Origins of High Catalyst Loading in Copper(I)-Catalyzed Ullmann-Goldberg C-N Coupling Reactions

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1. General methods and materials

1.1 Reagents and materials

Unless otherwise stated, all reactions were performed under an atmosphere of nitrogen, using flame-dried glassware. Reactions were set up using air-sensitive techniques on a Schlenk manifold or in a nitrogen-filled glovebox. Anhydrous solvents were dried by passing the solvent over activated alumina via the Dow-Grubbs solvent system (Pure Solv™) unless otherwise specified. Anhydrous N,N-dimethylformamide and acetonitrile (99.8%) were purchased from Sigma Aldrich. Reaction solvents were degassed by bubbling of nitrogen through for a minimum of 30 minutes. Anhydrous NMR solvents for air sensitive products were degassed using three freeze-thaw cycles. All other reagents were obtained from commercial suppliers and used without further purification.

1.2 General analytical data

1H and 13C NMR data were performed using deuterated chloroform (CDCl₃), unless otherwise stated and recorded on either an Avance 300 (Bruker Biospin GmbH), or Avance 500 (Bruker Biospin GmbH). All kinetic data was obtained on the Avance 500 and 133Cs NMR was run on an Avance 400 or 500 MHz spectrometer. Microanalysis data was obtained by Tanya Marinko-Covell of the University of Leeds. Hydrogenation of amides was performed using a 300 mL Parr Pressure Reactor. High resolution mass spectra were collected on a Bruker Daltonics (microTOF) instrument operating in the electrospray mode. GC/MS data was obtained using Agilent HP2890 series GC system, with an Agilent HP5973 mass selective detector on EI mode. Column chromatography was performed using Geduran© Si 60 silica gel with the stated solvents. FT-IR spectroscopy measurements were taken on a Bruker Alpha Platinum-ATR. HPLC data was collected from an Agilent 1200 HPLC system using a 30 x 4.6 mm Waters Acquity BEH C18 1.7 µm column and UV/Vis detector set at 285 nm. GC data was obtained from an Agilent Technologies 7890B gas chromatograph using an Agilent J&W HP-5 GC Column, 30 m, 0.32 mm, 0.25 µm.

1.3 Base suppliers, purity, and drying protocols

Cesium carbonate was obtained from three individual sources; Sigma Aldrich (99 %, Lot # BCBP3311V), Acros Organics (99.5 %, Lot # A0359643) and Chemetall (Milled, D₅₀ = 20 µm, D₉₀ = 50 µm, Bx # 27091B032) and oven dried at 80 °C before being used. Prior to SEM analysis, all bases were dried at 75 °C for a period of at least 24 hours, ensuring consistency between samples.

2. Synthesis of organic compounds

2.1 Tetrabutylammonium adipate (TBAA)

![Tetrabutylammonium adipate](image)

Tetrabutylammonium adipate was prepared based on literature procedures.¹ Tetrabutylammonium hydroxide (1M solution in MeOH, 3.4 mL, 3.42 mmol) was added with adipic acid (250 mg, 1.71 mmol) in a round bottomed flask with activated 4 Å molecular sieves. The reaction was stirred under an atmosphere of nitrogen at room temperature for 18 hours and upon completion, the solution was filtered over a short pad of
Celite with 50 mL MeOH. The majority of the solvent was removed using a rotary evaporator and the resulting thick slurry dried on a Schlenk line to give a white solid. The white solid was dried further under vacuum for 9 hours and stored under a nitrogen atmosphere without further purification.

$^1$H NMR (500 MHz, D$_2$O) $\delta$ = 3.21 (t, $J$ = 9.0 Hz, 16H), 2.20 (m, 4H), 1.66 (m, 16H), 1.56 (m, 4H), 1.39 (dt, $J$ = 21.2, 7.3 Hz, 16H), 0.93 (t, $J$ = 7.3 Hz, 24H).

Literature Values: $^1$H NMR (300 MHz, D$_2$O): $\delta$ 3.12 (t, $J$ = 9.1 Hz, 16H), 2.11 (m, 4H), 1.54 (m, 16H), 1.43 (m, 4H), 1.27 (dt, $J$ = 21.6, 7.2 Hz, 16H), 0.89 (t, $J$ = 7.2 Hz, 24H).

2.2 $N,N$-Dimethylglycine

Synthesis was performed as outlined by Makriyannis et al. $^2$ A mixture of glycine (10.0 g 0.133 mmol), formaldehyde (37% w/v in H$_2$O, 32.0 mL, 0.361 mmol) and palladised charcoal (10% w/w Pd, 4.0 g) was stirred in ethanol (150 mL) under 3 bar H$_2$ using a Parr pressure reactor for 12 hours. The resulting mixture was filtered over Celite with ethanol and evaporated to dryness. The product was crystallised from ethanol/diethyl ether and dried in vacuo, yielding of $N,N$-dimethylglycine as a white solid (11.8 g, 86%).

$^1$H NMR (500 MHz, D$_2$O) $\delta$ = 3.73 (s, 2H), 2.94 (s, 6H); $^{13}$C NMR (125 MHz, D$_2$O) $\delta$ = 60.0 (C-2), 43.7 (C-1); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3386, 3025, 1607 (C=O), 1470, 1391, 1356; HRMS (ESI) $m/z$ [M+Na]$^+$: Calcd for C$_4$H$_9$NNaO$_2$: 126.0531. Found: 126.0525.

Literature values: $^2$ $^1$H NMR (D$_2$O) $\delta$ = 3.96 (s, 2H), 2.80 (s, 6H)

2.3 Synthesis of sodium $N,N$-dimethylglycinate

NaH (60 % dispersion in mineral oil, 77.6 mg, 1.94 mmol) was weighed out into a flame-dried round bottom flask kept under nitrogen. The NaH was washed with three 6 ml batches of degassed pentane and the pentane removed via syringe. 2.5 ml of anhydrous THF was added at the NaH stirred as a suspension before being cooled down to 0 °C. $N,N$-dimethylglycine (200 mg, 1.94 mmol) was suspended in 2.5 ml MeCN and added slowly to the NaH, the reaction was stirred at 0 °C until no further bubbles were seen to evolve. The colourless solution was allowed to heat to room temperature and stirred for 30 minutes further before the solvent was removed in vacuo. The off-white solid was washed three times with degassed MeCN, giving 80 mg (33 % yield) of an insoluble white solid was obtained and stored in an N$_2$ filled glovebox. $^1$H NMR spectroscopy in $d_3$-MeCN showed no starting material peaks, indicating all L$^1$H had reacted. Further characterization of this salt was unsuccessful due to its very low solubility in organic solvents.
2.4 Synthesis of sodium pyrolidinide

\[
\begin{align*}
\text{N} & \quad \text{Na}^+ \\
\end{align*}
\]

NaH (60 % dispersion in mineral oil, 1.048 g, 26.2 mmol) was weighed out into a flame-dried round bottom flask kept under nitrogen. The NaH was washed with three 10 ml batches of degassed pentane and the pentane removed via syringe. 20 ml of anhydrous THF was added at the NaH stirred as a suspension before being cooled down to 0 °C. 2-Pyrrolidinone (2.0 ml, 26.2 mmol) was added dropwise and the reaction stirred at 0 °C until no further bubbles were observed to evolve. The colourless solution was allowed to warm up to room temperature and stirred for 30 minutes further before the solvent was removed in vacuo. 2.35 g (84 % yield) of an insoluble white solid was obtained and stored in an N\(_2\) filled glovebox. \(^1\)H NMR spectroscopy in \(d_3\)-MeCN showed no starting material peaks, indicating all 2-pyrrolidinone had reacted.

2.5 Synthesis of 1-(4-methoxyphenyl)-piperidine

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\end{align*}
\]

CuI (19.0 mg, 0.1 mmol), \(N,N\)-dimethylglycine (20.8 mg, 0.2 mmol), 4-idoanisole (236.0 mg, 1.0 mmol) and tetrabutylammonium adipate (942.0 mg, 1.5 mmol) were added to a flame dried Schlenk flask. The vessel was evacuated and backfilled with nitrogen three times before piperidine (158.0 µL, 1.5 mmol) and 4 mL of degassed anhydrous DMF were added by syringe. The Schlenk flask was sealed and the reaction stirred at 90 ºC for 71 hours. Upon completion, the reaction mixture was filtered over a short pad of silica with ethyl acetate and evaporated to give the organic compounds in DMF. The resulting solution was dilute with 50 mL water and extracted with 4 x 20 mL of diethyl ether, with the organic layers combined and evaporated to dryness to give the crude product. The crude product was purified by column chromatography, eluting with a 2:1 mixture of petroleum ether and diethyl ether (R\(_f\) = 0.82) to yield 1-(4-methoxyphenyl)piperidine as a yellow oil (73 mg, 38 % yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 6.92 (d, J = 9.0 \text{ Hz}, 2H), 6.83 (d, J = 9.1 \text{ Hz}, 2H), 3.77 (s, 3H), 3.02 (t, J = 5.4 \text{ Hz}, 4H), 1.72 (p, 5.5 Hz, 4H), 1.54 (p, 6.0 Hz, 4H); \(^{13}\)C NMR (125 MHz CDCl\(_3\)) \(\delta = 153.5, 146.9, 118.8, 114.4, 55.6, 52.3, 26.1, 24.2; \)HRMS (ESI) \(m/z [M+H]^+\): Calcd for C\(_{12}\)H\(_{18}\)NO: 192.1388. Found: 192.1394.

Literature values: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 6.91 (d, J = 9.0 \text{ Hz}, 2H), 6.82 (d, J = 9.0 \text{ Hz}, 2H), 3.76 (s, 3H), 3.02 (t, J = 5.5 Hz, 4H), 1.72 (p, J = 5.7 Hz, 4H), 1.54 (p, J = 6.1 Hz, 2H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 153.5, 146.9, 118.7, 114.3, 55.5, 52.3, 26.1, 24.2.\)
2.6 Synthesis of 1-(4-methoxyphenyl)pyrrolidin-2-one

Cul (19.0 mg, 0.1 mmol), N,N-dimethylglycine (20.6 mg, 0.2 mmol), Cs₂CO₃ (489.0 mg, 1.5 mmol) and 4-iodoanisole (234.0 mg, 1 mmol) were added to a flame dried Schlenk flask. 3 vacuum purge and nitrogen flush cycles were performed before addition of 2-pyrrolidinone (114 µl, 1.5 mmol) and 5 mL DMF and heated to 90 °C for 16 hours. The resulting brown liquid was filtered through a short silica plug using 50 mL ethyl acetate and concentrated to give the crude product, which was purified by column chromatography, eluting with a 7 : 3 mixture of n-hexane and ethyl acetate (Rᵣ = 0.74) to yield 1-(4-methoxyphenyl)pyrrolidin-2-one as a cream coloured solid (172.9 mg, 90% yield).

¹H NMR (500 MHz, CDCl₃) δ = 7.49 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 3.83 (t, J = 7.1 Hz, 2H), 3.80 (s, 3H), 2.58 (t, J = 8.0 Hz, 2H), 2.15 (qn, J = 7.8 Hz, 2H); ¹³C NMR (125 MHz CDCl₃) δ = 173.9, 156.6, 132.7, 121.9, 114.1, 55.5, 49.2, 32.5, 18.1; νmax (neat)/cm⁻¹ 2951, 1883, 1677 (C=O), 1508, 1391, 1223, 1125; Anal. Caled for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.20; H, 6.80; N, 7.20; HRMS (ESI) m/z [M+H]+: Caled for C₁₁H₁₃NNaO₂: 214.0844. Found: 214.0845.

Literature values:¹ ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 3.83 (t, J = 7.1 Hz, 2H), 3.80 (s, 3H), 2.59 (t, J = 8.1 Hz, 2H), 2.15 (qn, J = 7.6 Hz, 2H); ¹³C NMR (100MHz, CDCl₃): δ = 173.9, 156.6, 132.6, 121.9, 114.0, 55.5, 49.2, 32.5, 18.0.
3. NMR spectra of organic compounds

3.1 1-(4-Methoxyphenyl)pyrrolidin-2-one
3.2 1-(4-Methoxyphenyl)-piperidine
3.3 \( N,N\text{-Dimethylglycine} \)

![Diagram of N,N-Dimethylglycine]
3.4 Tetrabutylammonium adipate

\[ 2 \times \text{[NBu}_4^+ \text{]} \]

3.5 4-Methoxyphenol

\[ \text{MeO} \]

\[ \text{OH} \]
4. **In situ** \(^1\)H NMR kinetic study

4.1 General procedure for NMR experiments

Cul (1.2 mg, 0.0063 mmol) was added with \(N,N\)-dimethylglycine (1.3 mg, 0.0126 mmol) to a dry NMR tube with a Young valve and taken in to a nitrogen filled glovebox. Inside the glovebox, a solution of TBAA (59.0 mg, 0.0938 mmol) in \(d_7\)-DMF (0.25 mL) followed by piperidine (9.0 \(\mu\)L, 0.0911 mmol) were added and the reaction initiated when a solution of 4-iodoanisole (14.6 mg, 0.0624 mmol) in \(d_7\)-DMF (0.25 mL) was added. The NMR tube was removed and shaken to ensure homogeneity before the NMR experiment began.

4.2 Procedure for obtaining kinetic data

The NMR sample is prepared as outlined above and is then placed into the NMR machine. A scan is taken at 25 ºC to measure \(t_0\) for the reaction, before the temperature probe is heated to the desired temperature (70 ºC). After this temperature is reached, an NMR spectrum is collected every 10 minutes.

The resulting spectra are processed using the TopSpin\textsuperscript{TM} package and the integrals of all aromatic species (6 – 8 ppm) are normalised to 100. The conversions are noted for each known compound and the concentration of each species calculated based on the starting concentration of aryl iodide. Rate data were generated using differential function in Origin Pro 9.0.

4.3 Reaction conditions for **in situ** study

|                  | MW   | Density | Standard | 2x [2] | 2x [TBAA] | 2x [L\(^1\)H] | Product Inhibition | Same “Excess” | 0.5x Cul/L\(^1\)H |
|------------------|------|---------|----------|--------|-----------|----------------|-------------------|---------------|-----------------|
| Cul (mg)         | 190.44 |         | 1.2      | 1.2    | 1.2       | 1.2            | 1.2               | 1.2           | 0.6             |
| DMG (mg)         | 103.12 |         | 1.3      | 1.3    | 1.3       | 2.6            | 1.3               | 1.3           | 0.7             |
| TBAA (mg)        | 629.07 |         | 59.0     | 59.0   | 118.0     | 59.0           | 59.0              | 39.3          | 59.0            |
| DMF (µl)         | 500   |         | 500      | 500    | 500       | 500            | 500               | 500           | 500             |
| 4-Iodoanisole (mg) | 234.03 |         | 14.6     | 14.6   | 14.6      | 14.6           | 14.6              | 14.6          | 14.6            |
| Piperidine (µl)  | 85.15 | 0.862   | 9        | 18     | 9         | 9              | 9                 | 6             | 9               |
| Product (mg)     | 191.27 |         |          |        |           |                |                   | 7.4           |                 |
4.4 Characterisation of products ($d_7$-DMF)

4.4.1 $^1$H NMR Assignment

An example NMR taken from the kinetic monitoring study is shown below, many of the peaks belong to the tetrabutylammonium cation due to its stoichiometry and large number of protons. The integration of the *in situ* NMR spectra was performed on the aromatic peaks shown zoomed in due to significant overlap between peaks in the methoxy region. Aromatic peaks were assigned from ‘spiking’ experiments, COSY experiments and reference spectra.

![Figure S1. $^1$H NMR spectrum of a typical reaction mixture in $d_7$-DMF](image-url)
The NMR spectra of the main impurity matches well with literature data.  

4.4.2 4-Methoxyphenol speciation in reaction mixture (d$_7$-DMF)

4-Methoxyphenol appears to exist as 4-methoxyphenolate in the in situ NMR studies. When a reference spectrum of 4-methoxyphenol was taken in d$_7$-DMF, only one multiplet is seen in the aromatic region at 6.8 ppm, with the –OH peak seen at 9.1 ppm. When base is added, loss of the –OH signal is seen and splitting of the aromatic peaks is noted, giving the doublets seen in the in situ studies. Slight differences in ppm exist between reference samples and the in situ data as the in situ study is performed at 70 °C.
4.4.3 Characterisation of anisole as a side product

(a)

(b)

Figure S3. $^1$H NMR spectra of 4-methoxyphenol with and without TBAA

Figure S4. $^1$H NMR spectra of (a) an *in situ* reaction mixture; and (b) the same reaction mixture spiked with anisole after exposure to air
4.4.4 4-Chloroanisole and N,N-dimethylanisidine reference spectra in $d_7$-DMF

Figure S5. $^1$H NMR spectra of (a) an *in situ* reaction mixture, (b) a sample of 4-chloroanisole from Sigma, and (c) a sample of $N,N$-dimethylanisidine from Sigma Aldrich at room temperature.
4.4.5 $^1$H COSY spectrum of reaction mixture post-reaction

Figure S6. $^1$H COSY spectrum of reaction mixture post-reaction
4.4.6 GC/MS characterisation of the products

Figure S7. GC/MS chromatogram of the reaction mixture

| Retention time (min) | m/z  | Other                  | Compound                           |
|----------------------|------|------------------------|------------------------------------|
| 8.34                 | 230  | 215 Fragment (-CH₃)    | Bis-4,4’-methoxy phenylether        |
| 7.30                 | 191  | 176 Fragment (-CH₃)    | Coupling Product                   |
| 5.80                 | 234  | 219 Fragment (-CH₃)    | 4-Iodoanisole                      |
| 5.40                 | 124  | 109 Fragment (-CH₃)    | 4-Methoxyphenol                    |
| 4.67                 | 142  | 127 Fragment (-CH₃)    | 4-Chloroanisole                    |
|                      |      | Cl splitting pattern   |                                    |
| 3.23                 | 108  | 93 Fragment (-CH₃)     | Anisole                            |

4.4.7 Origin of N,N-dimethylanisidine

GC-MS analysis of the above reaction shows the presence of an impurity which appears on the chromatogram at 5.8 minutes with a mass of 151 (136 –CH₃), overlapping slightly with 4-methoxyphenol (m/z = 234).
Figure S8. GC profile of the reaction mixture and MS data for the peak at 5.8 minutes in reaction using DMF.

In $d_7$-DMF used in NMR experiments, the peak at 5.8 is seen as having a mass of 157 (142 –CH$_3$), showing that the origin of this impurity is reaction with the DMF solvent used in the reaction.
This can be confirmed with the GC/MS of pure \(N,N\)-dimethylanisidine, which appears on the chromatogram at 5.8 minutes with the same mass splitting of 151/136.
4.5 Kinetic data in \( \text{d}_7\)-DMF

4.5.1 Standard conditions

\([1]_0 = 0.125 \text{ M}\) was employed unless otherwise stated (protocol in section 4.1).

![Diagram of chemical reactions]

| Time (minutes) | \([A] (\text{M})\) | \([B] (\text{M})\) | \([C] (\text{M})\) | \([D] (\text{M})\) | \([E] (\text{M})\) |
|---------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 0             | 0.10927         | 0.01603         | 0               | 0               | 0               |
| 16            | 0.0904          | 0.031           | 9.91964 \times 10^{-4} | 0.00135       | 0.00125         |
| 26            | 0.08011         | 0.03906         | 0.00144         | 0.00188        | 0.00276         |
| 36            | 0.07367         | 0.04441         | 0.00173         | 0.00208        | 0.00292         |
| 46            | 0.06864         | 0.04855         | 0.00229         | 0.00233        | 0.00345         |
| 56            | 0.06415         | 0.0522          | 0.0023          | 0.00263        | 0.00338         |
| 66            | 0.06222         | 0.05441         | 0.00413         | 0.00278        | 0.0017          |
| 76            | 0.05794         | 0.05749         | 0.00288         | 0.00281        | 0.00341         |
| 86            | 0.05513         | 0.05997         | 0.00391         | 0.00298        | 0.00325         |
96  0.05306  0.06165  0.00343  0.00318  0.00307
106  0.05053  0.06353  0.00401  0.00328  0.00391
116  0.0486  0.06492  0.00388  0.00351  0.00464
126  0.04647  0.06706  0.00303  0.00331  0.00378
136  0.04541  0.06771  0.00401  0.00356  0.00485
146  0.04426  0.06891  0.00328  0.00353  0.00378
156  0.04208  0.07013  0.00371  0.00356  0.00485
166  0.04053  0.07132  0.0046  0.00358  0.00522
176  0.0396  0.07209  0.00361  0.00386  0.00519
186  0.039  0.07278  0.00501  0.00386  0.0046
196  0.0383  0.07346  0.00411  0.00386  0.0045
206  0.03757  0.07442  0.00504  0.00378  0.00443
216  0.03662  0.07466  0.00426  0.00411  0.00453
226  0.03677  0.07519  0.00523  0.00401  0.00405

4.5.2 Reaction with 2 x $[2]_0$

| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|---------------|----------|----------|----------|----------|----------|
| 0             | 0.09798  | 0.02382  | $5 \times 10^{-4}$ | 0.00112  | 0.00157  |
| 13            | 0.07917  | 0.0407   | 0.00171  | 0.00112  | 0.00229  |
| 23            | 0.0686   | 0.04994  | 0.00258  | 0.00135  | 0.00254  |
| 33            | 0.0611   | 0.05679  | 0.00336  | 0.00125  | 0.0025   |
| 43            | 0.05602  | 0.06112  | 0.00358  | 0.00175  | 0.00252  |
| 53            | 0.05155  | 0.06446  | 0.00399  | 0.0017   | 0.0033   |
| 63            | 0.04833  | 0.06744  | 0.00414  | 0.00175  | 0.00335  |
| 73            | 0.0456   | 0.06901  | 0.00446  | 0.00198  | 0.00395  |
| 83            | 0.04295  | 0.0711   | 0.00474  | 0.00215  | 0.00406  |
## 4.5.3 Reaction with 2 x [TBAAn]

| Time (minutes) | [A] (M)   | [B] (M)   | [C] (M)   | [D] (M)   | [E] (M)   |
|----------------|-----------|-----------|-----------|-----------|-----------|
| 0              | 0.11674   | 0.00806   | 0         | 0         | 0         |
| 13             | 0.10129   | 0.01878   | 8.6112 x 10^{-4} | 0.00187 | 0.002     |
| 23             | 0.09358   | 0.02502   | 0.00116   | 0.00267   | 0.00237   |
| 33             | 0.08761   | 0.0299    | 0.00158   | 0.00332   | 0.00238   |
| 43             | 0.08217   | 0.0336    | 0.00196   | 0.00397   | 0.00311   |
| 53             | 0.0775    | 0.03707   | 0.00235   | 0.00477   | 0.00312   |
| 63             | 0.07371   | 0.04027   | 0.00238   | 0.00512   | 0.00332   |
### 4.5.4 Reaction with $2 \times [L^1H]_0$

| Time (minutes) | [A] (M)     | [B] (M)     | [C] (M)     | [D] (M)     | [E] (M)     |
|---------------|-------------|-------------|-------------|-------------|-------------|
| 0             | 0.11284     | 0.00728     | 0.0022      | 0.00185     | 6.24 x 10^{-4} |
| 20            | 0.08956     | 0.02581     | 0.00387     | 0.00447     | 6.7392 x 10^{-4} |
| 30            | 0.07867     | 0.03486     | 0.00456     | 0.00514     | 9.984 x 10^{-4} |
| 40            | 0.07246     | 0.04036     | 0.00492     | 0.00547     | 0.00102     |
| 50            | 0.06744     | 0.04389     | 0.00534     | 0.00602     | 0.00112     |
| Time (minutes) | [A] (M)   | [B] (M)   | [C] (M)    | [D] (M)   | [E] (M)   |
|---------------|-----------|-----------|------------|-----------|-----------|
| 60            | 0.06345   | 0.04722   | 0.00548    | 0.00649   | 0.0011    |
| 70            | 0.05923   | 0.05064   | 0.00574    | 0.00686   | 0.00115   |
| 80            | 0.05641   | 0.05315   | 0.00567    | 0.00724   | 0.00118   |
| 90            | 0.05341   | 0.05547   | 0.00609    | 0.00726   | 0.00122   |
| 100           | 0.05119   | 0.05774   | 0.00624    | 0.00731   | 0.00107   |
| 110           | 0.0492    | 0.05953   | 0.0059     | 0.00794   | 7.982E-4  |
| 120           | 0.04643   | 0.06203   | 0.00636    | 0.00744   | 0.00115   |
| 130           | 0.0443    | 0.06359   | 0.00655    | 0.00774   | 0.0011    |
| 140           | 0.04271   | 0.06448   | 0.00675    | 0.00811   | 0.00112   |
| 150           | 0.04031   | 0.06638   | 0.00685    | 0.00829   | 0.00127   |
| 160           | 0.03906   | 0.06783   | 0.00685    | 0.00839   | 0.00102   |
| 170           | 0.03776   | 0.06885   | 0.00678    | 0.00854   | 0.00112   |
| 180           | 0.03642   | 0.06984   | 0.00695    | 0.00864   | 0.00112   |
| 190           | 0.03517   | 0.07099   | 0.00708    | 0.00856   | 0.00115   |
| 200           | 0.0336    | 0.07231   | 0.00721    | 0.00856   | 0.00125   |
| 210           | 0.03257   | 0.07296   | 0.00726    | 0.00881   | 0.00117   |
| 220           | 0.03135   | 0.07406   | 0.00725    | 0.00889   | 0.00117   |
| 230           | 0.03035   | 0.07502   | 0.00745    | 0.00881   | 0.00112   |
| 240           | 0.0291    | 0.07607   | 0.00738    | 0.00904   | 0.0011    |
| 250           | 0.02848   | 0.07666   | 0.00725    | 0.00926   | 9.2352E-4 |

4.5.5 Reaction with 0.5 \times [1]_0

| Time (minutes) | [A] (M)   | [B] (M)   | [C] (M)    | [D] (M)   | [E] (M)   |
|---------------|-----------|-----------|------------|-----------|-----------|
| 0             | 0.05383   | 0.00749   | 4.4928 \times 10^{-4} | 3.3696 \times 10^{-4} | 2.9952 \times 10^{-4} |
| 20            | 0.03605   | 0.02013   | 0.0021     | 0.00298   | 0.00114   |
| 30            | 0.03004   | 0.02417   | 0.00286    | 0.00366   | 0.00167   |
| Time (minutes) | [A] (M)     | [B] (M)       | All Side Products (M) |
|---------------|-------------|---------------|-----------------------|
| 40            | 0.02592     | 0.02774       | 0.00347               |
| 50            | 0.02291     | 0.02978       | 0.00358               |
| 60            | 0.02058     | 0.03191       | 0.00366               |
| 70            | 0.01813     | 0.03313       | 0.00407               |
| 80            | 0.01604     | 0.03497       | 0.00422               |
| 90            | 0.0143      | 0.03602       | 0.00427               |
| 100           | 0.01246     | 0.03691       | 0.00445               |
| 110           | 0.01153     | 0.03692       | 0.00448               |
| 120           | 0.01099     | 0.03776       | 0.00448               |
| 130           | 0.00955     | 0.03907       | 0.00489               |
| 140           | 0.00926     | 0.0389        | 0.00505               |
| 150           | 0.0083      | 0.03971       | 0.00495               |
| 160           | 0.00771     | 0.04028       | 0.00514               |
| 170           | 0.00725     | 0.04053       | 0.00512               |
| 180           | 0.00664     | 0.04092       | 0.00524               |
| 190           | 0.00609     | 0.0412        | 0.00544               |
| 200           | 0.00575     | 0.04129       | 0.00522               |
| 210           | 0.00512     | 0.04249       | 0.00525               |
| 220           | 0.00495     | 0.0422        | 0.00555               |
| 230           | 0.00483     | 0.04234       | 0.0054                |
| 240           | 0.00439     | 0.04276       | 0.00548               |
| 250           | 0.00394     | 0.04277       | 0.00565               |

4.5.6 Reaction with product inhibition (0.62 eq. of product at the beginning)

| Time (minutes) | [A] (M) | [B] (M) | All Side Products (M) |
|----------------|---------|---------|-----------------------|
| 0              | 0.125   | 0       | 0                     |

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| Value | Column 1 | Column 2 | Column 3 |
|-------|----------|----------|----------|
| 15    | 0.1149   | 0.00768  | 0.00242  |
| 25    | 0.10872  | 0.01196  | 0.00432  |
| 35    | 0.10583  | 0.01505  | 0.00412  |
| 45    | 0.10444  | 0.01576  | 0.00479  |
| 55    | 0.10143  | 0.01927  | 0.0043   |
| 65    | 0.09763  | 0.02127  | 0.0061   |
| 75    | 0.09494  | 0.02319  | 0.00687  |
| 85    | 0.09347  | 0.02458  | 0.00695  |
| 95    | 0.09129  | 0.02545  | 0.00826  |
| 105   | 0.09038  | 0.02749  | 0.00713  |
| 115   | 0.0888   | 0.02931  | 0.00689  |
| 125   | 0.08979  | 0.02763  | 0.00758  |
| 135   | 0.08721  | 0.0302   | 0.00758  |
| 145   | 0.08666  | 0.02909  | 0.00925  |
| 155   | 0.08567  | 0.03052  | 0.00881  |
| 165   | 0.08579  | 0.03075  | 0.00846  |
| 175   | 0.08369  | 0.03236  | 0.00895  |
| 185   | 0.08381  | 0.03175  | 0.00945  |
| 195   | 0.08151  | 0.0338   | 0.00968  |
| 205   | 0.08159  | 0.03396  | 0.00945  |
| 215   | 0.08139  | 0.03434  | 0.00927  |
| 225   | 0.08108  | 0.03426  | 0.00966  |
| 235   | 0.07965  | 0.03519  | 0.01016  |
| 245   | 0.0789   | 0.03614  | 0.00996  |
4.5.7 Product distribution ratios in d₇-DMF

| Experiment | [A] | [B] | [C] | [D] | [E] |
|------------|-----|-----|-----|-----|-----|
| 4.5.1      | 27  | 63  | 4   | 3   | 2   |
| Standard   |     |     |     |     |     |
| 4.5.2      | 20  | 69  | 5   | 2   | 2   |
| 2 x [2]₀   |     |     |     |     |     |
| 4.5.3      | 32  | 54  | 3   | 8   | 2   |
| 2 x [TBAA]₀|     |     |     |     |     |
| 4.5.4      | 23  | 62  | 6   | 7   | 1   |
| 2 x [L¹H]₀|     |     |     |     |     |
| 4.5.5      | 6   | 69  | 9   | 12  | 1   |
| 0.5 x [1]₀|     |     |     |     |     |

4.5.8 Same [“excess”] – Standard Conditions

| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|----------------|----------|----------|----------|----------|----------|
| 0              | 0.114013 | 0.010563 | 0.000000 | 0.000425 | 0.000000 |
| 10             | 0.104187 | 0.019716 | 0.000000 | 0.001097 | 0.000000 |
| 20             | 0.092545 | 0.027440 | 0.001193 | 0.002832 | 0.000990 |
| 30             | 0.086530 | 0.032762 | 0.001334 | 0.003409 | 0.000965 |
| 40             | 0.081524 | 0.036447 | 0.001686 | 0.004013 | 0.001329 |
4.5.9 Same [“excess”] conditions – [“Excess”] = 0.0625 M

| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|----------------|----------|----------|----------|----------|----------|
| 0              | 0.051556 | 0.009377 | 0.000564 | 0.000251 | 0.000752 |
| 10             | 0.041384 | 0.016654 | 0.000815 | 0.001981 | 0.001665 |
| 20             | 0.036901 | 0.020040 | 0.001282 | 0.002638 | 0.001640 |
| 30             | 0.033359 | 0.021878 | 0.001762 | 0.003298 | 0.002203 |
| 40             | 0.031074 | 0.023671 | 0.002016 | 0.003478 | 0.002262 |
| 50             | 0.029178 | 0.025176 | 0.002080 | 0.003479 | 0.002587 |
| 60             | 0.027574 | 0.026521 | 0.002398 | 0.003735 | 0.002272 |
| 70             | 0.026081 | 0.027654 | 0.002602 | 0.003877 | 0.002286 |
| 80             | 0.024529 | 0.028045 | 0.002487 | 0.004292 | 0.003147 |
| 90             | 0.023775 | 0.029134 | 0.002793 | 0.004158 | 0.002639 |
| 100            | 0.022700 | 0.029996 | 0.002921 | 0.004173 | 0.002709 |
| 110            | 0.021720 | 0.030809 | 0.002998 | 0.004326 | 0.002647 |
| 120            | 0.020791 | 0.031402 | 0.003088 | 0.004391 | 0.002828 |
4.6 Kinetic data in $d_3$-MeCN

4.6.1 Standard conditions

$[1]_0 = 0.125$ M was employed unless otherwise stated (protocol in section 4.1).

| Time (minutes) | [A] (M) | [B] (M) | [C] (M) | [D] (M) | [E] (M) |
|----------------|---------|---------|---------|---------|---------|
| 130            | 0.019959| 0.031881| 0.003126| 0.004417| 0.003117|
| 140            | 0.019114| 0.032496| 0.003331| 0.004687| 0.002872|
| 150            | 0.018449| 0.032978| 0.003241| 0.004584| 0.003248|
| 160            | 0.017634| 0.033545| 0.003550| 0.004944| 0.002827|
| 170            | 0.017108| 0.033335| 0.003640| 0.005047| 0.003370|
| 180            | 0.016358| 0.034427| 0.003421| 0.004790| 0.003504|
| 190            | 0.015889| 0.034654| 0.003408| 0.004777| 0.003773|
| 200            | 0.015238| 0.035180| 0.003550| 0.004868| 0.003664|
| 210            | 0.014693| 0.035440| 0.003550| 0.004906| 0.003911|
| 220            | 0.014138| 0.035840| 0.003601| 0.004983| 0.003937|
| 230            | 0.013587| 0.036226| 0.003730| 0.005214| 0.003743|
| 240            | 0.013156| 0.036531| 0.003730| 0.005125| 0.003958|
| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|---------------|---------|---------|---------|---------|---------|
| 0             | 0.100435| 0.020705| 0.002553| 0.000000| 0.001307|
| 15            | 0.086803| 0.032309| 0.003059| 0.000755| 0.002075|
| 25            | 0.081440| 0.037610| 0.003646| 0.001121| 0.001184|
| 35            | 0.077679| 0.041018| 0.003758| 0.001259| 0.001285|
| 45            | 0.074534| 0.043491| 0.003951| 0.001713| 0.001310|
| 55            | 0.072345| 0.046428| 0.003971| 0.001588| 0.000668|
| 65            | 0.069157| 0.048042| 0.004246| 0.001929| 0.001626|
| 75            | 0.067149| 0.049798| 0.004409| 0.001917| 0.001728|
| 85            | 0.065332| 0.051481| 0.004592| 0.001905| 0.001690|
| 95            | 0.064082| 0.053122| 0.004480| 0.001867| 0.001450|
| 105           | 0.062769| 0.054279| 0.004571| 0.002119| 0.001261|
| 115           | 0.061686| 0.055909| 0.004592| 0.001829| 0.000984|
| 125           | 0.060666| 0.056945| 0.004500| 0.001841| 0.001047|
| 135           | 0.059486| 0.057770| 0.004653| 0.001930| 0.001161|
| 145           | 0.058780| 0.058994| 0.004765| 0.001956| 0.000505|
| 155           | 0.057565| 0.059597| 0.004734| 0.001931| 0.001174|
| 165           | 0.056799| 0.060345| 0.004765| 0.001842| 0.001249|
| 175           | 0.055205| 0.061165| 0.005081| 0.002235| 0.001313|
| 185           | 0.054089| 0.061704| 0.005153| 0.002399| 0.001654|
| 195           | 0.053453| 0.062562| 0.005347| 0.002400| 0.001238|
| 205           | 0.053223| 0.062898| 0.005204| 0.002299| 0.001377|
| 215           | 0.052984| 0.063740| 0.004969| 0.002070| 0.001237|
| 225           | 0.051776| 0.064104| 0.005255| 0.002223| 0.001642|

4.6.2 Reaction with 2 x [2]₀

| Time (minutes) | [A] (M) | [B] (M) | [C] (M) | [D] (M) | [E] (M) |
|---------------|--------|--------|--------|--------|--------|
|               |        |        |        |        |        |
|   | 0.096364 | 0.023350 | 0.002422 | 0.001017 | 0.001846 |
|---|---|---|---|---|---|
| 12 | 0.081656 | 0.039156 | 0.002806 | 0.000578 | 0.000804 |
| 22 | 0.073698 | 0.046087 | 0.003403 | 0.000856 | 0.000956 |
| 32 | 0.068380 | 0.051490 | 0.003444 | 0.000831 | 0.000856 |
| 42 | 0.064085 | 0.055221 | 0.003616 | 0.001045 | 0.001032 |
| 52 | 0.060564 | 0.058511 | 0.003758 | 0.001121 | 0.001045 |
| 62 | 0.057708 | 0.061311 | 0.003890 | 0.001146 | 0.000945 |
| 72 | 0.055384 | 0.063662 | 0.003951 | 0.001096 | 0.000907 |
| 82 | 0.052833 | 0.065541 | 0.004256 | 0.001336 | 0.001034 |
| 92 | 0.051070 | 0.067584 | 0.004266 | 0.001286 | 0.000794 |
| 102 | 0.049430 | 0.069192 | 0.004134 | 0.001248 | 0.000996 |
| 112 | 0.047850 | 0.070830 | 0.004215 | 0.001160 | 0.000945 |
| 122 | 0.046194 | 0.071661 | 0.004297 | 0.001652 | 0.001198 |
| 132 | 0.044836 | 0.073495 | 0.004337 | 0.001261 | 0.001072 |
| 142 | 0.043347 | 0.074554 | 0.004765 | 0.001451 | 0.000883 |
| 152 | 0.042040 | 0.075690 | 0.004683 | 0.001476 | 0.001110 |
| 162 | 0.041172 | 0.076567 | 0.004561 | 0.001640 | 0.001060 |
| 172 | 0.040348 | 0.077569 | 0.004347 | 0.001803 | 0.000933 |
| 182 | 0.038910 | 0.078767 | 0.004836 | 0.001464 | 0.001022 |
| 192 | 0.037767 | 0.079811 | 0.004734 | 0.001489 | 0.001199 |
| 202 | 0.036807 | 0.080582 | 0.004898 | 0.001553 | 0.001161 |
| 212 | 0.036109 | 0.081240 | 0.004673 | 0.001653 | 0.001325 |
| 222 | 0.035027 | 0.082462 | 0.004898 | 0.001464 | 0.001149 |
| 232 | 0.034087 | 0.083128 | 0.005183 | 0.001528 | 0.001074 |
| 242 | 0.033220 | 0.083986 | 0.005255 | 0.001693 | 0.000846 |
4.6.3 Reaction with 2 x [TBAA]₀

| Time (minutes) | [A] (M) | [B] (M) | [C] (M) | [D] (M) | [E] (M) |
|----------------|---------|---------|---------|---------|---------|
| 0              | 0.102070| 0.019031| 0.002806| 0.000955| 0.000138|
| 14             | 0.090846| 0.028164| 0.003373| 0.002064| 0.000554|
| 24             | 0.084940| 0.033027| 0.003646| 0.002820| 0.000567|
| 34             | 0.079735| 0.036477| 0.004175| 0.003252| 0.001361|
| 44             | 0.077495| 0.038615| 0.004114| 0.003403| 0.001374|
| 54             | 0.074457| 0.041218| 0.004195| 0.003807| 0.001324|
| 64             | 0.072439| 0.042750| 0.004276| 0.004185| 0.001349|
| 74             | 0.070339| 0.045021| 0.004582| 0.003860| 0.001198|
| 84             | 0.067183| 0.047508| 0.005132| 0.004092| 0.001086|
| 94             | 0.064864| 0.049873| 0.005173| 0.004041| 0.001048|
| 104            | 0.063569| 0.051595| 0.005214| 0.004042| 0.000581|
| 114            | 0.062831| 0.051896| 0.005071| 0.004192| 0.001010|
| 124            | 0.061077| 0.054965| 0.005081| 0.003611| 0.000265|
| 134            | 0.060188| 0.055705| 0.005142| 0.003612| 0.000354|
| 144            | 0.058695| 0.057294| 0.004796| 0.004064| 0.000151|
| 154            | 0.056933| 0.059343| 0.004724| 0.003659| 0.000341|
| 164            | 0.055610| 0.060646| 0.004857| 0.003685| 0.000202|
| 174            | 0.054901| 0.060296| 0.005418| 0.003892| 0.000493|
| 184            | 0.053042| 0.061253| 0.005285| 0.004649| 0.000771|
| 194            | 0.053014| 0.062181| 0.005020| 0.004368| 0.000417|
| 204            | 0.051275| 0.063272| 0.005674| 0.004399| 0.000379|
| 214            | 0.051290| 0.062946| 0.005694| 0.004804| 0.000265|
| 224            | 0.050498| 0.064228| 0.005735| 0.004349| 0.000190|
| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|---------------|---------|---------|---------|---------|---------|
| 0             | 0.102871| 0.016937| 0.004083| 0.000681| 0.000428|
| 12            | 0.088218| 0.029419| 0.005040| 0.001187| 0.001136|
| 22            | 0.082437| 0.034789| 0.005428| 0.001087| 0.001074|
| 32            | 0.078544| 0.038867| 0.005623| 0.001492| 0.001656|
| 42            | 0.074541| 0.041689| 0.005960| 0.001606| 0.001391|
| 52            | 0.071593| 0.044449| 0.006104| 0.001544| 0.001151|
| 62            | 0.069564| 0.046637| 0.006104| 0.001506| 0.001075|
| 72            | 0.067982| 0.048333| 0.006104| 0.001987| 0.001101|
| 82            | 0.066193| 0.049461| 0.006257| 0.002165| 0.001215|
| 92            | 0.064251| 0.050958| 0.006411| 0.002165| 0.001215|
| 102           | 0.063029| 0.052265| 0.006565| 0.002026| 0.001114|
| 112           | 0.062361| 0.052980| 0.006380| 0.001937| 0.001342|
| 122           | 0.060898| 0.054235| 0.006637| 0.001963| 0.001267|
| 132           | 0.059711| 0.055214| 0.006668| 0.002153| 0.001254|
| 142           | 0.057968| 0.056397| 0.006935| 0.002446| 0.001255|
| 152           | 0.057349| 0.056969| 0.006842| 0.002420| 0.001419|
| 162           | 0.056515| 0.057897| 0.006976| 0.002243| 0.001369|
| 172           | 0.055814| 0.058754| 0.006935| 0.002231| 0.001267|
| 182           | 0.054924| 0.059436| 0.006914| 0.002433| 0.001293|
| 192           | 0.054686| 0.060020| 0.006822| 0.002217| 0.001254|
| 202           | 0.053667| 0.060663| 0.006894| 0.002218| 0.001559|

4.6.4 Reaction with 2 x $[L^1H]_0$
4.6.5 Reaction with 0.5 x [1]₀

| Time (minutes) | [A] (M)  | [B] (M)  | [C] (M)  | [D] (M)  | [E] (M)  |
|----------------|----------|----------|----------|----------|----------|
| 0              | 0.049732 | 0.009162 | 0.002225 | 0.000744 | 0.000637 |
| 11             | 0.036993 | 0.021243 | 0.003118 | 0.000911 | 0.000234 |
| 21             | 0.032365 | 0.025245 | 0.003395 | 0.001204 | 0.000291 |
| 31             | 0.029161 | 0.027988 | 0.003632 | 0.001332 | 0.000387 |
| 41             | 0.026528 | 0.030609 | 0.003915 | 0.001270 | 0.000178 |
| 51             | 0.024486 | 0.032069 | 0.004065 | 0.001537 | 0.000343 |
| 61             | 0.022608 | 0.033706 | 0.004241 | 0.001551 | 0.000394 |
| 71             | 0.020980 | 0.034886 | 0.004458 | 0.001679 | 0.000496 |
| 81             | 0.019519 | 0.036487 | 0.004572 | 0.001629 | 0.000293 |
| 91             | 0.018010 | 0.037449 | 0.004925 | 0.001784 | 0.000331 |
| 101            | 0.017101 | 0.038482 | 0.004764 | 0.001834 | 0.000318 |
| 111            | 0.016219 | 0.039262 | 0.004821 | 0.001873 | 0.000325 |
| 121            | 0.014984 | 0.040082 | 0.005055 | 0.001938 | 0.000440 |
| 131            | 0.013489 | 0.041265 | 0.005472 | 0.001737 | 0.000536 |
| 141            | 0.013122 | 0.041925 | 0.005175 | 0.001927 | 0.000351 |
| 151            | 0.012193 | 0.042499 | 0.005477 | 0.001942 | 0.000390 |
| 161            | 0.011725 | 0.043240 | 0.005441 | 0.001890 | 0.000204 |
| 171            | 0.010886 | 0.043641 | 0.005697 | 0.001892 | 0.000384 |
| 181            | 0.010361 | 0.044146 | 0.005660 | 0.001956 | 0.000377 |
5. Kinetic experiments using inorganic bases

5.1 General procedure for reactions with automated sampling

All experiments were performed as outlined in general procedure above. Reactions were performed in a 4 mL vial with a stirrer disk in a 24 well plate within a glovebox filled with an N₂ atmosphere. Heating, solution additions and sampling were executed by a Freeslate automation robot.

Inside a nitrogen-filled glovebox reaction vials containing magnetic stirrer disks were loaded with the corresponding amounts of CuI (0.1 eq., 0.05 mmol), ligand (L¹H or L²H, 0.1 mmol) and base (Cs₂CO₃ or K₃PO₄, 1.5 eq., see table below for quantities). Into separate vials, a solution of 4-iodoanisole 1 (0.625 M) in and a solution of 2-pyrrolidinone 4/1,1'-biphenyl (0.441 M and 0.0294 M, respectively) were made up in degassed and anhydrous DMF. The reaction vials were loaded into a 24 well stainless steel heating plate and loosely fitted with septum seal caps to prevent pressure fluctuations during charging and sampling. The reaction vials were each charged with the 2-pyrrolidinone/1,1'-biphenyl solution (1.7 mL), heated to 90 °C before being left to equilibrate for 30 minutes. The 4-iodoanisole solution was pre-heated to 90 °C and the reaction initiated through the addition of this solution (0.8 mL) to each vial.

For analysis, HPLC vials were loosely fitted with caps and injected with 500 µl MeCN by the Freeslate automation robot. Sampling of reactions was also performed by the robot at the desired time intervals, whereby 30 µl of reaction mixture was added to the MeCN. The samples were removed from the glovebox and filtered using Whatman Mini-UniPrep syringeless filters (0.2 µm pore size) prior to analysis.

For experiments varying the quantities of 4-iodoanisole 1 and 2-pyrrolidinone 4, separate solutions were made to adjust the reaction concentrations without changing the volume of the reaction mixtures.

The kinetic data above were collected using Cs₂CO₃ (99%) supplied by Chemetall (Base1) with particle size distribution D₅₀ = 20 µm (the value of the particle diameter at 50% in the cumulative distribution), D₉₀ = 50 µm (the value of the particle diameter at 90% in the cumulative distribution). Two other batches of Cs₂CO₃ supplied by Sigma-Aldrich (ReagentPlus® 99%, lot# BCBP3311V, Base2) and Acros Organic (99.5%, lot# A0359643, Base3) were included in the study for comparison.
5.2 HPLC calibration

UV lamp set at 285 nm and concentration of internal standard (IS) held at 0.000113 M.

| [3] (M) | 0.00113 | 0.00283 | 0.00566 | 0.00849 | 0.01018 | 0.01132 |
|---------|---------|---------|---------|---------|---------|---------|
| Area 3  | 129665.5| 323057.9| 646656.8| 929430.4| 1136975.0| 1257801.0|
| Area IS | 53605.9 | 54349.68| 55026.88| 54723.1 | 55208.0 | 55779.7 |
| Area 3/IS| 2.418865574| 5.944062 | 11.75165| 16.98424| 20.59438| 22.54942|

![HPLC calibration curve for product 5](image)

**Figure S11.** HPLC calibration curve for product 5

| [1] (M) | 0.00113 | 0.00283 | 0.00566 | 0.00849 | 0.01018 | 0.01132 |
|---------|---------|---------|---------|---------|---------|---------|
| Area 1  | 82035.7 | 207296.1| 419618.7| 605277.8| 745358.8| 842654.1|
| Area IS | 53605.9 | 54349.68| 55026.88| 54723.1 | 55208.0 | 55779.7 |
| Area 1/IS| 1.53035| 3.81411 | 7.62570| 11.06074| 13.50091| 15.10681|
Figure S12. HPLC calibration curve for starting material 1

5.3 Kinetic data with L^1H/Cs₂CO₃

5.3.1 Reaction conditions – experiment 1 (L^1H/Cs₂CO₃)

|                | MW (g.mol⁻¹) | Density (g.mL⁻¹) | 0.5x Standard [Cu/L₁] | 2x Standard Duplicate | 0.5x Product Inhibition | 1eq H₂O |
|----------------|--------------|------------------|-----------------------|------------------------|-------------------------|--------|
| CuI (mg)       | 190.44       |                  | 9.5                   | 4.8                    | 9.5                     | 4.7    |
| L¹H (mg)       | 103.12       |                  | 10.3                  | 5.2                    | 10.3                    | 10.3   |
| 1,1'-Biphenyl (mg) | 154.21    |                  | 7.7                   | 7.7                    | 7.7                     | 7.7    |
| Cs₂CO₃ (mg)    | 325.82       |                  | 244                   | 244                    | 244                     | 244    |
| DMF (µl)       |              |                  | 2500                  | 2500                   | 2500                    | 2500   |
| 1 (mg)         | 234.03       |                  | 117                   | 117                    | 117                     | 117    |
| 5 (mg)         | 191.23       |                  |                       |                        |                         | 47.8   |
| 4 (µl)         | 85.15        | 1.116            | 57                    | 57                     | 57                      | 57     |
| H₂O (µl)       | 18.02        | 1.000            |                       |                        |                         | 9      |

5.3.2 Reaction under standard conditions

| Time (mins) | PA ArI       | PA Prod     | PA Std     | [SM] | [Prod] | ArI % | Prod Form % |
|-------------|--------------|-------------|------------|------|--------|-------|-------------|
| 30          | 498951.3     | 21127.02    | 29759.44   | 0.012638 | 0.000353 | 90.91419 | 2.536422944 |
| 64          | 879169.5     | 151273.9    | 55923.59   | 0.011851 | 0.001344 | 85.24635 | 9.664451386 |
| 96          | 855307.5     | 223396.9    | 56583.15   | 0.011394 | 0.001961 | 81.96593 | 14.10581671 |
| 123         | 797383.1     | 324889.6    | 56540.12   | 0.010631 | 0.002854 | 76.47307 | 20.52991678 |
| 155         | 708246.2     | 438896.4    | 55260.62   | 0.009661 | 0.003945 | 69.49711 | 28.37620957 |
| 182         | 599410.8     | 600918.2    | 54782.09   | 0.008248 | 0.005448 | 59.33135 | 39.19087543 |
| 214         | 412324.1     | 1081729     | 62591.18   | 0.004966 | 0.008584 | 35.72102 | 61.74666773 |
| 241         | 213691.6     | 1208572     | 54767.2    | 0.002941 | 0.01096 | 21.15753 | 78.84246559 |
| 272         | 138214.1     | 1486008     | 60347.64   | 0.001726 | 0.01223 | 12.4191 | 87.97694524 |
| 332         | 69222.41     | 1563819     | 59706.41   | 0.000874 | 0.013009 | 6.286718 | 93.57796119 |
| 391         | 44125.58     | 1570611     | 58555.47   | 0.000568 | 0.013322 | 4.086214 | 95.8317181  |
### 5.3.3 Reaction with 0.5 x [CuI]₀ and 0.5 x [L₁H]₀

| Time (mins) | PA ArI | PA Prod | PA Std | [SM] | [Prod] | ArI % | Prod Form % |
|------------|--------|---------|--------|------|--------|-------|-------------|
| 30         | 1124885| 12793.02| 67790.99| 0.012508| 9.37E-05| 99.25624| 0.743759693|
| 64         | 1030062| 26688.04| 63274.18| 0.012271| 0.000209| 97.377416| 1.662346771|
| 96         | 916351.9| 34014.44| 57164.32| 0.012084| 0.000296| 95.868602| 2.345145784|
| 124        | 897989.6| 42435.16| 56426.82| 0.011996| 0.000374| 95.193511| 2.963956656|
| 155        | 869190.2| 50866.77| 54923.35| 0.011929| 0.00046| 94.662821| 3.650132841|
| 183        | 943638.2| 65705.97| 59037.24| 0.012049| 0.000553| 95.609496| 4.386420785|
| 214        | 865712.2| 69317.35| 54782.31| 0.011912| 0.000628| 94.526759| 4.986928162|
| 241        | 836998.2| 75867.35| 53332.25| 0.01183| 0.000707| 93.876351| 5.606560672|
| 273        | 920431.5| 94964.97| 58435.32| 0.011873| 0.000807| 94.218808| 6.405005821|
| 332        | 880682.1| 110840.6| 56492.69| 0.011751| 0.000974| 93.249936| 7.73281284|
| 391        | 817307.8| 122708.5| 53472.34| 0.011522| 0.00114| 91.42776| 9.044345825|
| 456        | 862200.5| 151564.5| 56879.81| 0.011426| 0.001323| 90.671698| 10.50196976|
| 514        | 870999.4| 174273.9| 58074.3| 0.011306| 0.00149| 89.713018| 11.82714605|
| 571        | 817662| 183848.3| 55291.25| 0.011147| 0.001651| 88.458386| 13.10492681|
| 633        | 770339.2| 198405.3| 53557| 0.010842| 0.00184| 86.037413| 14.60053034|
| 693        | 849009| 251720.5| 59601.61| 0.010738| 0.002098| 85.207122| 16.64531658|
| 753        | 761930.4| 345405.9| 58012.98| 0.00999| 0.002957| 78.561858| 23.46584348|
| 840        | 652614.4| 1074174| 79048.29| 0.006223| 0.006749| 49.383944| 53.55667792|

**Figure S13.** Conversion vs time under standard conditions

### 5.3.3 Reaction with 0.5 x [CuI]₀ and 0.5 x [L₁H]₀
### 5.3.4 Reaction using 2 x [4]₀

#### Figure S14. Conversion vs time with \( \frac{1}{2} \times [\text{CuI}] \) and [L₁H]

#### 3 - Cs₂CO₃ 2 x Amide

| Time (mins) | PA ArI | PA Prod | PA Std | [SM] | [Prod] | ArI % | Prod Form % |
|-------------|--------|---------|--------|------|--------|-------|-------------|
| 31          | 955348.5 | 27109.04 | 58907.93 | 0.012225 | 0.000229 | 94.17294 | 1.76071962 |
| 64          | 881045.8 | 73045.49 | 56791.54 | 0.011694 | 0.000639 | 90.08507 | 4.921048799 |
| 96          | 817376.4 | 105436.1 | 54066.25 | 0.011396 | 0.000969 | 87.78775 | 7.461238572 |
| 124         | 779018.6 | 143096.9 | 53189.74 | 0.01104  | 0.001336 | 85.0468 | 10.29319615 |
| 156         | 796517.9 | 197913.1 | 55944.04 | 0.010733 | 0.001757 | 82.67605 | 13.53532701 |
| 183         | 722931  | 221849.5 | 51968.16 | 0.010486 | 0.00212  | 80.77882 | 16.33311474 |
| 214         | 757748.1 | 284702.2 | 56019.99 | 0.010196 | 0.002524 | 78.54524 | 19.44445465 |
| 242         | 683490.1 | 301731.4 | 52224.71 | 0.009865 | 0.00287  | 75.99661 | 22.10509921 |
| 273         | 692725  | 356079.9 | 54515.76 | 0.009579 | 0.003244 | 73.78649 | 24.99041162 |
| 333         | 649292.7 | 441806.4 | 54987.78 | 0.008901 | 0.003991 | 68.56656 | 30.7407017 |
| 392         | 613512.5 | 524995.5 | 55732.05 | 0.008298 | 0.004679 | 63.92289 | 36.04113695 |
| 456         | 444620.9 | 824844.3 | 55914.8  | 0.005994 | 0.007327 | 46.17438 | 56.44079566 |
| 514         | 188432  | 1275712 | 59750.99 | 0.002377 | 0.010604 | 18.31249 | 81.6875059 |
| 571         | 63652.2  | 1329487 | 54794.99 | 0.000876 | 0.012051 | 6.745445 | 92.83063389 |
| 634         | 22013.35 | 1469802 | 57902.72 | 0.000287 | 0.012608 | 2.207624 | 97.11982023 |
| 694         | 9095.169 | 1518308 | 59349.71 | 0.000116 | 0.012706 | 0.889878 | 97.87894854 |
| 753         | 3629.191 | 1482465 | 57273.65 | 4.78E-05 | 0.012856 | 0.367954 | 99.03245728 |
5.3.5 Repeat of reaction under standard conditions

| Time (mins) | PA ArI  | PA Prod  | PA Std  | [SM]   | [Prod]   | ArI %   | Prod Form % |
|------------|---------|----------|---------|--------|----------|---------|-------------|
| 31         | 1037740 | 45770.55 | 64791.31| 0.012073| 0.000351 | 92.82792| 2.697649544 |
| 65         | 861996.8| 92424.58 | 56403.08| 0.01152 | 0.000814 | 88.574569| 6.257498857 |
| 97         | 818517.6| 163376.4 | 56530.99| 0.010914| 0.001435 | 83.916555| 11.0361813 |
| 125        | 729028.3| 229189   | 53313.49| 0.010308| 0.002135 | 79.252585| 16.4162027 |
| 156        | 675564  | 320437   | 53437.91| 0.00953 | 0.000297 | 73.269501| 22.89862465|
| 184        | 602074.8| 374588.1 | 50076.58| 0.009063| 0.003715 | 69.682222| 28.56507822|
| 215        | 618281.2| 558230.9 | 58077.5 | 0.008025| 0.004774 | 61.699877| 36.70473269|
| 242        | 498490.2| 554229.5 | 49820.29| 0.007542| 0.005525 | 57.99046 | 42.48146771|
| 273        | 348323  | 847009.5 | 53567.33| 0.004902| 0.007853 | 37.686722| 60.38157435|
| 333        | 109582.7| 1227578  | 53128.4 | 0.001555| 0.011476 | 11.954228| 88.23455635|
| 392        | 47245.4 | 1341448  | 53916.27| 0.000661| 0.012357 | 5.0786219| 95.01015088|
| 456        | 23267.45| 1410894  | 55226.41| 0.00318 | 0.012689 | 2.4417894| 97.55821056|
| 515        | 14185.83| 1516637  | 58691.41| 0.00182 | 0.012834 | 1.4008328| 98.6786388 |
| 572        | 8489.127| 1461659  | 56269.36| 0.000114| 0.012902 | 0.874374 | 99.19509911 |
| 634        | 4979.362| 1453973  | 56033.48| 6.7E-05 | 0.012888 | 0.5150297| 99.08883533 |
Figure S16. Conversion vs time under standard conditions (repeat)

5.3.6 Reaction with 0.5 x [CuI]

| Time (mins) | PA ArI | PA Prod | PA Std | [SM] | [Prod] | ArI %  | Prod Form % |
|------------|--------|---------|--------|------|--------|--------|-------------|
| 31         | 1001805| 17102.66| 60057.87| 0.012574| 0.000141| 94.30725| 1.060805203 |
| 65         | 941578.2| 42322.84| 57940.68| 0.01225 | 0.000363| 91.87655| 2.721027982 |
| 97         | 902367.2| 58514.66| 56302.38| 0.012081| 0.000516| 90.61257| 3.871504907 |
| 125        | 800768.1| 70924.81| 50903.31| 0.011858| 0.000692| 88.93908| 5.190318391 |
| 156        | 844400.3| 102991.1| 54298.01| 0.011723| 0.000942| 87.92175| 7.065741363 |
| 184        | 800178.2| 132372.1| 52194.76| 0.011556| 0.00126 | 86.67457| 9.447380594 |
| 215        | 847612.4| 197985.2| 56940.01| 0.011221| 0.001727| 84.16114| 12.95259863 |
| 243        | 708995.1| 201942  | 49186.32| 0.010866| 0.002039| 81.49497| 15.29410865 |
| 274        | 758364.7| 289973  | 54586.47| 0.010473| 0.002638| 78.54617| 19.78856484 |
| 333        | 711714.1| 352845.5| 54048.74| 0.009926| 0.003242| 74.4478 | 24.31872591 |
| 392        | 685271.4| 451094.9| 55768.48| 0.009263| 0.004017| 69.47135| 30.13151368 |
| 457        | 654148  | 558412.9| 57289.22| 0.008607| 0.004841| 64.55576| 36.3098399  |
| 515        | 579752.6| 696658  | 59396.41| 0.007358| 0.005825| 55.18416| 43.69193222 |
| 572        | 359376.7| 1047975 | 59753.46| 0.004534| 0.008711| 34.00312| 65.33257194 |
| 634        | 203751.8| 1325913 | 62249.21| 0.002467| 0.010579| 18.50544| 79.34562146 |
| 695        | 112256.8| 1411357 | 59046.26| 0.001433| 0.011872| 10.74861| 89.04022383 |
| 754        | 78355   | 1653047 | 66008.15| 0.000895| 0.012438| 6.711214| 93.28878617 |
Figure S17. Conversion vs time with $\frac{1}{2}$ [CuI]

5.3.7 Reaction with 0.5 eq. of product 5 at the beginning

| Time (mins) | PA ArI   | PA Prod  | PA Std   | [SM]     | [Prod]    | ArI %   | Prod Form % |
|-------------|----------|----------|----------|----------|-----------|---------|-------------|
| 33          | 910903.7 | 459431.7 | 58322.67 | 0.011773 | 0.003912 | 100     | 0           |
| 67          | 843571.5 | 555496.6 | 58216.72 | 0.010923 | 0.004739 | 92.7763 | 5.27035422  |
| 99          | 772858.2 | 791353   | 60802.72 | 0.009582 | 0.006464 | 81.3844 | 16.26794758 |
| 127         | 477088.9 | 760115.8 | 46156.43 | 0.007792 | 0.008179 | 49.6733 | 52.14509135 |
| 158         | 364852.8 | 1355119  | 61552.88 | 0.004468 | 0.010935 | 28.4855 | 69.70996456 |
| 186         | 327912.3 | 1809954  | 72043.29 | 0.003431 | 0.012478 | 21.8735 | 79.54994252 |
| 217         | 219230.2 | 1650212  | 61862.14 | 0.002671 | 0.013249 | 17.0306 | 84.46576869 |
| 244         | 149247.4 | 1398011  | 50820.53 | 0.002214 | 0.013663 | 14.1131 | 87.10382062 |
| 275         | 136168.4 | 1540463  | 54341.93 | 0.001889 | 0.014079 | 12.0419 | 89.75985034 |
| 335         | 117974.1 | 1644142  | 57321.14 | 0.001551 | 0.014246 | 9.8907  | 90.82184218 |
| 394         | 91071.04 | 1556874  | 52941.99 | 0.001297 | 0.014606 | 8.2667  | 93.11488061 |
| 458         | 75378.04 | 1608370  | 53814.68 | 0.001056 | 0.014844 | 6.7313  | 94.63486322 |
| 517         | 60251.01 | 1591394  | 52825.14 | 0.00086  | 0.014963 | 5.4812  | 95.39005259 |
| 574         | 51067.94 | 1663114  | 54634.89 | 0.000705 | 0.015119 | 4.4919  | 96.38681218 |
| 636         | 41346.34 | 1706435  | 55868.5  | 0.000558 | 0.01517  | 3.5565  | 96.71383295 |
| 696         | 33512.85 | 1740238  | 56603.03 | 0.000446 | 0.01527  | 2.8453  | 97.34974328 |
5.3.8 Reaction with 1.0 eq of H₂O at the beginning

| Time (mins) | PA ArI | PA Prod | PA Std | [SM]    | [Prod]   | Arl %  | Prod Form % |
|-------------|--------|---------|--------|---------|----------|--------|-------------|
| 32          | 980636.7 | 54478.95 | 62448.46 | 0.011837 | 0.000433 | 91.930558 | 3.365041774 |
| 69          | 816739.5 | 126456.7 | 55584.89 | 0.011076 | 0.00113  | 86.020176 | 8.775434455 |
| 98          | 749461.4 | 181962.4 | 53393.05 | 0.010581 | 0.001693 | 82.17468 | 13.14560172 |
| 129         | 684268.9 | 239412.8 | 51481.43 | 0.010019 | 0.00231  | 77.812563 | 17.9382562 |
| 157         | 633410.4 | 290698.7 | 49833.81 | 0.009581 | 0.002897 | 74.410568 | 22.50103244 |
| 188         | 641972.5 | 384752.3 | 54180.11 | 0.008932 | 0.003527 | 69.36654 | 27.39205982 |
| 216         | 461594.2 | 351018.1 | 40877.43 | 0.008512 | 0.004265 | 66.107436 | 33.12298044 |
| 247         | 439286.1 | 399724.5 | 42749.02 | 0.007746 | 0.004644 | 60.158184 | 36.06766261 |
| 274         | 376747.4 | 432595  | 37988.81 | 0.007476 | 0.005656 | 58.058808 | 43.92474669 |
| 334         | 158115.5 | 809519.2 | 40555.78 | 0.002939 | 0.009914 | 22.824176 | 76.99416116 |
| 393         | 61986.28 | 968976.3 | 41357.68 | 0.00113  | 0.011637 | 8.7743086 | 90.37335456 |
| 457         | 25221.56 | 915894.7 | 36805.34 | 0.000517 | 0.01236  | 4.0117559 | 95.98824405 |
| 515         | 16041.85 | 1116561 | 44066.72 | 0.000274 | 0.012585 | 2.1311648 | 97.73612517 |
| 573         | 7410.274 | 947561.5 | 36864.27 | 0.000152 | 0.012766 | 1.1767985 | 99.14828248 |
| 639         | 4603.591 | 1097073 | 42911.34 | 8.09E-05 | 0.012698 | 0.6280556 | 98.61591688 |

Figure S18. Conversion vs time (a) with 0.5 eq. of 5 and (b) under standard conditions.
5.4 Kinetic data with L\textsuperscript{2}H/K\textsubscript{3}PO\textsubscript{4}

Protocol described in section 5.1 was followed. The detailed quantities of reagents are summarised below.

|               | MW (g.mol\textsuperscript{-1}) | Density (g.mL\textsuperscript{-1}) | Standard | 0.5x [Cu/L\textsuperscript{1}] | 2x [L\textsuperscript{1}] | Std Duplicate | 0.5x Cu | 2x [L\textsuperscript{1}H] | 2x K\textsubscript{3}PO\textsubscript{4} |
|---------------|---------------------------------|------------------------------------|----------|---------------------------------|---------------------------|----------------|---------|---------------------------|---------------------|
| Cul (mg)      | 190.44                          | 9.5                                | 4.8      | 9.5                             | 9.5                       | 4.7            | 9.5     | 9.5                       | 9.5                 |
| L\textsuperscript{2}H (mg) | 193.24                          | 19.3                               | 9.7      | 19.3                            | 19.3                      | 19.3           | 38.6    | 19.3                      | 19.3                |
| 1,1'-Biphenyl (mg) | 154.21                          | 7.7                                | 7.7      | 7.7                             | 7.7                       | 7.7            | 7.7     | 7.7                       | 7.7                 |
| K\textsubscript{3}PO\textsubscript{4} (mg) | 325.82                          | 244                                | 244      | 244                             | 244                       | 244            | 488     | 244                       | 488                 |
| DMF (µl)      |                                 | 2500                               | 2500     | 2500                            | 2500                      | 2500           | 2500    | 2500                      | 2500                |
| 1 (mg)        | 234.03                          | 117                                | 117      | 117                             | 117                       | 117            | 117     | 117                       | 117                 |
| 4 (µl)        | 85.15                           | 57                                 | 57       | 114                             | 57                        | 57             | 57      | 57                        | 57                  |

5.4.1 Reaction under standard conditions

| Time (mins) | PA Arl  | PA Prod  | PA Std  | [SM]    | [Prod]   | Arl % | Prod Form |
|-------------|---------|----------|---------|---------|----------|-------|-----------|
| 50          | 832326.2| 93074.82 | 56224.53| 0.011159| 0.000822 | 98.6  | 7.3       |
| 112         | 1083567 | 506569.4 | 86675.3 | 0.009424| 0.002903 | 83.2  | 25.6      |
| 173         | 536204.2| 468594.1 | 52788.2 | 0.007657| 0.004409 | 67.6  | 38.9      |
| 242         | 437313.6| 575471.9 | 51004.6 | 0.006463| 0.005604 | 57.1  | 49.5      |
| 300         | 844376.4| 1372924  | 105182.8| 0.006051| 0.006483 | 53.5  | 57.3      |
| 363         | 702414.7| 1404938  | 98290.64| 0.005387| 0.007099 | 47.6  | 62.7      |
| 420         | 359939.1| 868231.1 | 57427.54| 0.004725| 0.007509 | 41.7  | 66.3      |
| 482         | 316525.6| 891033.7 | 55912.07| 0.004267| 0.007915 | 37.7  | 69.9      |
| 539         | 297969  | 924630.4 | 56243.88| 0.003994| 0.008165 | 35.3  | 72.1      |
| 602         | 295750.2| 1038246  | 60669.82| 0.003675| 0.0085  | 32.5  | 75.1      |
| 622         | 258655.1| 930763   | 54605.9 | 0.003571| 0.008466 | 31.5  | 74.8      |
5.4.2 Repeat of reaction under standard conditions

| Time (mins) | PA ArI | PA Prod | PA Std | [SM]   | [Prod]   | ArI %   | Prod Form % |
|-------------|--------|---------|--------|--------|---------|---------|-------------|
| 51          | 828865.7 | 107468.4 | 57556.79 | 0.010855 | 0.00927 | 95.9    | 8.2         |
| 112         | 622736.6 | 319247.6 | 52802.93 | 0.00889  | 0.003003 | 78.5    | 26.5        |
| 173         | 538756.7 | 496317.3 | 54597.42 | 0.007438 | 0.004515 | 65.7    | 39.9        |
| 243         | 546897.3 | 736080.7 | 64485.01 | 0.006393 | 0.005669 | 56.5    | 50.1        |
| 300         | 618573.5 | 104294.3 | 80361.22 | 0.005802 | 0.006446 | 51.3    | 56.9        |
| 363         | 567948.2 | 1163954 | 81985.56 | 0.005222 | 0.007051 | 46.1    | 62.3        |
| 420         | 310109.4 | 745863.7 | 50170.19 | 0.004659 | 0.007384 | 41.2    | 65.2        |
| 482         | 259074.8 | 734641.5 | 46808.73 | 0.004172 | 0.007795 | 36.9    | 68.9        |
| 539         | 295858.7 | 925900.9 | 56942.64 | 0.003917 | 0.008076 | 34.6    | 71.3        |
| 602         | 228828.7 | 819406.2 | 48387.98 | 0.003565 | 0.008411 | 31.5    | 74.3        |
| 622         | 242222.2 | 893004.2 | 52468.78 | 0.00348  | 0.008453 | 30.7    | 74.7        |
| 662         | 282122.6 | 1086148 | 62527.93 | 0.003401 | 0.008628 | 30.0    | 76.2        |
| 720         | 215202.7 | 898119.6 | 51440.98 | 0.003154 | 0.008672 | 27.9    | 76.6        |
| 774         | 224170.4 | 1007039 | 56403.85 | 0.002996 | 0.008868 | 26.5    | 78.3        |

Figure S20. Conversion vs time under standard conditions

5.4.2 Repeat of reaction under standard conditions
5.4.3 Reaction with 0.5 x [CuI]₀ and 0.5 x [L₂H]₀

| Time (mins) | PA ArI | PA Prod | PA Std | [SM]    | [Prod]   | ArI % | Prod Form % |
|------------|--------|---------|--------|---------|---------|------|--------------|
| 51         | 831365.4 | 15285.59 | 55791.87 | 0.011233 | 0.000136 | 99.2 | 1.2          |
| 112        | 1250241 | 52067.97 | 84983.67 | 0.01109  | 0.000304 | 98.0 | 2.7          |
| 173        | 727560.7 | 47407.76 | 51426   | 0.010665 | 0.000458 | 94.2 | 4.0          |
| 243        | 716555.1 | 63413.94 | 51474.53 | 0.010493 | 0.000612 | 92.7 | 5.4          |
| 300        | 1439793 | 162612.3 | 101130.2 | 0.010732 | 0.000799 | 94.8 | 7.1          |
| 363        | 713530.2 | 96291.08 | 52546.56 | 0.010236 | 0.00091  | 90.4 | 8.0          |
| 420        | 689202.1 | 110539.3 | 51613.7 | 0.010066 | 0.001064 | 88.9 | 9.4          |
| 482        | 695442  | 128090.6 | 52846.46 | 0.00992  | 0.001204 | 87.6 | 10.6         |
| 540        | 743596.3 | 154324.4 | 59572.53 | 0.009409 | 0.001287 | 83.1 | 11.4         |
| 602        | 755952.3 | 179783.9 | 58894.47 | 0.009676 | 0.001516 | 85.5 | 13.4         |
| 662        | 748864.8 | 185480.9 | 58731.95 | 0.009611 | 0.001569 | 84.9 | 13.9         |
| 720        | 894931.2 | 239562.5 | 70360.11 | 0.009588 | 0.001691 | 84.7 | 14.9         |
| 774        | 723825   | 212114.3 | 58586.88 | 0.009313 | 0.001798 | 82.3 | 15.9         |
| 834        | 651044.6 | 209610.1 | 53851.51 | 0.009113 | 0.001933 | 80.5 | 17.1         |
### Figure S22. Conversion vs time at ½ × [CuI] and [L₁H₁]

#### 5.4.4 Reaction with 2 × [L₂H]₀

| Time (mins) | PA ArI  | PA Prod | PA Std | [SM]   | [Prod]  | ArI % | Prod Form |
|-------------|---------|---------|--------|--------|---------|-------|-----------|
| 51          | 743267.8| 215545.5| 61703.72| 0.00908| 0.001735| 80.2  | 15.3      |
| 112         | 574745.2| 419893.5| 58501.2 | 0.007406| 0.003565| 65.4  | 31.5      |
| 173         | 493400.1| 544480.5| 57890.17| 0.006425| 0.004671| 56.8  | 41.3      |
| 243         | 438624  | 659176.8| 58974.67| 0.005606| 0.005551| 49.5  | 49.0      |
| 301         | 717778.3| 1272141| 102517.4| 0.005278| 0.006163| 46.6  | 54.4      |
| 363         | 681146.7| 1426335| 106561.6| 0.004818| 0.006648| 42.6  | 58.7      |
| 420         | 353960.8| 881610.6| 62577.32| 0.004264| 0.006997| 37.7  | 61.8      |
| 482         | 447450.9| 1237535| 83782.04| 0.004026| 0.007336| 35.6  | 64.8      |
| 540         | 285598.9| 895244.3| 58747.74| 0.003665| 0.007569| 32.4  | 66.9      |
| 603         | 276763.6| 952953.9| 60805.26| 0.003431| 0.007784| 30.3  | 68.8      |
| 622         | 267237.1| 944561.5| 59967.42| 0.003359| 0.007823| 29.7  | 69.1      |
| 662         | 214400.7| 812531.1| 50740.39| 0.003185| 0.007953| 28.1  | 70.3      |
| 721         | 207805.9| 853448  | 52273.61| 0.002997| 0.008109| 26.5  | 71.6      |
| 774         | 235108.3| 1001362| 60555.71| 0.002927| 0.008213| 25.9  | 72.6      |
5.4.5 Reaction with $0.5 \times [L^2H]_0$

**Figure S23.** Conversion vs time at $2 \times [CuI]$ and $[L^1H]$  

| Time (mins) | PA ArI | PA Prod | PA Std | [SM]    | [Prod]  | ArI % | Prod Form % |
|------------|--------|---------|--------|---------|---------|--------|-------------|
| 51         | 1381208| 47337.94| 89008.24| 0.011697| 0.000264| 103.3  | 2.3         |
| 112        | 1140044| 102487.1| 76352.37| 0.011255| 0.000667| 99.4   | 5.9         |
| 173        | 858005.1| 163705  | 61671.29| 0.010487| 0.001318| 92.6   | 11.6        |
| 243        | 659901.2| 308394.9| 55229.58| 0.009007| 0.002773| 79.6   | 24.5        |
| 301        | 1347611| 1114004 | 127165.1| 0.007988| 0.004351| 70.6   | 38.4        |
| 364        | 432781.4| 526612.5| 50091.76| 0.006513| 0.005221| 57.5   | 46.1        |
| 420        | 420064  | 679791.7| 55493.56| 0.005706| 0.006084| 50.4   | 53.7        |
| 483        | 371328.5| 759560.6| 55784.94| 0.005018| 0.006763| 44.3   | 59.7        |
| 540        | 331265.4| 817441  | 55675.72| 0.004485| 0.007292| 39.6   | 64.4        |
| 603        | 299267  | 871479.8| 56134.44| 0.004019| 0.007711| 35.5   | 68.1        |
| 623        | 318385.3| 968847.5| 61307.83| 0.003915| 0.007849| 34.6   | 69.3        |
| 663        | 250623.4| 853109.6| 52291.96| 0.003613| 0.008103| 31.9   | 71.6        |
| 721        | 259571.8| 995108.5| 59203.3 | 0.003305| 0.008348| 29.2   | 73.7        |
| 775        | 223251.3| 943141.5| 54818.82| 0.00307 | 0.008545| 27.1   | 75.5        |
| 834        | 221073.3| 1031762 | 58603.17| 0.002844| 0.008744| 25.1   | 77.2        |
Figure S 24. Conversion vs time at $\frac{1}{2}$ x $[\text{L}^1\text{H}]$

5.4.6 Reaction with 2 x $\text{K}_3\text{PO}_4$

| Time (mins) | 2 x $[\text{K}_3\text{PO}_4]$ |
|-------------|-------------------------------|
|             | PA Arl | PA Prod | PA Std | [SM] | [Prod] | ArI % | Prod Form % |
| 51          | 793376 | 24602.04 | 56105.54 | 0.010659 | 0.000218 | 94.2  | 1.9          |
| 113         | 841502.3 | 57108.17 | 60483.55 | 0.010488 | 0.000469 | 92.6  | 4.1          |
| 174         | 784065.9 | 82299.16 | 58057.55 | 0.01018 | 0.000704 | 89.9  | 6.2          |
| 244         | 676057.1 | 100953.6 | 51462.76 | 0.009903 | 0.000974 | 87.5  | 8.6          |
| 301         | 649321.5 | 120757.2 | 50605.91 | 0.009672 | 0.001185 | 85.4  | 10.5         |
| 364         | 1317189 | 303659.1 | 101453.8 | 0.009787 | 0.001487 | 86.5  | 13.1         |
| 421         | 617657.1 | 165451.3 | 50472.34 | 0.009225 | 0.001628 | 81.5  | 14.4         |
| 483         | 673499.1 | 213116.2 | 56107.71 | 0.009048 | 0.001887 | 79.9  | 16.7         |
| 540         | 605689 | 215824.1 | 51904.72 | 0.008796 | 0.002065 | 77.7  | 18.2         |
| 603         | 591231.2 | 240354.2 | 51981.47 | 0.008574 | 0.002297 | 75.7  | 20.3         |
| 623         | 464994.9 | 196600.1 | 41746.9 | 0.008396 | 0.002339 | 74.2  | 20.7         |
| 663         | 612322.4 | 279472.7 | 55248.23 | 0.008355 | 0.002512 | 73.8  | 22.2         |
| 721         | 659479.3 | 329015.8 | 60808.72 | 0.008175 | 0.002687 | 72.2  | 23.7         |
| 775         | 598169.1 | 327601.4 | 56850.52 | 0.007931 | 0.002862 | 71.0  | 25.3         |
| 834         | 569422.7 | 344306.7 | 55684.46 | 0.007708 | 0.003071 | 68.1  | 27.1         |
Figure S25. Conversion vs time at 2 x K$_3$PO$_4$

5.4.7 Reaction with 2 x [4]$_0$

| Time (mins) | PA ArI  | PA Prod | PA Std | [SM] | [Prod]  | ArI | Prod Form |
|------------|---------|---------|--------|------|---------|-----|-----------|
| 52         | 764835.4| 28043.44| 52765.33| 0.010926| 0.000264 | 96.5 | 2.3       |
| 113        | 725752.6| 63779.2 | 51730.08| 0.010576| 0.000612 | 93.4 | 5.4       |
| 174        | 659249.9| 95482.65| 48751.91| 0.010193| 0.000973 | 90.0 | 8.6       |
| 244        | 949262  | 226673  | 72461.42| 0.009875| 0.001554 | 87.2 | 13.7      |
| 302        | 770540.2| 274661.6| 63126.34| 0.009201| 0.002161 | 81.3 | 19.1      |
| 364        | 605539.9| 334609.9| 55197.42| 0.00827 | 0.003011 | 73.1 | 26.6      |
| 421        | 553979.6| 437704.8| 56278.44| 0.00742 | 0.003863 | 65.5 | 34.1      |
| 483        | 450503.4| 499282.5| 52249.56| 0.006499| 0.004746 | 57.4 | 41.9      |
| 541        | 433399.1| 630050.6| 56835.14| 0.005748| 0.005506 | 50.8 | 48.6      |
| 604        | 405054.6| 762469  | 60781.93| 0.005023| 0.00623 | 44.4 | 55.0      |
| 624        | 359090.5| 731685.3| 56718.33| 0.004772| 0.006407 | 42.2 | 56.6      |
| 663        | 373673.3| 882732.8| 64182.55| 0.004389| 0.006831 | 38.8 | 60.3      |
| 722        | 228225.1| 666694.5| 45897.11| 0.003748| 0.007215 | 33.1 | 63.7      |
| 775        | 250217.6| 881425  | 56840.74| 0.003318| 0.007702 | 29.3 | 68.0      |
| 835        | 198948.2| 844650.3| 52086.95| 0.002879| 0.008054 | 25.4 | 71.1      |
5.5 Reaction with L^3/Cs_2CO_3

A reaction protocol similar to one described in section 5.1 was employed, with L^3 replacing L^1H. When using oven dried, milled Cs_2CO_3, the above reaction was extremely slow, with kinetic monitoring over the first 4 hours showing up to 8% product. After 48 hours, GC analysis showed 45% conversion to product. In a repeat of the experiment without sampling, conversion to product reached 57%.
6. Reaction with additional halide salts

CuI (19 mg, 0.1 mmol, 10 mol%), 1,10-phenanthroline L³ (36 mg, 0.2 mmol), Cs₂CO₃ (489 mg, 1.5 mmol), 4-iodoanisole 1 (234 mg, 1 mmol) and the halide salt (1 mmol, 1 eq.) were added to a flame dried Schlenk flask. The vessel was evacuated and backfilled with argon gas three times before the 2-pyrrolidinone 4 (114 µl, 1.5 mmol) and degassed, anhydrous DMF (5 mL) were added. The reaction was stirred at 90 °C under a gentle flow of argon for 14 hours. Upon completion, 100 µl of the reaction mixture was diluted to 1.5 ml with MeCN and analysed by GC (calibration data in section 10.1).

| Additive | Conversion to product 5 (%) | Side products |
|----------|-----------------------------|--------------|
| None     | 87                          | Side products |
| NaI      | 14                          | 4-Bromoanisole (5%) |
| NaBr     | 14                          | 4-Chloroanisole (trace) |
| NaCl     | 26                          | Side products |
| CsI      | 32                          | Side products |

Figure S28. Conversion at 14 hours in the presence of halide salts

7. EPR experiments

7.1 In situ EPR experiment

Reaction protocol from section 5.1 was scaled for 2.5 g of 4-iodoanisole 1 (10.7 mmol), with one difference: CuI was added last to the pre-equilibrated reaction mixture containing all other components to enable EPR background measurements. The reaction was performed under argon using in a jacketed glass reactor at 80 °C and the solution (with in situ filtration) was circulated through the EPR cavity using an FEP tube (ID 0.8 mm) using a Milligat pump at a flow rate of 3.0 mL/min. EPR spectra were recorded on a Brücker ELEXYS spectrometer at room temperature in X-band with a microwave power of 6.9 mW, a modulation frequency of 100 kHz and modulation amplitude of up to 5 G.
**Figure S29.** *In situ* EPR measurements over the course of the experiment. Immediately after addition of CuI an isotropic Cu(II) signal emerged, which vanished after about 5-10 min of heating. The Cu(II) signal was not observed afterwards.

### 7.2 CuI/LH/DMF experiment

Sample was prepared using a standard EPR tube in a glovebox with degassed DMF and measured using the same equipment as described above. The sample was cooled with liquid nitrogen during this measurement.
Slight line broadening is observed in CuII signal of reaction solution (red graph) which lead to loss in intensity at high field peaks. These effects could be caused by a slower tumbling rate due to interaction with other reaction components (substrate, base etc.) which were absent in the CuI+DMG experiment (black).

8. Characterization of commercial Cs₂CO₃ samples

8.1 Sample preparation

Bases were analysed by SEM either fresh from the bottle or following drying in a 75 ºC oven when specified. Samples were stored under argon prior to analysis.

8.2 SEM/EDX experiments

All samples were mounted in powder form, under exclusion of ambient moisture, on SEM sample stubs using adhesive carbon film. The samples were then coated with a thin layer of iridium using a Cressington 208HR sputter coater. Samples were imaged using an FEI Nova NanoSEM 450 operating typically at 3 kV. The gun voltage was increased to 10 keV to collect EDX point spectra.
8.2.1 Sigma Aldrich, 99 %. Lot # BCBP3311V. PCode 101550748

Figure S31. SEM pictures of Base 2
8.2.2 Acros Organics, 99.5 %. Lot # A0359643. Code 192041000

Figure S32. SEM pictures of Base 3
Figure S33. SEM pictures of Base 1
8.3 Surface area measurements

Nitrogen adsorption measurements indicate that all three base powders have very small specific surface areas (<1 m²/g). Nitrogen adsorption measurements are not suited to accurately quantify such low specific surface areas, so a comparison between the three bases using this method is not feasible.

9. Characterisation of solid during and after reaction

Reactions were performed as outlined in section 5.1. Following completion of the reaction, the solution stopped stirring and was removed via syringe at 90 °C, the solid was then washed three times with hot, anhydrous Et₂O and evaporated to dryness. The dried solid was stored under argon until analysis was performed.

9.1 SEM/EDX experiments

9.1.1 Base Isolated Post-reaction – Chemmetal Cs₂CO₃

In order to probe the link the morphology and surface area of the bases with their kinetic behavior, solid samples were recovered from the reaction mixtures using Base1 and Base2 at 2.5 and 5.0 hours. SEM pictures of these are shown in Figure S34. Chemical speciation was achieved by a combination of EDX data and power X-ray diffraction (Figure S37). Comparing Figure S34a-d showed that, as the reaction progresses, bright cubic crystals of CsI (in SEM pictures, Figure S34e), assigned based on EDX characterization (Figure S35-S37), accumulates on the solids. More importantly, the soft-edge structure of Cs₂CO₃ gave way to a crystalline material which was identified by EDX to contain Cs, C, and O. Powder X-ray diffraction data of the sample recovered from reaction using Base2 at 5 hours indicated that these crystals are CsHCO₃ (Figure S34e). No diffraction signal for Cs₂CO₃ was detected for this sample. Thus, during the reaction, the morphology all Cs₂CO₃ samples changes toward a common final state. The difference in the initial rates of reaction using Base1, Base2 and Base3 must therefore originated from their initial states. We hypothesized that the difference in surface area, and hence their rates of dissolution in DMF,⁶ are the main reason for the observed induction period with Base1.
Figure S34. SEM images of inorganic solids from the reaction mixture using (a) Base1 at 2.5 hour; (b) Base2 at 2.5 hours; (c) Base1 at 5 hours; (d) Base2 at 5 hours of reaction time; (e) Powder diffraction patterns of the recovered solid (Base2) after 5 hours.

Figure S35. Comparison between the powder diffraction patterns of Base1 at 5 hours and a fresh sample of Base1. Some observable common peaks are highlighted in red.
Figure S36. SEM/EDX results of isolated base post reaction: (a) SEM imaging of bulk material post-reaction, low magnification; (b) zoomed in picture of the region of which EDX spectra relates to; and (c) iodine distribution.

| Spot | Cs  | O   | I   | Cu  |
|------|-----|-----|-----|-----|
| A    | 22at% | 72at% | 5at% | 1at% |
| B    | 21at% | 78at% | 0.5at% | 0.5at% |

Figure S37. Elemental compositions of recovered Base1 and Base2, as probed locally by EDX point spectra in two different areas of each sample (indicated by Spot A and Spot B in the SEM images).

| Spot | Cs  | O   | I   | Cu  |
|------|-----|-----|-----|-----|
| A    | 46at% | 22at% | 31.5at% | 0.5at% |
| B    | 69at% | 27at% | 3at% | 1at% |
9.2 XRD measurements

X-Ray powder diffraction data was collected on a Bruker D2 Phaser Diffractometer. Powdered samples were mounted on a silicon wafer by evenly distributing the powder over the wafer. All samples were rotated during data collection to ensure more homogeneous (i.e. isotropic) diffraction patterns. Data collection was carried out at room temperature, using Cu Kα radiation ($\lambda = 1.54184 \, \text{Å}$). Diffraction patterns were recorded in step-scan mode with a step size of $(2\theta) 0.7^\circ$, from $(2\theta) 5^\circ$ to $55^\circ$ (30 secs per step) using a 0.1 or 0.6mm divergent slit. Samples showed no significant evidence of degradation within the X-ray beam. The software package Diffrac.Suite Eva14 was used to process the experimental powder X-ray diffraction data collected, and Mercury 3.3 was used to simulate the powder diffraction pattern of the single crystal structures taken from literature.

10. Base-less coupling reaction

10.1 GC Calibrations

1,1'-Biphenyl used as an internal standard (IS).

| [1] (M) | 0.0167 | 0.0133 | 0.0067 | 0.0033 | 0.0013 |
|---------|-------|-------|-------|-------|-------|
| Area 1  | 1003.5| 788.1 | 400   | 201.8 | 76.3  |
| Area IS – 0.000133 M | 159.6 | 157.6 | 159   | 158.1 | 157.2 |
| Area 1/IS | 6.29  | 5.00  | 2.52  | 1.28  | 0.49  |
Product 5 = 1-(4-methoxyphenyl)pyrrolidin-2-one

| [I] | 0.0167 | 0.0133 | 0.0067 | 0.0033 | 0.0013 |
|-----|--------|--------|--------|--------|--------|
| Area 5 | 1272.4 | 1002.7 | 491.8  | 231.7  | 83.8   |
| Area IS – 0.000133 M | 127 | 124.3 | 122 | 119.5 | 117.2 |
| Area 5/IS | 10.02 | 8.07 | 4.03 | 1.94 | 0.72 |

Calibration for 1

Calibration for 5
10.2 Mass spectrometry experiments for base-less reaction

**Figure S39.** Positive ion HRMS of a mixture of CuI, L₃ and Cs₂CO₃ in DMF before and after treatment with salt 6, showing consumption of [Cu(L₃)₂]⁺ and formation of the deactivated complex II (observed indirectly through the formation of L₃ and [Na(L₃)₂⁺]).

10.3 Reaction Procedures

10.3.1 Sampling air-sensitive reactions

To ensure no oxygen is introduced into the reaction system by standard sampling techniques, enough needles for the desired amount of samples are introduced prior to the vacuum/inert gas cycles, with each needle thoroughly flushed. The set-up as shown below has been found to be a simple method of obtaining kinetic data with these reactions.
10.3.2 Experiment with a single addition of 6

CuI (19 mg, 0.1 mmol), 1,10-phenanthroline \( L_3 \) (36 mg, 0.2 mmol), 1,1'-biphenyl (15.4 mg, 0.1 mmol) and 4-iodoanisole 1 (234 mg, 1 mmol) were added to a flame-dried Schlenk flask under nitrogen. Three purge/flush cycles were performed prior to addition of degassed DMF (2.5 mL). In a separate flask, Na-pyrrolidinone 6 (160 mg, 1.5 mmol) was mixed with degassed DMF (2.5 mL) under nitrogen to give a suspension. Both flasks were heated to 90 °C and the Na-pyrrolidinone 6 suspension was added in three portions at 0, 1 and 2 hours. The reaction was stopped after 20 hours and GC analysis showed 60 % conversion to product.

10.3.3 Experiment with portion-wise addition of 6

The same procedure as above was performed with three additions of added dropwise over 5 minutes which is represented by the blue line in Figure S37. Samples were quenched by exposure to air and dilution with MeCN, GC analysis was used to give conversion data and a final sample at 20 hours gave 60 % conversion to product.
11. Base Solubility by $^{133}$Cs NMR

$^{133}$Cs NMR spectra were collected at 90 °C in DMF. An insert tube was used to include 0.1 M aqueous solution of CsNO$_3$ as external standard, while preventing Cs exchange between the standard and the sample. Samples were prepared by stirring saturated solutions of CsI, CsHCO$_3$ and Cs$_2$CO$_3$ (Acros Organics, Lot A0359643) in anhydrous DMF at 90 °C for 2 hours. After the mixture was allowed to settle, the supernatants (0.5 mL) were transferred to an NMR tube via a syringe fitted with a metal needle (pre-flushed with hot DMF). An insert tube filled with 0.1 M CsNO$_3$ in D$_2$O was inserted into the NMR tube and the samples kept at 90 °C. The samples were inserted to the NMR spectrometer at 70 °C and quickly heated to 90 °C before data acquisition.

The $^{133}$Cs NMR data (Figure S38), referenced to the 0.1 M CsNO$_3$ standard, showed that the saturated concentrations of the caesium salts are:

| Salt     | Saturated concentration in DMF at 90 °C (M) |
|----------|-------------------------------------------|
| Cs$_2$CO$_3$ | 0.05                                      |
| CsHCO$_3$      | 0.12                                      |
| CsI            | 1.92                                      |

The saturated concentration of CsI was much higher than those of Cs$_2$CO$_3$ and CsHCO$_3$. Thus, monitoring Cs content of the reaction mixtures does not reflect the solubility of Cs$_2$CO$_3$ in these systems.
Figure S42. $^{133}$Cs NMR spectra of saturated solutions of CsI, Cs$_2$CO$_3$ and CsHCO$_3$ in DMF at 90 °C

12. References

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