Electronic Supplementary Information for Faraday Discussions

Investigations Into the Mechanism of Copper-Mediated Glaser-Hay Couplings Using Electrochemical Techniques

Peter W. Seavill, Katherine B. Holt and Jonathan D. Wilden*

Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK. *Corresponding author, E-mail: j.wilden@ucl.ac.uk

General Information:

Solvents and reagents were purchased from suppliers and used without any further purification unless otherwise stated. Normal phase silica gel (Merck KGaA) and sand (VWR) were used for column chromatography. All reactions were monitored by TLC unless otherwise stated. TLC plates pre-coated with silica gel 60 F₂₅₄ on aluminium (Merck KGaA) were used, detection by UV (254 nm) and chemical stain (potassium permanganate). Mass spectra were measured on Thermo Finnigan MAT900 XE and Waters LCT Premier XE machines operating in ESI mode. ¹H NMR spectra were recorded at 300 or 600 MHz and ¹³C NMR spectra were recorded at 150 or 176 MHz on Bruker Avance spectrometers at ambient temperature. All chemical shifts were referenced to the residual proton impurity of the deuterated solvent. In ¹H NMR the multiplicity of the signal is indicated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet), defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. The ¹³C NMR is assigned as C (quaternary), CH, CH₂ and CH₃ as determined by DEPT 135. Coupling constants are defined as J and quoted in Hz to one decimal place. Infrared spectra were obtained on a Bruker Alpha FTIR Spectrometer operating in ATR mode and peaks were assigned as 'w', 'm' or 's' denoting weak, medium or strong peaks respectively. Melting points were measured with a Gallenkamp apparatus and are uncorrected. In vacuo is used to describe solvent removal by Büchi rotary evaporation between 17-40 °C. For NMR experiments, CDCl₃ denotes deuterated (d_1) chloroform and $(CD_3)_2$ SO denotes deuterated (d_6) DMSO. Electrochemical reactions were carried out using an Ivium Technologies Vertex model potentiostat operating in chronoamperometry mode. CV plots were carried out using this same potentiostat with a glassy carbon working-electrode, a Pt wire counter-electrode and a Ag wire quasi reference-electrode and were referenced against the ferrocene redox couple.

Details of Electrochemical Methods:

The general experimental setup we used for electrochemical reactions was designed to be as simple and accessible as possible. In doing so we hope to minimise the disparity and lack of reproducibility of results inherent in electro-organic synthesis due to there being a lack of standardised experimental setups. For all reactions we used a divided 'H' cell as our reaction vessel (dimensions shown in Figure S1 in Supplementary Information) with each chamber having a size B19 ground-glass neck and a total volume of 20 mL. A semi-porous sintered glass divider sits between each chamber. All reactions were however carried out using 10 mL of electrolyte solution in each chamber as this was sufficient to sit above the line of the sintered glass divider and thus allow sufficient ion transfer. Copper electrodes were made by cutting strips from a roll of metallic copper sheet metal (around 0.5 mm thickness) to create plates with dimensions of 10 mm x 40 mm. When used, these were placed into solution to a depth of 25 mm, meaning the area of electrode exposed to solution was approximately 530 mm². A silver wire, which was 1 mm thick, was used as a quasi reference-electrode and was likewise placed into solution to a depth of 25 mm giving an effective area of 79 mm². Both the copper plate and the silver wire were placed into the same chamber to minimise the potential drop deriving from resistance and kept 10 mm apart. A platinum wire of 1 mm thickness was used as the counter-electrode and placed in the other chamber of the H cell, this time at a depth of 40 mm giving an effective area of 126 mm². Where graphite electrodes were used for the working-electrode and/or counter electrode, rods of 5 mm diameter were used at a depth of 25 mm giving an effective area of 412 mm². Reactions were run using an Ivium Technologies Vertex model potentiostat operating in chronoamperometry mode. This model allowed for real-time charge over time and current over time graphs to be generated which we found exceedingly useful for this work, especially for measuring charge passed over the course of reactions. Where a Cu-coated graphite electrode was used, it was prepared by placing a graphite rod working-electrode (4.12 cm² area) into an undivided cell containing a 0.5 M CuSO_{4(aq.)} solution. A Ag wire quasi reference-electrode (0.79 cm² area) and a Pt wire counter-electrode (1.26 cm² area) were added and all electrodes were then connected up to a potentiostat. The voltage was set to -0.50 V for 600 s and the charge passed was recorded and used to determine how much copper had been plated onto the graphite surface with the use of the Faraday equations (Equation 1).



Figure S1. Image of H Cell and electrodes used with dimensions.

Procedure for Electrochemical Glaser-Hay Reaction in DCM:

1,4-Diphenylbuta-1,3-diyne



Bu₄NPF₆ (0.39 g, 1.0 mmol, 0.5 eq) was dissolved in DCM (20 mL) to make up a 0.05 M solution. A divided (H) cell was charged with this solution (10 mL each side). A copper sheet (6.00 cm² area) and a silver wire (0.95 cm² area) were then placed into one chamber, and a platinum wire (0.95 cm² area) was placed into the other chamber. These electrodes were connected up to a potentiostat (Cu = WE, Ag = ref.) Pt = CE) and the potential was set to run at +0.50 V for 30 min whilst stirring at RT and exposed to air. Phenylacetylene (0.22 mL, 2.0 mmol, 1.0 eq) was then added to the chamber containing the copper sheet, followed by DABCO (0.27 g, 2.4 mmol, 1.2 eq) which had been dried in a vacuum oven overnight. The potentiostat was set to run at +0.50 V for a further 2.5 h whilst stirring at RT, then the solution was left to stir for a further 13 h exposed to air. The solution was then filtered into a separating funnel and extracted once with brine (30 mL), before the aqueous layer was diluted with DCM (30 mL). The organic layer was extracted and combined with the other organic layer, then washed once with H₂O (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The resulting yellow solid was dissolved in 20% EtOAc/pet. ether. and passed through a plug of silica gel to give the product as a white crystalline solid (0.17 g, 0.84 mmol, 84%); m.p. 86-88 °C (lit.,1 86-88 °C); Rf 0.54 (20% EtOAc/pet. ether.); IR vmax (solid) 3047 (w), 2143 (w), 1483 (m), 1438 (m), 914 (m), 751 (s), 682 (s), 523 (s) cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ_H 7.53-7.55 (4H, m, ArH), 7.33-7.40 (6H, m, ArH) ppm; ¹³C NMR (150 MHz, CDCl₃) δ_C 132.6 (CH), 129.3 (*C*H), 128.6 (*C*H), 121.9 (*C*), 81.7 (*C*), 74.0 (*C*) ppm; LRMS (ESI) m/z 203 ([M+H]⁺, 6%), 201 (48%), 199 (100%). Data in agreement with literature.¹





1-(Chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride

A flame-dried flask, that had been back-filled with argon, was charged with DCM (25 mL), followed by DABCO (0.29 g, 2.58 mmol, 1.0 eq). The solution was then left to stir under argon for 16 h. The solution was then carefully concentrated *in vacuo* and immediately stored under argon at -20 °C to prevent decomposition of the resulting hygroscopic white salt (0.47 g, 2.39 mmol, 92%); m.p. 146-148 °C (decomp.) (lit.,² 148 °C decomp.); IR v_{max} (solid) 3413 (m), 3372 (m), 3004 (w), 2968 (w), 1637 (w), 1460 (m), 1362 (m), 1092 (s), 1051 (s), 840 (s), 619 (s), 534 (s) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO) $\delta_{\rm H}$ 5.39 (2H, s, CH₂Cl), 3.41 (6H, t, *J* = 7.5, (CH₂)₃N), 3.08 (6H, t, *J* = 7.5, (CH₂)₃N⁺) ppm; ¹³C NMR (176 MHz, (CD₃)₂SO) $\delta_{\rm C}$ 67.5 (CH₂), 50.6 (CH₂), 44.4 (CH₂) ppm. Data supported by literature.^{2,3}





Examination of Other Bases in the Electrochemical Glaser-Hay Reaction:

Table S1: The use of different bases and the effect on the isolated yield of the dimerised product.

Cu WE/Pt CE (oxidative potential)		
	$H \xrightarrow{\text{Base}} O_2 \text{ (air)}$	
Entry	Base ^a	Isolated Yield (%)
1	None ^a	0
2	DBU	36
3	Et_3N	2
4	Pyridine	37
5	K ₂ CO ₃	<1
6	NaOH	<1

^{*a*} All bases were used in a 1.2 eq ratio as compared to the phenylacetylene starting material (1.0 eq) except for Entry 1, where no base was used.

Procedure for Glaser-Hay Control Reaction Using Pre-Prepared Jagner's Complex:⁴

A flask was charged with Cu(I)Cl (0.24 g, 2.42 mmol, 2.0 eq), followed by DCM (5 mL), to create a slurry. The solution was degassed with argon before DABCO (0.14 g, 1.25 mmol, 1.0 eq), dissolved in DCM (3 mL), was added *via* syrringe. The orange solution was degassed further, then cooled to -78 °C for 3 h. A portion (3.13 mL, equating to a maximum possible catalyst loading of 45 mol% if all DABCO has reacted with DCM) of the solution was decanted into a flask containing phenylacetylene (0.06 mL, 0.55 mmol, 1.0 eq), DABCO (68 mg, 0.61 mmol, 1.1 eq) and DCM (5 mL), making sure to leave behind any unreacted, insoluble Cu(I)Cl. The solution was stirred at RT for 16 h, whilst exposed to air. The solution was then filtered into a separating funnel and extracted once with brine (30 mL), before the aqueous layer was diluted with DCM (30 mL). The organic layer was extracted and combined with the other organic layer, then washed once with H₂O (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The resulting yellow solid was dissolved in 20% EtOAc/pet. ether. and passed through a plug of silica gel to give the diyne product as a white crystalline solid (0.02 g, 0.10 mmol, 36%). Procedure adapted from Jagner *et al.*⁴

References:

- 1 M. L. N. Rao, P. Dasgupta, B. S. Ramakrishna and V. N. Murty, *Tetrahedron Lett.*, 2014, 55, 3529.
- 2 R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf and I. Sharif, *J. Fluorine Chem.*, 1997, **81**, 157.
- 3 J. C. Sarie, C. Thiehoff, R. J. Mudd, C. G. Daniliuc, G. Kehr and R. Gilmour, *J. Org. Chem.*, 2017, **82**, 11792.
- 4 B. Gustafsson, M. Håkansson and S. Jagner, Inorg. Chim. Acta. 2005, 358, 1309.