent mixture due to competing hydration. Each competition experiment is plotted as a separate point.

trend when selectivity is plotted versus \( \sigma_p \), the selectivity is largely insensitive to the electronic properties of the aryl halide and is instead dominated by coordination to aldehydes and ketones. The highly selective cross-coupling of ketone- and aldehyde-functionalized aryl halides is therefore possible in the presence of other aryl halides. Control experiments with ketone-functionalized boronic acids did not lead to selective cross-coupling of these species (see the Supporting Information); coordination occurs to Ni° only, and not to the sterically-crowded and less electron-rich Ni° intermediates.

The selective cross-coupling of aldehyde- and ketone-functionalized aryl halides was extended to examples where the normal order of reactivity is reversed. Using the reaction conditions in Figure 3 (a) (THF/water), we achieved the selective cross coupling of 2a-Br in the presence of aryl iodide 5-I (Figure 4 (a)). Furthermore, aryl chloride 2a-Cl undergoes selective cross-coupling in the presence of 5-Br (ca. 201) and even in the presence of aryl iodide 5-I (1:6:1). While the intrinsic differences in the reactivities of aryl chlorides, bromides, and iodides have been leveraged in the past for selective cross-coupling reactions,27 this work shows that the substitution pattern of the aryl halide can significantly change the expected order of reactivity, opening up new avenues for creative organic synthesis. Additional competition experiments establish the relative ‘directing power’ of aldehyde- and ketone-containing aryl halides (Figure 4 (b)), and show that a directing effect is only observed if the carbonyl group is in conjugation with the aryl halide π-system; benzophenone and benzaldehyde both undergo cross-coupling selectively in the presence of 8.
2.4 DFT Calculations

DFT calculations gave further quantitative insight into these reactions. All energies reported are free energies, with respect to [Ni(dppf)(η^1-benzene)] (10). Consistent with experiment, aldehydes and ketones coordinate the [Ni(dppf)] fragment exergonically via the carbonyl group (Figure 5). In contrast, the binding of substrates to [Ni(dppf)] via heteroatoms in amine, ether, or sulfoxide functional groups is endergonic (see the Supporting Information).

![Figure 5: Coordination of aldehydes, ketones, and esters to [Ni(dppf)]; free energies are quoted in kcal mol⁻¹ in toluene solution, relative to [Ni(dppf)(η^1-benzene)].](image)

Free energy profiles were calculated for the oxidative addition reactions of aryl bromides; selected examples (with NMe₂, H, CF₃, and CHO substituents) are presented in Figure 6. These reactions proceed via the formation of transition state B to irreversibly form Niᴵᴵ oxidative addition product C; experimentally, this is followed by deproportionation with Niᴵ to form [NiBr(dppf)]. The aldehyde-functionalized substrate can also form the η¹-(CO) complex (Figure 5). These data show that aldehyde- and ketone-functionalized aryl halides coordinate the Niᴵ catalyst more strongly than other aryl halides can, and so this leads to selectivity in competition reactions.

Calculations of the oxidative addition pathway were also carried out for a wider range of substrates, comprising para-substituted bromobenzenes with the following substituents: SO₂Me, CF₃, COMe, CO₂Me, CHO, OCF₃, H, OMe, NHPh, and NMe₂. Figure 7 displays a plot of the energies of (i) the η¹-complexes, (ii) the oxidative addition transition states, and (iii) the difference between these species, all versus σₚ; the full dataset can be found in the Supporting Information. The ketone- and aldehyde-bearing aryl halides fit the observed trends between ΔG and σₚ and so the enhanced selectivity observed is not likely to arise simply from the lowering of the energy of the transition state for oxidative addition.

These data are consistent with selective functionalization of aryl halides that have aldehydes and ketones in conjugation with the aryl halide site, enabled by the coordination of these functional groups to the Niᴵ catalyst.

2.5 Robustness Screening

The coordination of ketones and aldehydes to Niᴵ might have a detrimental effect on the performance of cross-coupling reactions if this behavior sequesters the active catalyst. To explore this, a ‘robustness screen’ was carried out, in which the model reaction was carried out in the presence of 1 equiv. of each of a series of additives (11 – 21). GC-FID analysis – calibrated using authentic samples of each reagent, product, and additive – was used to measure the reaction conversion, and quantify how much of the additive remained at the end of the reaction. This provides a rapid and quantitative measure of the effect of each additive, as well as an indication of whether the additive is undergoing a competing side-reaction.
A palette of additives was examined (Figure 8). Ester (11), amide (13), amine (18, 20), ether (19), and sulfide (21) additives had little effect on the reaction conversion. In contrast, the aldehyde and ketone additives – with the exception of acetylphenone (17) – had a significant and detrimental effect, with the reaction almost completely ceasing when 1 equiv. 2,2,2-trifluoroacetophenone (16) was present. The degree of inhibition of the reaction is correlated to the measured equilibrium constant for the displacement of COD from 1 (vide supra).

![Chemical structure and reaction](image)

**Figure 8.** Results from the robustness screen.

### 3. CONCLUSIONS

This work establishes that aldehydes and ketones can have either a positive or a negative effect in nickel catalysis, and that their effects depend on where in the reaction they are located.

Aldehyde- and ketone-bearing aryl halides undergo rapid oxidative addition to Ni^0, via formation of an intermediate η¹(CO). We have shown that aryl aldehydes and ketones can displace ligands such as COD from a Ni^0 center. The resulting selectivity is likely due to a subsequent ‘ring-walking’ process.37-39 as selectivity is only obtained when the aryl halide site is in conjugation with the aldehyde or ketone. This coordination behavior results in selectivity in catalytic cross-coupling reactions, to the extent that the normal order of reactivity of aryl halides (I > Br > Cl) is changed substantially.

In contrast, aryl aldehydes and ketones present in the reaction that are not conjugated to the aryl iodide act as inhibitors in cross-coupling reactions. The compounds that bind Ni^0 most strongly have the most significant detrimental effects on the rate of the cross-coupling reaction.

This study provides a fuller understanding of structure-reactivity relationships in nickel catalysis, and highlights two effects that arise when aldehydes and ketones are present in nickel-catalyzed cross-coupling reactions. Given the importance of these functional groups in organic synthesis, it is crucial to be able to confidently deploy substrates bearing these groups in cross-coupling reactions. The potential to change the normal order of reactivity of aryl halides provides opportunities for predictable site-selectivity in cross-coupling reactions of functionalized substrates.

Further work is underway within our laboratories to understand the effects of other functional groups on nickel-catalyzed cross-coupling reactions and their fundamental steps.

### ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures; characterization data for compounds prepared; coordinates and energies from DFT studies. This material is available free of charge via the Internet at http://pubs.acs.org. The raw data underpinning this study can be retrieved from the University of Strathclyde PURE data repository at the following URL: http://dx.doi.org/[TBA].

### AUTHOR INFORMATION

* Corresponding Author
  ✉ David J. Nelson: david.nelson@strath.ac.uk

**Present Addresses**

§ Current Address for DKL: Leibniz-Institute for Catalysis, Albert-Einstein-Straße 29a, 18059 Rostock, Germany.

& Current Address for SB: Institute for Chemical Research (IIQ), CSIC-University of Sevilla, Avda. Américo Vespucio 49, 41092 Sevilla, Spain.

**Author Contributions**

All authors have given approval to the final version of the manuscript.

### ACKNOWLEDGMENT

We thank Syngenta and the Engineering and Physical Sciences Research Council (EPSRC) for an Industrial CASE Studentship (EP/P50166X/1), the EPSRC for a First Grant to DJN (EP/M027678/1), and the University of Strathclyde for a Chancellor’s Fellowship for DJN (2014-2018). We thank the Department of Pure and Applied Chemistry at the University of Strathclyde for consumables and facilities funding for DKL. We thank Mr Gavin Bain, Mr Craig Irving, Ms Patricia Keating, and Dr John Parkinson for assistance with technical and analytical facilities. We thank Dr James Sanderson for assistance with initial factorial experimental design studies. Some of these results were reported here and were obtained using the EPSRC-funded ARCHE-WeST high performance computer (archie-west.ac.uk) (EP/K000586/1) and we are grateful to Mr J. Buzzard, Dr K. Kubiak-Ossowska, and Dr R. Martin for their assistance with this facility. We thank Dr Allan Watson (University of St Andrews) for helpful discussions.

### ABBREVIATIONS

COD, 1,5-cyclooctadiene; dpff, 1,1’-bis(diphenylphosphino)ferrocene.
Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal’s Instructions for Authors for TOC graphic specifications.
**SUPPORTING INFORMATION FOR**

**Aldehydes and Ketones Influence Reactivity and Selectivity in Nickel-Catalysed Suzuki-Miyaura Cross-Coupling Reactions**

Alasdair K. Cooper, David K. Leonard, Sonia Bajo, Paul Burton, and David J. Nelson

[a] WestCHEM Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK. david.nelson@strath.ac.uk

[b] Syngenta, Jealott’s Hill Research Centre, Bracknell, Berkshire, RG42 6EX

**CONTENTS**

| Section                                                                 | Page |
|-------------------------------------------------------------------------|------|
| General experimental details                                           | S2   |
| Kinetic data for oxidative addition to nickel(0)                        | S3   |
| Equilibrium constants for the binding of aldehydes and ketones to nickel(0) | S4   |
| Design of experiments data for reaction optimisation                    | S5   |
| Synthesis of cross-coupling substrates                                  | Sxx  |
| GC-FID calibration                                                      | Sxx  |
| Data from competitive cross-coupling reactions                          | Sxx  |
| Energies and coordinates from DFT calculations                          | Sxx  |
| Data from robustness screening                                          | Sxx  |
| NMR spectra                                                             | Sxx  |
GENERAL EXPERIMENTAL DETAILS

- Most aryl halides were obtained from commercial sources and used as supplied; others were prepared as detailed below.
- Complexes 1 and 7 were prepared using literature methods. 1,2
- Anhydrous toluene and THF were obtained from an Inert Technology PureSolv apparatus; regular Karl-Fisher analyses ensured that water content was always below 10 ppm. Anhydrous benzene-$d_6$ was obtained by drying over 4 Å molecular sieves that had been activated by heating under high vacuum.
- Distilled water was degassed by sparging with nitrogen or argon before use.
- Potassium phosphate was obtained from Alfa Aesar, dried overnight in a vacuum oven at 50 °C before use, and stored in a desiccator.
- All cross-coupling reactions were carried out in degassed, anhydrous solvent, with a specific volume of water added, under an atmosphere of nitrogen or argon.
- Manipulations of air-sensitive nickel complexes were carried out under argon using Schlenk and glovebox techniques.
- NMR spectra were obtained using a Bruker AV3-400 instrument with either a QNP probe or a liquid nitrogen Prodigy cryoprobe. $^1$H NMR spectra are referenced to residual protonated solvent, $^1$3C NMR spectra are referenced to solvent signals, $^1$19F signals are externally referenced to CFCl$_3$, and $^{31}$P NMR signals are externally referenced to H$_3$PO$_4$.
- GC-MS analyses were carried out using an Agilent 7890A gas chromatograph fitted with a RESTEK RXi-5Sil column (30 m x 0.32 mm I.D. x 0.25 μm) and an Agilent 5975C MSD running in EI mode.
- GC-FID analyses were carried out using an Agilent 7890A gas chromatograph fitted with an Agilent HP5 column (30 m x 0.25 mm I.D. x 0.25 μm).
KINETIC DATA FOR OXIDATIVE ADDITION TO NICKEL(0)

Kinetic data were obtained in the same manner as that used for our previous paper. Liquid substrates were added neat to a septum-fitted NMR tube containing a solution of [Ni(COD)(dppf)] in benzene-$d_6$ that had been equilibrated at 20 °C. For solid substrates, a solution of [Ni(COD)(dppf)] in benzene-$d_6$, equilibrated at 20 °C, was added to the solid substrate. $^{31}$P NMR spectra were acquired at intervals, with a long D1 (25 seconds) and without $^1$H decoupling.

Data for 5-Cl, 5-Br, 5-I, and 6-Cl can be found in our previous manuscript.

| Substrate | $k_{obs}$ (rep. 1) | $k_{obs}$ (rep. 2) | $k_{obs}$ (mean) |
|-----------|--------------------|--------------------|------------------|
| 2a-Cl     | $2.20 \times 10^{-4}$ s$^{-1}$ | $2.87 \times 10^{-4}$ s$^{-1}$ | $2.5(3) \times 10^{-4}$ s$^{-1}$ |
| 2b-Cl     | $3.89 \times 10^{-4}$ s$^{-1}$ | $4.50 \times 10^{-4}$ s$^{-1}$ | $4.2(3) \times 10^{-4}$ s$^{-1}$ |
| 2c-Cl     | $3.25 \times 10^{-4}$ s$^{-1}$ | $2.79 \times 10^{-4}$ s$^{-1}$ | $3.0(2) \times 10^{-4}$ s$^{-1}$ |
| 3-Cl      | $1.40 \times 10^{-4}$ s$^{-1}$ | $1.42 \times 10^{-4}$ s$^{-1}$ | $1.41(1) \times 10^{-4}$ s$^{-1}$ |
| 4-Cl      | $9.41 \times 10^{-5}$ s$^{-1}$ | $9.06 \times 10^{-5}$ s$^{-1}$ | $9.2(2) \times 10^{-5}$ s$^{-1}$ |
EQUILIBRIUM CONSTANTS FOR THE BINDING OF ALDEHYDES AND KETONES TO NICKEL(0)

Equilibrium constant determination

\[
K_{eq} = \frac{[Ni - L][COD]}{[L][Ni - COD]} = \frac{[Ni - L][Ni - COD]_0 - [Ni - COD]}{([L]_0 - [Ni - L])[Ni - COD]}
\]

L is the aldehyde or ketone, Ni-COD = [Ni(COD)(dppf)], and Ni-L = [Ni(L)(dppf)], with concentrations determined from \(^{31}\text{P}\) NMR analyses. A plot of \([Ni-L]·([Ni-COD]_0 - [Ni-COD])\) versus \(([L]_0 - [Ni-L])·[Ni-COD]\) should yield a straight line of gradient \(K_{eq}\).

Acetophenone

![Acetophenone Plot](image)

Benzaldehyde

The addition of 1 equiv. benzaldehyde to [Ni(COD)(dppf)] led to complete formation of [Ni(η²-OHCPh)(dppf)] and so \(K_{eq}\) is estimated at > 20.

Benzophenone

![Benzophenone Plot](image)
DESIGN OF EXPERIMENTS DATA FOR REACTION OPTIMISATION

For each reaction, solid components were loaded into a microwave tube equipped with a stir bar, sealed with a septum-fitted crimp-cap, and evacuated and backfilled with argon or nitrogen several times. The liquid reagents and the reaction solvent were added via syringe through the septum. The reactions were then heated, with stirring, for 18 h. After this time, the reaction was cooled to room temperature, and an accurately-known mass of dodecane or tetradecane was added. A sample of the solution was then diluted in chloroform for analysis by GC-FID.

The DoE study was initially conducted using the dppe ligand, but comparable results are obtained using dppf under the same conditions. All other work was conducted with dppf as the model nickel(0) complex for kinetic studies and ligand binding studies used a dppf ligand.

**Initial Screen**

| Run | T (°C) | Cat. Loading (mol%) | Boronic Acid equiv. | Base equiv. | Water equiv. | Conversion (%) |
|-----|--------|---------------------|---------------------|------------|--------------|----------------|
| 1   | 30     | 10                  | 1                   | 1          | 0            | 0              |
| 2   | 110    | 1                   | 1                   | 1          | 0            | 62             |
| 3   | 110    | 10                  | 2                   | 1          | 0            | 96             |
| 4   | 110    | 1                   | 2                   | 1          | 20           | 0              |
| 5   | 30     | 1                   | 1                   | 5          | 0            | 2              |
| 6   | 110    | 10                  | 1                   | 5          | 0            | 69             |
| 7   | 110    | 1                   | 2                   | 5          | 0            | 80             |
| 8   | 110    | 10                  | 1                   | 1          | 20           | 75             |
| 9   | 30     | 1                   | 2                   | 5          | 20           | 20             |
| 10  | 70     | 5.5                 | 1.5                 | 3          | 10           | >99            |
| 11  | 30     | 10                  | 1                   | 5          | 20           | 0              |
| 12  | 110    | 1                   | 1                   | 5          | 20           | 78             |
| 13  | 70     | 5.5                 | 1.5                 | 3          | 10           | >99            |
| 14  | 30     | 1                   | 1                   | 1          | 20           | 5              |
| 15  | 30     | 10                  | 2                   | 5          | 0            | 18             |
| 16  | 30     | 1                   | 2                   | 1          | 0            | 0              |
| 17  | 70     | 5.5                 | 1.5                 | 3          | 10           | >99            |
| 18  | 30     | 10                  | 2                   | 1          | 20           | 15             |
| 19  | 70     | 5.5                 | 1.5                 | 3          | 10           | >99            |
| 20  | 110    | 10                  | 2                   | 5          | 20           | 97             |
Data were analysed using DesignExpert 8. From this, it was deduced that the catalyst loading had a positive effect on conversion, though it was not as significant as the temperature effect. Overall, this initial screen gave positive results, since the centre points appeared to proceed to full conversion. In order to further probe the reaction conditions, and potentially reduce factors such as catalyst loading, the experiment design was augmented to narrow in on optimised conditions.

![Half-normal plot](image1)
![3D response surface](image2)

**Second Screen**

| Run | T (°C) | Cat. Loading (mol%) | Boronic Acid eq. | Base eq. | Water eq. | Conversion (%) |
|-----|--------|---------------------|------------------|----------|-----------|----------------|
| 21  | 70     | 1                   | 1.5              | 3        | 10        | 0              |
| 22  | 70     | 5.5                 | 1.5              | 5        | 10        | 91             |
| 23  | 70     | 5.5                 | 1.5              | 3        | 0         | 90             |
| 24  | 70     | 5.5                 | 1.5              | 1        | 10        | 21             |
| 25  | 110    | 5.5                 | 1.5              | 3        | 10        | 97             |
| 26  | 70     | 5.5                 | 1                 | 3        | 10        | 81             |
| 27  | 70     | 5.5                 | 1.5              | 3        | 10        | 98             |
| 28  | 70     | 5.5                 | 1.5              | 3        | 10        | 97             |
| 29  | 70     | 5.5                 | 1.5              | 3        | 20        | 58             |
| 30  | 30     | 5.5                 | 1.5              | 3        | 10        | 0              |
| 31  | 70     | 5.5                 | 2                 | 3        | 10        | 70             |
| 32  | 70     | 10                  | 1.5              | 3        | 10        | 91             |
Using these data, the software suggested that the optimum conditions were:

- 5 mol % catalyst loading
- 1.1 equivalents of boronic acid
- Temperature of 85 °C
- equivalents of base
- 10 equivalents of water

These conditions were used in triplicate to verify that the reaction was reproducible, and tested also on a non-carbonyl substrate.

\[
\begin{align*}
&\text{Substrate} & \text{Conversion (\%)} \\
&4'\text{-chloroacetophenone} & 92 \\
&4'\text{-chloroacetophenone} & 95 \\
&4'\text{-chloroacetophenone} & >99 \\
&4\text{-chlorobenzotrifluoride} & 91
\end{align*}
\]

A small time study was conducted, using these optimised conditions, in an effort to reduce the reaction time.

\[
\begin{align*}
&\text{Substrate} & \text{Reaction Time (h)} & \text{Conversion (\%)} \\
&4'\text{-chloroacetophenone} & 2 & 99* \\
&4'\text{-chloroacetophenone} & 4 & 99* \\
&4'\text{-chloroacetophenone} & 6 & 99* \\
&4'\text{-chloroacetophenone} & 8 & 99*
\end{align*}
\]
SYNTHESIS OF CROSS-COUPLING SUBSTRATES

**General Procedure A.** To a microwave vial equipped with a stirrer bar, 4-tolylboronic acid (1.1 eq.), [PdCl$_2$(dppf)] (1 – 5 mol%), K$_3$PO$_4$ (3 eq.) and, if solid, aryl halide (1 mmol, 1 eq.) were added. The vial was capped and purged/backfilled with N$_2$. Anhydrous toluene (2 mL) was added via oven-dried glass syringe. If the aryl halide was a liquid, it was added here. H$_2$O (10 eq.) was then added. The reaction was stirred for 2 hours at 85 °C. The reaction was then cooled to room temperature. The mixture was filtered through celite and analysed via GC-FID. The reaction was then analysed via TLC. The mixture was evaporated to dryness in vacuo and purified via flash column chromatography to furnish the product as a white solid.

**4-methyl-4′-(trifluoromethyl)-1,1′-biphenyl**

Synthesised according to the General Procedure A using 4-bromobenzotrifluoride (140 µL, 225.0 mg, 1 mmol), 4-tolylboronic acid (149.7 mg, 1.1 mmol), [PdCl$_2$(dppf)] (36.5 mg, 5 mol %) and K$_3$PO$_4$ (634.2 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with hexane) to yield a white solid (163.7 mg, 69%).

**$^1$H NMR (400 MHz, CDCl$_3$):** δ$_H$ 7.70 (s, 4H, 4 x ArH), 7.53 (d, 2H, 2 x ArH, J = 8.3 Hz), 7.31 (d, 2H, 2 x ArH, J = 7.9 Hz), 2.44 (s, 3H, CH$_3$).

**$^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$):** δ$_C$ 144.2, 137.7, 136.4, 129.2 (2C), 128.5 (q, $^1$J$_{CF}$ = 32.5 Hz), 126.7 (2C), 126.6 (2C), 125.2 (q, 2C, $^3$J$_{CF}$ = 3.7 Hz), 123.9 (q, $^1$J$_{CF}$ = 271.9 Hz), 20.6. **$^{19}$F NMR (376 MHz, CDCl$_3$):** δ$_F$ -62.4 (s, 3F, CF$_3$).

**m/z (GC-MS EI):** 236.1 (M$^+$). NMR data are consistent with the literature.

**methyl 4′-methyl-[1,1′-biphenyl]-4-carboxylate**

Synthesised according to the General Procedure A using methyl 4-bromobenzoate (214.6 mg, 1 mmol), 4-tolylboronic acid (150.1 mg, 1.1 mmol), [PdCl$_2$(dppf)] (36.4 mg, 5 mol %) and K$_3$PO$_4$ (634.0 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (209.1 mg, 92%).

**$^1$H NMR (400 MHz, CDCl$_3$):** δ$_H$ 8.11 (d, 2H, 2 x ArH, J = 8.6 Hz), 7.67 (d, 2H, 2 x ArH, J = 8.5 Hz), 7.55 (d, 2H, 2 x ArH, J = 8.1 Hz), 7.31 (s, 2H, 2 x ArH), 3.96 (s, 3H, CO$_2$CH$_3$), 2.43 (s, 3H, CH$_3$).

**$^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$):** δ$_C$ 166.6, 145.1, 137.6, 136.6, 129.6 (2C), 129.2 (2C), 128.1, 126.6 (2C), 126.3 (2C), 51.6, 20.7. **$\nu_{\text{max}}$ (neat):** 3024, 2943, 2845, 1701, 1597, 1491 cm$^{-1}$. **m/z (GC-MS EI):** 226.1 (M$^+$). NMR data are consistent with the literature.

**N,N,4′-trimethyl-[1,1′-biphenyl]-4-amine**

Synthesised according to the General Procedure A using 4-bromo-N,N-dimethylaniline (200.9 mg, 1 mmol), 4-tolylboronic acid (149.6 mg, 1.1 mmol), [PdCl$_2$(dppf)] (36.5 mg, 5 mol %) and K$_3$PO$_4$ (634.4 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography...
(eluting with 0 – 10 % EtOAc in hexane) to yield a white solid (174.8 mg, 83 %). ¹H NMR (400 MHz, CDCl₃): δₗ 7.52 – 7.46 (m, 4H, 4 x ArH, J = 22.1 Hz), 7.23 (d, 2H, 2 x ArH, J = 8.0 Hz), 6.83 (d, 2H, 2 x ArH, J = 8.9 Hz), 3.02 (s, 6H, N(CH₃)₂), 2.40 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 149.3, 137.9, 135.1, 128.9 (2C), 127.0 (2C), 125.7 (2C), 112.4 (2C), 40.2 (2C), 20.5. m/z (GCMS EI): 211.1 (M⁺). NMR data are consistent with the literature.

4-methoxy-4’-methyl-1,1’-biphenyl

Synthesised according to the General Procedure A using 4-bromoanisole (125 µL, 186.8 mg, 1 mmol), 4-tolylboronic acid (149.3 mg, 1.1 mmol), [PdCl₂(dppf)] (36.7 mg, 5 mol %) and K₃PO₄ (634.4 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 10 % EtOAc in hexane) to yield a white solid (99.6 mg, 50 %). ¹H NMR (400 MHz, CDCl₃): δₗ 7.53 (d, 2H, 2 x ArH, J = 9.0 Hz), 7.47 (d, 2H, 2 x ArH, J = 8.3 Hz), 7.25 (d, 2H, 2 x ArH, J = 7.8 Hz), 6.99 (d, 2H, 2 x ArH, J = 8.8 Hz), 3.88 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 158.4, 137.5, 135.9, 133.3, 128.9 (2C), 127.5 (2C), 126.1 (2C), 113.7 (2C), 54.9, 20.5. m/z (GCMS EI): 198.1 (M⁺). NMR data are consistent with the literature.

4’-methyl-[1,1’-biphenyl]-4-carbaldehyde

Synthesised according to the General Procedure A using 4-bromobenzaldehyde (186.2 mg, 1 mmol), 4-tolylboronic acid (150.1 mg, 1.1 mmol), [PdCl₂(dppf)] (37.0 mg, 5 mol %) and K₃PO₄ (634.7 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (115.2 mg, 59 %). ¹H NMR (400 MHz, CDCl₃): δₗ 10.08 (s, 1H, C(O)H), 7.96 (d, 2H, 2 x ArH, J = 8.6 Hz), 7.77 (d, 2H, 2 x ArH, J = 8.3 Hz), 7.57 (d, 2H, 2 x ArH, J = 8.1 Hz), 7.32 (d, 2H, 2 x ArH, J = 7.9 Hz), 2.45 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 191.4, 146.7, 138.0, 136.3, 134.5, 129.8 (2C), 129.3 (2C), 126.9 (2C), 126.7 (2C), 20.7. νmax (neat): 3022, 2845, 1694, 1597, 1493 cm⁻¹. m/z (GCMS EI): 196.1 (M⁺). NMR data are consistent with the literature.

1-(4’-methyl-[1,1’-biphenyl]-4-yl)ethan-1-one

Synthesised according to the General Procedure A using 4’-bromoacetophenone (201.4 mg, 1 mmol), 4-tolylboronic acid (150.2 mg, 1.1 mmol), [PdCl₂(dppf)] (36.4 mg, 5 mol %) and K₃PO₄ (634.7 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (160.8 mg, 77 %). ¹H NMR (400 MHz, CDCl₃): δₗ 8.05 (d, 2H, 2 x ArH, J = 8.7 Hz), 7.70 (d, 2H, 2 x ArH, J = 8.7 Hz), 7.56 (d, 2H, 2 x ArH, J = 8.2 Hz), 7.31 (d, 2H, 2 x ArH, J = 8.2 Hz), 2.66 (s, 3H, C(O)CH₃), 2.44 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 197.3, 145.3, 137.8, 136.5, 135.1, 129.2 (2C), 128.4 (2C), 126.6 (2C), 126.5 (2C), 26.1, 20.7.
\( \nu_{\text{max}} \) (neat): 3026, 2928, 1674, 1597, 1522, 1491, 1420 cm\(^{-1}\). \( m/z \) (GCMS EI): 210.1 (M\(^+\)). NMR data are consistent with the literature.\(^6\)

**4'-methyl-[1,1'-biphenyl]-4-yl](phenyl)methanone**

Synthesised according to the General Procedure A using 4-bromobenzophenone (261.1 mg, 1 mmol), 4-tolylboronic acid (150.3 mg, 1.1 mmol), \([\text{PdCl}_2(\text{dppf})]\) (36.7 mg, 5 mol %) and \( \text{K}_3\text{PO}_4 \) (634.9 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (136.3 mg, 50 %).

\( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.91 (d, 2H, 2 x ArH, \( J = 8.5 \) Hz), 7.86 (d, 2H, 2 x ArH, \( J = 7.1 \) Hz), 7.72 (d, 2H, 2 x ArH, \( J = 8.6 \) Hz), 7.63 (t, 1H, 1 x ArH, \( J = 8.3 \) Hz), 7.58 (d, 2H, 2 x ArH, \( J = 8.3 \) Hz), 7.53 (d, 2H, 2 x ArH, \( J = 8.1 \) Hz), 7.32 (d, 2H, 2 x ArH, \( J = 8.1 \) Hz), 2.45 (s, 3H, CH\(_3\)).

\( ^{13}C\{^1H\} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta \) 195.9, 144.7, 137.7, 137.4, 136.6, 135.5, 131.8, 130.2 (2C), 129.5 (2C), 129.2 (2C), 127.8 (2C), 126.6 (2C), 126.2 (2C), 20.7.

\( \nu_{\text{max}} \) (neat): 3022, 2911, 2853, 1643, 1595, 1528, 1491, 1443 cm\(^{-1}\).

\( m/z \) (GCMS EI): 272.1 (M\(^+\)). NMR data are consistent with the literature.

**4-fluoro-4'-methyl-1,1'-biphenyl**

Synthesised according to the General Procedure A using 4-bromofluorobenzene (110 µL, 175.2 mg 1 mmol), 4-tolylboronic acid (135.6 mg, 1 mmol), \([\text{PdCl}_2(\text{dppf})]\) (7.5 mg, 1 mol %) and \( \text{K}_3\text{PO}_4 \) (633.3 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with hexane) to yield a white solid (160.1 mg, 86 %).

\( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.57 – 7.53 (dd, 2H, 2 x ArH, \( J_{H-H} = 8.8 \) Hz, \( J_{H-F} = 5.3 \) Hz), 7.46 (d, 2H, 2 x ArH, \( J = 8.1 \) Hz), 7.27 (d, 2H, 2 x ArH, \( J = 8.0 \) Hz), 7.13 (t, 2H, 2 x ArH, \( J = 8.8 \) Hz), 2.42 (s, 3H, CH\(_3\)).

\( ^{13}C\{^1H\} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta \) 161.8 (d, \( J_{C-F} = 245.6 \) Hz), 136.9, 136.8 (d, \( J_{C-F} = 3.3 \) Hz), 136.5, 129.0 (2C), 128.0 (d, 2C, \( J_{C-F} = 7.7 \) Hz), 126.4 (2C), 115.1 (d, 2C, \( J_{C-F} = 21.2 \) Hz), 20.6. \( ^{19}F \text{NMR} \) (376 MHz, CDCl\(_3\)): \( \delta \) -116.3 (tt, 1F, 1 x ArF, \( J_{F-H} = 8.7 \) Hz, \( J_{F-H} = 5.3 \) Hz). \( ^{19}F\{^1H\} \text{NMR} \) (376 MHz, CDCl\(_3\)): \( \delta \) -116.3 (s, 1F, 1 x ArF).

\( m/z \) (GCMS EI): 186.1 (M\(^+\)). NMR data are consistent with the literature.\(^7\)

**4-(difluoromethoxy)-4'-methyl-1,1'-biphenyl**

Synthesised according to the General Procedure A using 1-bromo-4-(difluoromethoxy)benzene (137 µL, 223.4 mg, 1 mmol), 4-tolylboronic acid (135.4 mg, 1 mmol), \([\text{PdCl}_2(\text{dppf})]\) (6.8 mg, 1 mol %) and \( \text{K}_3\text{PO}_4 \) (637.5 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with hexane) to yield a white solid (182.7 mg, 78 %).

\( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.58 (d, 2H, 2 x ArH, \( J = 8.8 \) Hz), 7.48 (d, 2H, 2 x ArH, \( J = 8.2 \) Hz), 7.28 (d, 2H, 2 x ArH, \( J = 8.0 \) Hz), 6.56 (t, 1H, CF\(_2\)H, \( J = 8.5 \) Hz), 7.50 (d, 2H, 2 x ArH, \( J = 8.5 \) Hz), 6.56 (t, 1H, CF\(_2\)H, \( J = 74.2 \) Hz), 2.42 (s, 3H, CH\(_3\)). \( ^{13}C\{^1H\} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta \) 149.9, 138.1, 136.8, 136.7, 129.1 (2C), 127.8 (2C), 126.4 (2C), 119.3 (2C), 115.5 (t, \( J_{C-F} = 259.7 \) Hz), 20.6. \( ^{19}F \text{NMR} \) (376 MHz, CDCl\(_3\)): \( \delta \) -80.6 (d, 2F, CHF\(_2\)), \( J = 73.8 \) Hz). \( m/z \) (GCMS EI): 234.1 (M\(^+\)). NMR data are consistent with the literature.\(^8\)
4-methyl-4'-{(trifluoromethoxy)-1,1'-biphenyl

Synthesised according to the General Procedure A using 1-bromo-4-(trifluoromethoxy)benzene (149 µL, 241.7 mg, 1 mmol), 4-tolylboronic acid (136.7 mg, 1 mmol), [PdCl₂(dppf)] (7.1 mg, 1 mol %) and K₃PO₄ (641.9 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with hexane) to yield a white solid (180.1 mg, 71 %). ¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, 2H, 2 x ArH, J = 8.2 Hz), 7.48 (d, 2H, 2 x ArH, J = 8.2 Hz), 2.42 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 148.0, 139.4, 137.0, 136.5, 129.1 (2C), 127.7 (2C), 126.4 (2C), 120.7 (2C), 119.6 (q, J_C-F = 256.9 Hz), 20.6. ¹⁹F NMR (376 MHz, CDCl₃): δF -57.8 (s, 3F, OCF₃). m/z (GCMS EI): 252.1 (M⁺). NMR data are consistent with the literature.⁹

4'-methyl-4-ispropyl-1,1'-biphenyl

Synthesised according to the General Procedure A using 1-bromo-4-isopropylbenzene (155 µL, 199.3 mg, 1 mmol), 4-tolylboronic acid (135.7 mg, 1 mmol), [PdCl₂(dppf)] (7.3 mg, 1 mol %) and K₃PO₄ (633.3 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with hexane) to yield a white solid (155.0 mg, 74 %). ¹H NMR (400 MHz, CDCl₃): δ 7.55 – 7.50 (m, 4H, 4 x ArH, J = 20.4 Hz), 7.31 (d, 2H, 2 x ArH, J = 7.9 Hz), 7.26 (d, 2H, 2 x ArH, J = 7.9 Hz), 2.97 (h, 1H, C(CH₃)₂H, J = 7.1 Hz), 2.41 (s, 3H, CH₃), 1.31 (d, 6H, (CH₃)₂, J = 6.9 Hz). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 147.2, 138.2, 137.8, 136.2, 128.9 (2C), 126.4 (2C), 126.3 (2C), 33.3, 23.5 (2C), 20.6. m/z (GCMS EI): 210.1 (M⁺). NMR data are consistent with the literature.¹⁰

N,N-diethyl-4'-methyl-[1,1'-biphenyl]-4-amine

Synthesised according to the General Procedure A using 4-bromo-N,N-diethylaniline (228.2 mg, 1 mmol), 4-tolylboronic acid (135.5 mg, 1 mmol), [PdCl₂(dppf)] (7.2 mg, 1 mol %) and K₃PO₄ (635.3 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (214.6 mg, 90 %). ¹H NMR (400 MHz, CDCl₃): δH 7.51 – 7.47 (m, 4H, 4 x ArH, J = 14.1 Hz), 7.23 (d, 2H, 2 x ArH, J = 8.0 Hz), 6.78 (d, 2H, 2 x ArH, J = 8.5 Hz), 3.43 (q, 4H, (CH₂)₂, J = 7.1 Hz), 2.41 (s, 3H, CH₃), 1.23 (t, 6H, (CH₃)₂, J = 7.1 Hz). ¹³C{¹H} NMR (101 MHz, CDCl₃): δc 146.5, 138.0, 134.9, 128.9 (2C), 127.7, 127.3 (2C), 125.6 (2C), 115.1 (2C), 43.9 (2C), 20.6, 12.2 (2C). m/z (GCMS EI): 239.4 (M⁺).
2,2,2-trifluoro-1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one

Synthesised according to the General Procedure A using 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (253.0 mg, 1 mmol), 4-tolylboronic acid (134.8 mg, 1 mmol), [PdCl₂(dpdpf)] (7.1 mg, 1 mol %) and K₃PO₄ (638.2 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (178.6 mg, 68 %). ¹H NMR (400 MHz, CDCl₃): δH 8.17 (d, 2H, 2 x ArH, J = 7.6 Hz), 7.79 (d, 2H, 2 x ArH, J = 8.7 Hz), 7.59 (d, 2H, 2 x ArH, J = 8.2 Hz), 7.34 (d, 2H, 2 x ArH, J = 8.0 Hz), 2.46 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δC 179.6 (q, ²JCF = 34.5 Hz), 147.7, 138.6, 135.7, 130.3 (2C), 129.4 (2C), 127.8 (2C), 126.8, 126.7 (2C), 116.4 (q, ¹JCF = 291.1 Hz), 20.7. ¹⁹F NMR (376 MHz, CDCl₃): δF -71.3 (s, 3F, CF₃). m/z (GCMS EI): 264.3 (M⁺). NMR data are consistent with the literature.

4'-methyl-N-phenyl-[1,1'-biphenyl]-4-amine

Synthesised according to the General Procedure A using 4-bromo-N-phenylaniline (248.1 mg, 1 mmol), 4-tolylboronic acid (135.5 mg, 1 mmol), [PdCl₂(dpdpf)] (7.4 mg, 1 mol %) and K₃PO₄ (637.4 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 5 % EtOAc in hexane) to yield a white solid (216.0 mg, 83 %). ¹H NMR (400 MHz, CDCl₃): δH 7.52 (t, 5H, 5 x ArH, J = 8.4 Hz), 7.32 (t, 3H, 3 x ArH, J = 6.9 Hz), 7.26 (d, 3H, 3 x ArH, J = 7.7 Hz), 7.17 (bs, 4H, 4 x ArH), 6.99 (bs, 1H, 1 x ArH), 2.42 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δC 142.5, 141.7, 137.5, 135.8 (2C), 133.4, 129.0 (2C), 128.9 (2C), 127.3 (2C), 125.9 (2C), 120.7 (2C), 117.5 (2C), 20.6. m/z (GCMS EI): 259.4 (M⁺). NMR data are consistent with the literature.

4-methyl-4'-(methylsulfonyl)-1,1'-biphenyl

Synthesised according to the General Procedure A using 1-bromo-4-(methylsulfonyl)benzene (235.4 mg, 1 mmol), 4-tolylboronic acid (135.2 mg, 1 mmol), [PdCl₂(dpdpf)] (7.0 mg, 1 mol %) and K₃PO₄ (635.4 mg, 3 mmol) in 2 mL toluene. The desired product was purified via flash column chromatography (eluting with 0 – 10 % EtOAc in hexane) to yield a white solid (174.1 mg, 71 %). ¹H NMR (400 MHz, CDCl₃): δH 8.02 (d, 2H, 2 x ArH, J = 7.8 Hz), 7.79 (d, 2H, 2 x ArH, J = 7.4 Hz), 7.55 (d, 2H, 2 x ArH, J = 7.4 Hz), 7.33 (d, 2H, 2 x ArH, J = 7.8 Hz), 3.12 (s, SO₂CH₃), 2.46 (s, 3H, CH₃). ¹³C{¹H} NMR (101 MHz, CDCl₃): δC 146.2, 138.3 (2C), 135.7, 129.3 (2C), 127.4 (2C), 127.2 (2C), 126.7 (2C), 44.2, 20.7. m/z (GCMS EI): 246.3 (M⁺). NMR data are consistent with the literature.
**Synthesis of Chalcone Derivatives**

**General Procedure B**

**Chalcone.** In a round bottom flask equipped with a stirrer bar, aldehyde (1 eq.) and ketone (1 eq.) were dissolved in EtOH (14 mL) or a mixture of EtOH (25 mL) and THF (25 mL). Once dissolved, 10% w/v solution of NaOH (6 mL) was added. The mixture was stirred for 5-15 minutes at room temperature and the resulting chalcone was filtered and washed with EtOH (3 x 5 mL) to give a white or off-white solid. GC-MS was carried out to check conversion and crude material was carried through to the next step.

**Allylic Alcohol.** In a round bottom flask equipped with a stirrer bar, chalcone (1 eq.) and CeCl₃·7H₂O (1 eq.) were dissolved in MeOH (10 mL) and THF (50 mL). Once dissolved, the mixture was cooled to 0 °C with an ice bath. At 0 °C, NaBH₄ (1.5 eq.) was slowly added in portions to avoid exothermic reaction. Once all the NaBH₄ was added, the mixture was warmed to room temperature and stirred for 15 minutes. The reaction was neutralised to pH 7 with 1 M HCl and distilled water (100 mL) was added. The mixture was extracted 3 times with Et₂O (3 x 50 mL). The combined organic phases were dried over MgSO₄, which was filtered and the Et₂O removed under vacuum to furnish the allylic alcohol as a white oil. NMR was carried out to check conversion and crude material was carried through to the next step.

**Rearrangement to Saturated Chalcone.** In a microwave vial equipped with a stirrer bar, allylic alcohol (1 eq.), [IrCl(IPr)(COD)] (0.1 mol%) and KOH (10 mol%) were dissolved (KOH suspended) in THF (2 – 4 mL). The reaction was heated in a Biotage Initiator Microwave Synthesiser at 150 °C for 2 – 4 hours. The resulting mixture was filtered through celite and the solvent removed under reduced pressure. ¹H NMR was carried out to check conversion. The desired compound was either:

i. purified via flash column chromatography, eluting with hexane to yield a white or off-white solid

ii. recrystallised from hot hexane and filtered to yield a white or off-white solid

1,3-bis(4-chlorophenyl)propan-1-one

![Chemical Structure]

**Chalcone.** Synthesised according to the General Procedure B using 4'-chloroacetophenone (1.1162 g, 1.20 mL, 7.22 mmol) and 4-chlorobenzaldehyde (1.0141 g, 7.22 mmol) to give an off-white solid (1.9724 g, 99%).

**Allylic Alcohol.** Synthesised according to the General Procedure B using chalcone (1.9724 g, 7.12 mmol), CeCl₃·7H₂O (2.6516 g, 7.12 mmol) and NaBH₄ (0.40410 g, 10.68 mmol) to yield a white oil (0.5384 g, 27%).

**Saturated Chalcone.** Synthesised according to the General Procedure B using allylic alcohol (0.5384 g, 1.93 mmol), [IrCl(IPr)(COD)] (0.0014 g, 0.1 mol%) and KOH (0.0081 g, 10 mol%). The product was purified via flash column chromatography, eluting with hexane to yield a white solid (286.3 mg, 53%). ¹H NMR (400 MHz, CDCl₃): δH 7.89 (d, 2H, 2 x ArH, J = 8.0 Hz), 7.44 (d, 2H, 2 x ArH, J = 8.0 Hz), 7.27 (d, 2H, 2 x ArH, J = 8.0 Hz), 7.18 (d, 2H, 2 x ArH, J = 8.4 Hz), 3.25 (t, 2H, CH₂, J = 7.5 Hz), 3.04 (t, 2H, CH₂, J = 7.5 Hz). ¹³C{¹H} NMR (101 MHz, CDCl₃): δC 197.1, 139.1, 139.0, 134.6, 131.5, 129.3 (2C), 128.9 (2C), 128.5 (2C), 128.1 (2C), 39.6, 28.8. m/z (GCMS EI): 278.0 (M⁺). NMR data are consistent with the literature. ¹³
1-([1,1'-biphenyl]-4-yl)-3-(4-chlorophenyl)propan-1-one

**Chalcone.** Synthesised according to the General Procedure B using 1-([1,1'-biphenyl]-4-yl)ethan-1-one (1.2324 g, 6.27 mmol) and 4-chlorobenzaldehyde (0.8814 g, 6.27 mmol) to give an off-white solid (1.9347 g, 97 %).

**Allylic Alcohol.** Synthesised according to the General Procedure B using chalcone (1.9347 g, 6.07 mmol), CeCl$_3$·7H$_2$O (2.2805 g, 6.07 mmol) and NaBH$_4$ (0.4731 g, 9.11 mmol) to yield a white oil (0.7032 g, 36 %).

**Saturated Chalcone.** Synthesised according to the General Procedure B using allylic alcohol (0.7032 g, 2.19 mmol), [IrCl(IPr)(COD)] (0.0014 g, 0.1 mol%) and KOH (0.0089 g, 10 mol%). The product was purified via recrystallisation from hexane to yield a white solid (469.9 mg, 67 %).

**1H NMR** (400 MHz, CDCl$_3$): $\delta$H $8.06$ (d, 2H, 2 x ArH, $J = 8.0$ Hz), $7.71$ (d, 2H, 2 x ArH, $J = 8.0$ Hz), $7.65$ (d, 2H, 2 x ArH, $J = 7.2$ Hz), $7.50$ (t, 2H, 2 x ArH, $J = 8.0$ Hz), $7.43$ (t, 1H, 1 x ArH, $J = 8.0$ Hz), $7.30$ (d, 2H, 2 x ArH, $J = 8.0$ Hz), $7.23$ (d, 2H, 2 x ArH, $J = 8.0$ Hz), $3.34$ (t, 2H, CH$_2$, $J = 7.4$ Hz), $3.10$ (t, 2H, CH$_2$, $J = 7.8$ Hz).

**13C{1H} NMR** (101 MHz, CDCl$_3$): $\delta$C $197.9$, $145.4$, $139.3$, $139.3$, $135.0$, $131.4$, $129.3$ (2C), $128.5$ (2C), $128.1$ (4C), $127.8$ (2C), $126.8$ (3C), $39.7$, $29.0$. m/z (GCMS EI): 320.1 (M$^+$). NMR data are consistent with the literature.$^{14}$

$1,3$-di([1,1'-biphenyl]-4-yl)propan-1-one

**Chalcone (dibromo).** Synthesised according to the General Procedure B using 4'-bromoacetophenone (1.092 g, 5.46 mmol) and 4-bromobenzaldehyde (1.017 g, 5.46 mmol) to give an off-white solid (1.7970 g, 90 %).

**Allylic Alcohol (dibromo).** Synthesised according to the General Procedure B using chalcone (1.7970 g, 4.88 mmol), CeCl$_3$·7H$_2$O (1.8192 g, 4.88 mmol) and NaBH$_4$ (0.3773 g, 7.98 mmol) to yield a white oil (1.1037 g, 61 %).

**Saturated Chalcone (dibromo).** Synthesised according to the General Procedure B using allylic alcohol (1.1037 g, 3.00 mmol), [IrCl(IPr)(COD)] (0.0022 g, 0.1 mol%) and KOH (0.0126 g, 10 mol%). The product was purified via recrystallisation from hexane to yield a white solid (734.3 mg, 67 %).

**Saturated Chalcone (diphenyl).** Synthesised according to the General Procedure A using dibromo saturated chalcone (734.3 mg, 2.00 mmol), phenyl boronic acid (487.7 mg, 4.00 mmol), [PdCl$_2$(dppf)] (14.9 mg, 1 mol%) and K$_3$PO$_4$ (1.3013 g, 6.00 mmol) in 4 mL 4:1 THF:H$_2$O. The desired product was purified via flash column chromatography, eluting with hexane to give a white solid (502.9 mg, 69 %).

**1H NMR** (400 MHz, CDCl$_3$): $\delta$H $8.09$ (d, 2H, 2 x ArH, $J = 8.5$ Hz), $7.72$ (d, 2H, 2 x ArH, $J = 8.5$ Hz), $7.66$ (d, 2H, 2 x ArH, $J = 7.4$ Hz), $7.61$ (d, 2H, 2 x ArH, $J = 7.4$ Hz), $7.58$ (d, 2H, 2 x ArH, $J = 8.1$ Hz), $7.52$ – $7.43$ (m, 5H, 5 x ArH, $J = 35.9$ Hz), $7.39$ – $7.37$ (m, 3H, 3 x ArH, $J = 8.1$ Hz), $3.41$ (t, 2H, CH$_2$, $J = 8.0$ Hz), $3.18$ (t, 2H, CH$_2$, $J = 7.6$ Hz). **13C{1H} NMR** (101 MHz, CDCl$_3$): $\delta$C $198.3$, $145.3$, $140.5$, $139.9$, $139.4$, $138.7$, $135.1$, $128.5$ (2C), $128.4$ (2C), $128.3$ (2C), $128.2$ (2C), $127.7$ (2C), $126.8$ (4C), $126.6$ (2C), $126.5$ (2C), $39.9$, $29.3$. m/z (GCMS EI): 362.2 (M$^+$).
GC-FID CALIBRATION

The GC-FID apparatus was calibrated for each analyte using a series of standards, accurately prepared, containing varying ratios of internal standard and analyte. In each case, a plot of the relative peak areas versus the molar ratio gave a straight line, and the slope of this line was used as the response factor.

| Substrate                                                                 | Internal Standard | Response Factor |
|---------------------------------------------------------------------------|-------------------|-----------------|
| 4-methyl-1,1′-biphenyl                                                  | n-dodecane        | 0.9947          |
| 4,4′-dimethyl-1,1′-biphenyl                                               | n-dodecane        | 0.9516          |
| 4-methyl-4′-(trifluoromethyl)-1,1′-biphenyl                               | n-dodecane        | 1.0982          |
| methyl 4′-methyl-[1,1′-biphenyl]-4-carboxylate                            | n-dodecane        | 0.7552          |
| N,N,4′-trimethyl-[1,1′-biphenyl]-4-amine                                  | n-dodecane        | 0.2497          |
| 4-methoxy-4′-methyl-1,1′-biphenyl                                        | n-dodecane        | 0.8421          |
| 1-(4′-methyl-[1,1′-biphenyl]-4-yl)ethan-1-one                             | n-dodecane        | 0.7493          |
| (4′-methyl-[1,1′-biphenyl]-4-yl)(phenyl)methanone                         | n-dodecane        | 1.1964          |
| 4′-methyl-[1,1′-biphenyl]-4-carbaldehyde                                 | n-dodecane        | 0.7491          |
| 4-fluoro-4′-methyl-1,1′-biphenyl                                         | n-dodecane        | 0.9598          |
| 4-(difluoromethoxy)-4′-methyl-1,1′-biphenyl                              | n-dodecane        | 1.1663          |
| 4-methyl-4′-(trifluoromethoxy)-1,1′-biphenyl                             | n-dodecane        | 1.1355          |
| 4′-methyl-4-isopropyl-1,1′-biphenyl                                      | n-dodecane        | 1.0987          |
| 4′-methyl-N-phenyl-[1,1′-biphenyl]-4-amine                                | n-dodecane        | 0.7828          |
| N,N-diethyl-4′-methyl-[1,1′-biphenyl]-4-amine                             | n-dodecane        | 0.8638          |
| 2,2,2-trifluoro-1-(4′-methyl-[1,1′-biphenyl]-4-yl)ethan-1-one             | n-dodecane        | 1.0027          |
| 4-methyl-4′-(methylsulfonyl)-1,1′-biphenyl                               | n-dodecane        | 0.7081          |
DATA FROM COMPETITIVE CROSS-COUPLING REACTIONS

Competition reactions carried out between bromobenzene and a selection of substrates of the form \( p-XC_6H_4Br \). Solid components were loaded into a microwave tube equipped with a stir bar, sealed with a septum-fitted crimp-cap, and evacuated and backfilled with argon or nitrogen several times. Liquid reagents and the reaction solvent were added via syringe through the septum. The reactions were then heated, with stirring, for 2 h. After this time, the reaction was cooled to room temperature, and an accurately-known mass of dodecane or tetradecane (depending on the retention times of compounds used) was added. A sample of the solution was then diluted in chloroform for analysis by GC-FID.

### Reactions in Toluene Solution

| Substrate | Product from PhBr | Product from \( p-XC_6H_4Br \) | Total conversion | Selectivity | \( \sigma_p(X) \) |
|-----------|------------------|-------------------------------|------------------|------------|-----------------|
| NMe₂      | 59               | 38                           | 97               | -0.23      | -0.83           |
| NEt₂      | 60               | 54                           | 114              | -0.05      | -0.72           |
| NHPh      | 44               | 45                           | 99               | 0.01       | -0.56           |
| OMe       | 57               | 42                           | 99               | -0.15      | -0.27           |
| i-Pr      | 63               | 33                           | 96               | -0.32      | -0.15           |
| OCF₂H     | 52               | 37                           | 89               | -0.18      | 0.18            |
| OCF₃      | 54               | 40                           | 94               | -0.16      | 0.35            |
| CO₂Me     | 37               | 76                           | 113              | 0.35       | 0.45            |
| CF₃       | 62               | 48                           | 110              | -0.13      | 0.54            |
| SO₂Me     | 22               | 78                           | 100              | 0.56       | 0.72            |
| CHO       | 8                | 96                           | 104              | 0.85       | 0.42            |
| C(O)Ph    | 11               | 75                           | 86               | 0.75       | 0.43            |
| C(O)Me    | 15               | 95                           | 110              | 0.74       | 0.50            |
| C(O)CF₃   | 5                | 72                           | 77               | 0.88       | 0.80            |

### Reactions in THF/Water Solution

| Substrate | Product from PhBr | Product from \( p-XC_6H_4Br \) | Total conversion | Selectivity | \( \sigma_p(X) \) |
|-----------|------------------|-------------------------------|------------------|------------|-----------------|
| NMe₂      | 37               | 58                           | 95               | 0.22       | -0.83           |
| NEt₂      | 43               | 20                           | 63               | -0.37      | -0.72           |
| NHPh      | 42               | 24                           | 66               | -0.28      | -0.56           |
| OMe       | 38               | 23                           | 61               | -0.25      | -0.27           |
| i-Pr      | 38               | 16                           | 54               | -0.40      | -0.15           |
| OCF₂H     | 52               | 32                           | 84               | -0.24      | 0.18            |
| OCF₃      | 50               | 28                           | 78               | -0.33      | 0.35            |
| CO₂Me     | 32               | 38                           | 70               | 0.09       | 0.45            |
| CF₃       | 38               | 35                           | 73               | -0.05      | 0.54            |
| SO₂Me     | 40               | 30                           | 70               | -0.15      | 0.72            |
| CHO       | 0                | 108                          | 108              | 1.00       | 0.42            |
| C(O)Ph    | 6                | 58                           | 64               | 0.83       | 0.43            |
| C(O)Me    | 5                | 95                           | 100              | 0.91       | 0.50            |

\(a\) – all values quoted as an average of two replicate reactions

N/A – ketone undergoes hydration
ENERGIES AND COORDINATES FROM DFT CALCULATIONS

- Calculations were carried out using Gaussian09 Rev. D01 using desktop machines and the ARCHIE-WeSt High Performance Computer.
- The B3LYP functional was used with Grimme’s D3 corrections to account for dispersive interactions.¹⁻⁷
- Solvation (toluene) was treated using the SMD implicit solvation model.⁸
- The LANL2TZ(f) basis set was used for Ni and Fe, LANL2DZ(d,p) was used for Br, and 6-31G(d) was used for all other atoms for optimisation.⁹⁻¹²
- Geometry optimisation was carried out in solvent, without symmetry constraints.
- The nature of each stationary point was verified using frequency calculations.
- Energies were then refined using single point energy calculations with 6-311+G(d,p) for all atoms except Ni, Fe, and Br, which were treated as noted above.
- Coordinates can be found in a separate Supporting Information file specifically for this content.
- The energies of intermediates A, B, and C for a series of substrates are tabulated on this page.
- Energies are tabulated on the following pages in Hartrees. Electronic energies (E), and corrections to enthalpy (H corr) and free energy (G corr) are reported here with the smaller basis set (6-31G(d) on H/C/N/O/F/P), along with electronic energies using the larger 6-311+G(d,p) basis set on these atoms (denoted E').

| p-XC₄H₄Br | σ_p | η²-complex (A) | OA TS (B) | [Ni(Ar)Br(dppf)] (C) | ΔG¹ α |
|-----------|-----|----------------|-----------|----------------------|-------|
| X = SO₂Me | 0.72| -8.0           | 1.1       | -25.3                | 9.1   |
| X = CF₃   | 0.54| -6.4           | 1.9       | -24.3                | 8.3   |
| X = Ac    | 0.50| -6.9           | 2.2       | -23.4                | 9.1   |
| X = CO₂Me | 0.45| -6.0           | 2.1       | -22.6                | 8.1   |
| X = CHO   | 0.42| -8.5           | 0.8       | -24.5                | 9.4   |
| X = OCF₃  | 0.35| -6.0           | 3.2       | -23.9                | 9.3   |
| X = H     | 0   | -2.6           | 4.7       | -21.8                | 7.3   |
| X = OMe   | -0.27| -0.5           | 5.8       | -18.6                | 6.2   |
| X = NHPh  | -0.56| -2.9           | 4.6       | -18.8                | 7.4   |
| X = NMe₂  | -0.83| -1.1           | 6.3       | -17.2                | 7.4   |

a) Defined as the difference in energy between A and C.
| μ      | [Benzene] | SO₂Me | CF₃ | COMe | CO₂Me | CHO |
|--------|-----------|-------|-----|------|-------|-----|
| σₚ    | 0.72      | 0.54  | 0.5 | 0.45 | 0.42  |     |
| E     | -232.256720814 | -832.727169108 | -581.869595304 | -397.486124379 | -472.717048769 | -358.159249082 |
| Hₜ     | 0.106172000  | 0.140283000  | 0.105610000  | 0.138462000  | 0.145097000  | 0.108648000 |
| Gₜ     | 0.073387000  | 0.090432000  | 0.058212000  | 0.092200000  | 0.096084000  | 0.066092000 |
| H     | -232.150548814 | -832.58686108  | -581.76395304  | -397.347662379 | -472.571951769 | -358.050619762 |
| G     | -232.18333814  | -832.63737108  | -581.81138304  | -397.39294379  | -472.620964769 | -358.093157082 |
| H     | -14567.668775084 | -52245.158960929 | -365062.412410254 | -29653.376881719 | -22468.014350350 | -22470.68463525 |
| G     | -14569.21673190  | -52248.440935717  | -365092.15403045  | -29657.133003568  | -22470.68463525  | -22470.68463525 |
| H     | -145719.090250992 | -52255.623695682 | -365175.169344166 | -29662.371165544 | -22474.073876569 | -22474.073876569 |
| G     | -145739.66314907  | -52258.903567047  | -365204.912038215  | -29665.178384044  | -22474.073876569 | -22474.073876569 |

| kJ/mol | Hₜ     | Gₜ     |     |     |     |     |
|--------|-------|-------|-----|-----|-----|-----|
| E     | -2520.387200460 | -3120.880169300 | -2870.188113600 | -2685.634914720 | -2760.865643300 | -2646.30845950 |
| Hₜ     | 0.660970000 | 0.691370000 | 0.661200000 | 0.692850000 | 0.701034000 | 0.664514000 |
| Gₜ     | 0.549576000 | 0.570303000 | 0.538513000 | 0.571746000 | 0.576422000 | 0.545317000 |
| H     | -2519.726304600 | -3120.184032300 | -2869.357611360 | -2684.940629720 | -2760.164093000 | -2645.64431950 |
| G     | -2519.837624460 | -3120.309866300 | -2869.480289360 | -2685.063186720 | -2760.289213000 | -2645.763682950 |
| H     | -158115.081499960 | -195794.005917700 | -180054.854242100 | -168482.682276830 | -173209.424135260 | -166016.945889370 |
| G     | -158121.982290 | -195804.022919 | -180062.7027677 | -168490.576660 | -173210.673746 | -166024.743131 |

| kcal | Hₜ     | Gₜ     |     |     |     |     |
|------|-------|-------|-----|-----|-----|-----|
| E     | -2520.387200460 | -3120.880169300 | -2870.188113600 | -2685.634914720 | -2760.865643300 | -2646.30845950 |
| Hₜ     | 0.660970000 | 0.691370000 | 0.661200000 | 0.692850000 | 0.701034000 | 0.664514000 |
| Gₜ     | 0.549576000 | 0.570303000 | 0.538513000 | 0.571746000 | 0.576422000 | 0.545317000 |
| H     | -2519.726304600 | -3120.184032300 | -2869.357611360 | -2684.940629720 | -2760.164093000 | -2645.64431950 |
| G     | -2519.837624460 | -3120.309866300 | -2869.480289360 | -2685.063186720 | -2760.289213000 | -2645.763682950 |
| H     | -158115.081499960 | -195794.005917700 | -180054.854242100 | -168482.682276830 | -173209.424135260 | -166016.945889370 |
| G     | -158121.982290 | -195804.022919 | -180062.7027677 | -168490.576660 | -173210.673746 | -166024.743131 |

| Grel | 0.0 | -10.6 | -7.3 | -8.4 | -7.3 | -9.7 |
|        | Small Basis | Large Basis | Hartrees | kcal | kcal | Hartrees | kcal | kcal | Hartrees | kcal | kcal | Hartrees | kcal | kcal | Hartrees | kcal |
|--------|-------------|-------------|----------|------|------|----------|------|------|----------|------|------|----------|------|------|----------|------|
|        | OCF₃       | H           | OMe      | NHPH | NMe₂ |
|        | σₚ        | 0.35        | 0        | -0.27 | -0.56 | -0.83 |
| Arene  |            |             |         |       |      |         |      |      |         |      |      |         |      |      |         |      |
| E      | -657.087443715 | 244.832936134 | -359.358545579 | -531.249941422 | -378.808962646 |
| H corr | 0.110681000    | 0.097386000   | 0.132758000   | 0.201136000   | 0.175255000   |
| G corr | 0.060866000    | 0.059788000   | 0.089051000   | 0.148319000   | 0.127395000   |
| H      | -656.976762715 | -244.735550134 | -359.225787579 | -531.048805422 | -376.633707646 |
| G      | -657.026577715 | -244.773148134 | -359.269494579 | -531.101622422 | -376.81567646 |
|        | -412259.142801512 | -153573.876333687 | -225417.585010934 | -333238.156558688 | -237596.28723611 |
| H      | -412290.402185960 | -153597.469434890 | -225445.011567514 | -333271.299726576 | -237626.271327037 |
| G      | -412385.518763671 | -153614.19067395 | -225480.03102682 | -333328.493595029 | -237660.633996209 |
|        | -412416.778148119 | -153637.783168598 | -225507.461659262 | -333361.636762917 | -237690.666599635 |
|        |             |             |         |       |      |         |      |      |         |      |      |         |      |      |         |      |
|        | n°-Ips/orthio-complex |         |       |       |      |         |      |      |         |      |      |         |      |      |         |      |
| E      | -2945.231076650 | -2532.971304160 | -2647.493273320 | -2819.391392120 | -2666.948327140 |
| H corr | 0.666165000    | 0.652631000   | 0.687881000   | 0.756907000   | 0.730644000   |
| G corr | 0.539214000    | 0.537172000   | 0.566085000   | 0.627999000   | 0.606832000   |
| H      | -2944.564911650 | -2532.318673160 | -2646.805392320 | -2818.636222120 | -2666.217683140 |
| G      | -2944.691862650 | -2532.435126160 | -2646.921788320 | -2818.765140210 | -2666.341954150 |
|        | -1847742.37868350 | -1589053.95895010 | -1660895.459515090 | -1768720.939471440 | -1673076.855916680 |
| H      | -1847822.041824 | -1589126.410211 | -1660971.887659 | -1768801.830463 | -1673154.549120 |
| G      | -1847850.346605 | -1589376.498392 | -1661290.237869 | -1769017.859794 | -1673393.753893 |
|        | -1848201.99404102 | -1589419.77897948 | -1661287.49107654 | -1769144.68441417 | -1673471.447096 |
| G rel  |       -6.6       |         -3.3     |       -1.4     |      -4.4     |      -2.1     |
| $\sigma_p$ | $SO_2Me$ | $CF_3$ | $COMe$ | $CO_2Me$ | $CHO$ |
|------|--------|--------|--------|---------|-------|
| 0.72 | -3120.86698347 | -2870.00637787 | -2685.61999239 | -2760.85059089 | -2646.29413396 |
| 0.54 | 0.69555000 | 0.6604400 | 0.69299800 | 0.69957800 | 0.66315900 |
| 0.5  | 0.57085800 | 0.53651200 | 0.56987800 | 0.57343600 | 0.54291600 |
| 0.45 | -3120.29612547 | -2869.92629464 | -2685.44084147 | -2760.68928648 | -2646.13437907 |
| 0.42 | -1957937.13500659 | -1800541.75768680 | -1684817.12597807 | -1732020.91025917 | -1660158.50149526 |

**Oxidative Addition TS**

| $\eta_2$ to TS |
|----------------|
| Small Basis |
| Hartrees |
| Large Basis |
| hartrees | kcal |
| $E$ | -3121.42235647 | -2870.58673864 |
| $H_{corr}$ | 0.69555000 | 0.6604400 |
| $G_{corr}$ | 0.57085800 | 0.53651200 |
| $H$ | -3120.29612547 | -2869.92629464 |
| $G$ | -1958015.38041792 | -1800619.52619093 |
| $G_{rel}$ | -1.3 | -0.1 |

| Large Basis |
| Hartrees | kcal |
| $E$ | -3120.72680647 | -2869.92629464 |
| $H$ | -3120.85149847 | -2870.05022664 |
| $G$ | -1958285.63682569 | -1800905.93956832 |
| $G_{rel}$ | -1.3 | -0.1 |

| $\eta_2$ to TS |
|----------------|
| Large Basis |
| kcal |
| $\Delta G^1$ | 8.6 | 6.5 | 8.2 | 7.6 | 7.8 |
| $\Delta G^2$ | 9.3 | 7.1 | 8.3 | 7.2 | 8.3 |
|                | OCF₃ | H    | OMe  | NHPh | NMe₂  |
|----------------|------|------|------|------|-------|
|                |      |      |      |      |       |
| Oxidative Addition TS |      |      |      |      |       |
|                |      |      |      |      |       |
|                |      |      |      |      |       |
| Small Basis    |      |      |      |      |       |
| E              | -2945.22124005 | -2532.96360392 | -2647.48692276 | -2819.38002048 | -2666.938074 |
| Hcorr          | 0.66530400 | 0.65171500 | 0.68709800 | 0.75558300 | 0.729564 |
| Gcorr          | 0.53758300 | 0.53523500 | 0.56419900 | 0.62558500 | 0.604492 |
| H              | -2944.55593605 | -2532.31188892 | -2646.79982476 | -2818.62443748 | -2666.208510 |
| G              | -2944.68365705 | -2532.42836892 | -2646.92272376 | -2818.75443548 | -2666.333582 |
| Grel           | -0.4 | 1.3  | 2.4  | 2.7  | 3.8  |
| ΔG¹            | 5.1  | 3.6  | 2.8  | 6.7  | 5.0  |
| Large Basis    |      |      |      |      |       |
| E              | -2945.82509057 | -2533.42949762 | -2647.98827832 | -2819.92577764 | -2667.441544 |
| H              | -2945.15978657 | -2532.77778262 | -2647.30118032 | -2819.17019464 | -2666.711980 |
| G              | -2945.28750757 | -2532.89426262 | -2647.42407932 | -2819.30019264 | -2666.837052 |
| Grel           | -0.4 | 1.3  | 2.4  | 2.7  | 3.8  |
| ΔG¹            | 6.2  | 4.6  | 3.8  | 7.1  | 5.9  |

η₂ to TS

|                |      |      |      |      |       |
| Small Basis    |      |      |      |      |       |
| ΔG¹            | 5.1  | 3.6  | 2.8  | 6.7  | 5.0  |
| Large Basis    |      |      |      |      |       |
| ΔG¹            | 6.2  | 4.6  | 3.8  | 7.1  | 5.9  |
|       | Oxidative Addition Product |       |       | Coordination to C=O |
|-------|---------------------------|-------|-------|---------------------|
|       | Small Basis               | Large Basis |       |                     |
|       | Hartrees                  | Hartrees |       |                     |
|       | kcal                      | kcal    |       |                     |
|       |                           |         |       |                     |
|       |                           |         |       |                     |
| E    | -3120.915108              | -3121.473028 |       |                     |
| H_{corr} | 0.697071                  | 0.570613 |       |                     |
| G_{corr} | 0.37884                  | 0.537884 |       |                     |
| H    | -3120.218037              | -3120.34495 |       |                     |
| G    | -3120.218037              | -3120.34495 |       |                     |
| H    | -195796.379213            | -195804.732806 |       |                     |
| G    | -195796.379213            | -195804.732806 |       |                     |
| G_{rel} | -33.3                     | -33.3 |       |                     |
| COMe | 0.5                       | 0.5     |       |                     |
| CO_{2}Me | 0.45                     | 0.45 |       |                     |
| CHO  | 0.42                      | 0.42    |       |                     |
| COCF_{3} | 0.5                      | 0.5     |       |                     |
| COPh | 0.42                      | 0.42    |       |                     |

S22
| Coordination to Heteroatom | Small Basis | Large Basis |
|-----------------------------|-------------|-------------|
|                             | Hartrees    | kcal        |
|                             | Hartrees    | kcal        |
| $E$                         | -3120.854   | -3121.411   |
| $H_{\text{corr}}$           | 0.696       | -1957928.3  |
| $G_{\text{corr}}$           | 0.567       | -1958009.1  |
| $H$                         | -3120.157   | -3120.714   |
| $G$                         | -3120.286   | -3120.843   |
| $H_{\text{corr}}$           | 0.758       | -1958277.9  |
| $G_{\text{corr}}$           | 0.630       | -1958358.7  |
| $H$                         | -2819.384   | -2819.930   |
| $G$                         | -2818.626   | -2819.300   |
| $H_{\text{corr}}$           | 0.731       | -1768714.5  |
| $G_{\text{corr}}$           | 0.606       | -1768794.7  |
| $H$                         | -2666.939   | -2666.714   |
| $G$                         | -2666.208   | -2666.334   |
| $H_{\text{corr}}$           | 0.711       | -1673070.9  |
| $G_{\text{corr}}$           | 0.606       | -1673149.6  |
| $H$                         | -2666.334   | -2666.445   |
| $G$                         | -2666.334   | -2666.839   |
| $H_{\text{corr}}$           | 0.731       | -1673388.2  |
| $G_{\text{corr}}$           | 0.606       | -1673466.9  |
| $G_{\text{rel}}$            | 3.9         | 2.9         |

$\sigma_p$ values:
- $SO_2Me$: 0.72, $NHPh$: -0.56, $NMe_2$: -0.83
DATA FROM ROBUSTNESS SCREENING

A microwave tube equipped with a stir bar was charged with 7 (5 mol%), K₃PO₄ (3 equiv.), p-tolB(OH)₂ (1.1 equiv.) and the additive (if solid). The tube was sealed with a crimp cap, and evacuated and backfilled with nitrogen or argon. 4-(Trifluoromethyl)bromobenzene was added via syringe (0.25 mmol, 1 equiv.), followed by the additive (if liquid), anhydrous toluene (1 mL), and degassed distilled water (10 equiv.). The reaction was heated to 85 °C with stirring for 2 h. Upon cooling, the tube was opened, a known mass of tetradecane or dodecane was added, and the mixture was stirred briefly. A sample was withdrawn, diluted with chloroform, and analysed by GC-FID.

| Additive              | Conversion (%) | Additive Remaining (%) |
|-----------------------|----------------|------------------------|
|                       | Replicate 1    | Replicate 2    | Average | Replicate 1 | Replicate 2 |
| None                  | 88             | 93             | 88      | N/A         | N/A         |
| Phenyl acetate        | 75             | 81             | 78      | 60          | 82          |
| Methyl benzoate       | 87             | 89             | 88      | 91          | 98          |
| Benzamide             | 86             | 87             | 86      | 0 a         | 0 a         |
| Benzophenone          | 33             | 43             | 38      | 100         | 100         |
| Benzoic acid          | 11             | 13             | 12      | 98          | 100         |
| 2,2,2-Trifluoroacetophenone | 1           | 1              | 1       | 85          | 88          |
| Acetophenone          | 73             | 83             | 78      | 92          | 95          |
| Diphenylamine         | 72             | 81             | 77      | 100         | 100         |
| Anisole               | 82             | 84             | 83      | 100         | 100         |
| N,N-Dimethylaniline   | 81             | 90             | 86      | 97          | 100         |
| Methyl phenyl sulfone | 85             | 88             | 87      | 7           | 8           |

a) Analysis of a control reaction without a nickel catalyst also shows no recovery of the additive.
NMR SPECTRA

4-methyl-4'-{(trifluoromethyl)-1,1'-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
Methyl 4'-methyl-[1,1'-biphenyl]-4-carboxylate

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
**N,N,4′-trimethyl-[1,1′-biphenyl]-4-amine**

\(^1\)H NMR (400 MHz, CDCl\(_3\))

\(^{13}\)C\(^{(1}H\)) NMR (101 MHz, CDCl\(_3\))
4-methoxy-4'-methyl-1,1'-biphenyl

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \text{)} \]

\[ ^{13}C\{^1H\} \text{ NMR (101 MHz, CDCl}_3 \text{)} \]
4'-methyl-[1,1'-biphenyl]-4-carbaldehyde

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
1-(4'°-methyl-[1,1°'-biphenyl]-4-yl)ethan-1-one

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
(4'-methyl-[1,1'-biphenyl]-4-yl)(phenyl)methanone

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C$^1$H NMR (101 MHz, CDCl$_3$)
4-fluoro-4’-methyl-1,1'-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C$^1$H NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$)
4-(difluoromethoxy)-4'-methyl-1,1'-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
4-methyl-4’-(trifluoromethoxy)-1,1’-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
4’-methyl-4-isopropyl-1,1’-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
N,N-diethyl-4'-methyl-[1,1'-biphenyl]-4-amine

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
2,2,2-trifluoro-1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
4'-methyl-N-phenyl-[1,1'-biphenyl]-4-amine

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
4-methyl-4'-(methylsulfonyl)-1,1'-biphenyl

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
1,3-bis(4-chlorophenyl)propan-1-one

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
1-([1,1'-biphenyl]-4-yl)-3-(4-chlorophenyl)propan-1-one

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
1,3-di([1,1'-biphenyl]-4-yl)propan-1-one

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$)
REFERENCES

1. G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164-4172.
2. E. A. Standley, S. J. Smith, P. Müller and T. F. Jamison, *Organometallics*, 2014, **33**, 2012-2018.
3. G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176-2179.
4. S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules and D. J. Nelson, *Organometallics*, 2017, **36**, 1662-1672.
5. S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104-154119.
6. U. Ryde, R. A. Mata and S. Grimme, *Dalton Trans.*, 2011.
7. N. Fey, B. M. Ridgway, J. Jover, C. L. McMullin and J. N. Harvey, *Dalton Trans.*, 2011, **40**, 11184-11191.
8. A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378-6396.
9. P. J. Hay and W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 299-310.
10. W. R. Wadt and P. J. Hay, *J. Chem. Phys.*, 1985, **82**, 284-298.
11. P. J. Hay and W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 270-283.
12. C. E. Check, T. O. Faust, J. M. Bailey, B. J. Wright, T. M. Gilbert and L. S. Sunderlin, *J. Phys. Chem. A*, 2001, **105**, 8111-8116.
