

[CuI(PPh₃)₃]-Mediated Arylation of 1,2,3-Triazoles

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The arylation of 1,4-disubstituted triazoles with [CuI(PPh₃)₃] is reported. The reactions were carried out in relatively concentrated solutions of hot DMF in the presence of air and moisture. These conditions were suitable for a range of substrates, specifi-

cally triazoles containing a pyridyl group, which are of interest in diverse applications such as ancillary ligands or bioactive compounds.

1. Introduction

Heterocycles are essential motifs in chemistry and biology and often considered as a field on their own. Despite the importance of N-heterocycles, not many among them have seen such a raise in popularity as 1,2,3-triazoles did following the discovery of copper-mediated azide-alkyne cycloaddition reactions^[1] and the advent of Click chemistry.^[2] Synthetic advances have enabled the discovery of new and broad applications of this scaffold in key fields, such as drug discovery and advanced materials.^[3] With powerful catalytic methodologies in place for regioselectively accessing 1,4-disubstituted or 1,5-disubstituted triazoles,^[4] the selective formation of 1,4,5-trisubstituted 1,2,3-triazoles still has challenges to overcome.^[5] Ruthenium complexes have been shown to react with disubstituted alkynes,^[6,7] but complete regioselectivity is only possible with strongly biased substrates.^[8] Alternatively, 5-iodotriazoles can be cross-coupled in the presence of a palladium complex.^[9] However, iodotriazoles are prone to dehalogenation, only a limited number of copper complexes have been reported for their synthesis,^[10,11] and the preparation of the required iodoalkynes can be difficult, particularly when bearing functional groups.

Alternatively, direct arylation reactions can offer the shortest and most cost-effective route to functionalized heterocycles in general,^[12] and fully decorated 1,2,3-triazoles in particular. Nevertheless, this is a challenging reaction and reports with established palladium systems require forcing conditions including high temperatures (100–120 °C) and metal loadings around

5 mol%.^[13] On the other hand, reactions are not limited to aryl iodides or bromides, and readily available aryl chlorides and tosylates have been reported. Whilst examples with lower palladium loadings are also known, reaction temperatures ranging between 150 and 250 °C are required in those cases.^[14]

Reported copper-based catalytic systems for arylation reactions still suffer from similar drawbacks, but the use of a less expensive and toxic transition metal is an obvious advantage. Ackerman and co-workers first reported the copper-mediated arylation of 5-*H*-1,2,3-triazoles with 10 mol% of CuI (Scheme 1, top).^[15] Similar conditions have also been applied to a number of elegant tandem reactions where the arylation step is intramolecular and therefore milder conditions^[16] or aryl bromides can be used (Scheme 1, bottom).^[17] Although, no mechanistic studies have been reported to date, this transformation has been proposed to proceed through the deprotonation of the 5-*H*-triazole by *t*-BuOLi, followed by a lithium/copper transmetalation, then reaction with the aryl iodide and a reductive elimination step.^[5]

Herein, we disclose the screening of two series of phosphorous and NHC-based copper catalysts and their application in arylation reactions, including pyridyl-containing 1,4,5-trisubstituted triazoles.

2. Results and Discussion

With triazole **1a** and 4-iodoanisole as model substrates, a selection of NHC and phosphorous ligand bearing complexes (5 mol%) were tested with *t*-BuOLi in a 0.5 M DMF solution (Table 1 and Scheme 2). All reactions were performed without any precautions to exclude air or moisture and using technical DMF (water content measured to be 0.04%). Among the different NHC-based catalysts, only [CuCl(SIMes)] provided more than 50% of the desired triazole (Table 1, entry 5), and lower yields were observed with more sterically hindered complexes (Table 1, entries 1–4) or those bearing a saturated NHC (Table 1, entry 7). Series of phosphite, phosphonite, and phosphinite copper complexes led to average conversions in **2a** and overall the best results were obtained with [CuI(PPh₃)₃] as catalyst. Only moderate yields were observed with monophosphine copper complexes, indicative of a key role of triphenylphosphine in mitigating catalyst deactivation (Table 1, entries 19–21). Unsurpris-

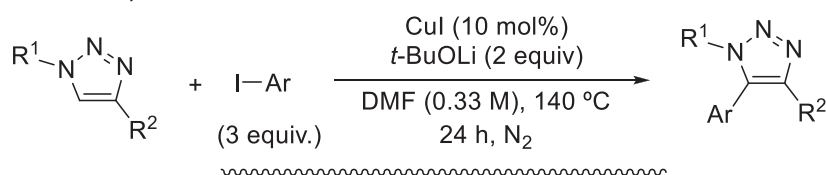
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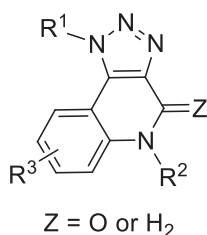
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Ackermann, 2008



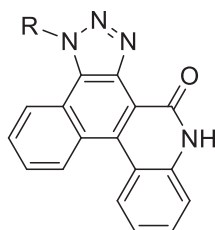
Cai, 2012

CuI (10 mol%)
K₂CO₃ (2 equiv)
DMSO, RT



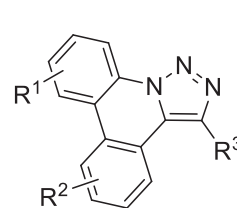
Qian, 2013

CuI (10 mol%), DMEDA (20 mol%)
K₂CO₃ (3 equiv)
Dioxane, 120 °C



Huang & Wen, 2014

CuI (10 mol%)
NaHCO₃ (5 equiv)
DMSO, 50–60 °C

Scheme 1. Reported copper-mediated arylation of 5-*H*-1,2,3-triazoles.Table 1. Catalyst screening.^{a)}

Entry	[Cu]	Yield (%) ^{b)}	Entry	[Cu]	Yield (%) ^{b)}
1	[CuCl(IPr)]	19	12	{CuBr[PPh ₂ (OMe)]}	42
2	[CuBr(IPr)]	21	13	{CuBr[PPh ₂ (OPh)]}	43
3	[CuI(IPr)]	>5	14	{CuBr[PPh ₂ (OPh-2-OMe)]}	44
4	[Cu(IPr) ₂]PF ₆	>5	15	{CuBr[PPh ₂ (OPh-4-OMe)]}	73
5	[CuCl(IMes)]	53	16	[CuCl(PPh ₃) ₃]	31
6	[Cu(IMes) ₂]PF ₆	10	17	[CuBr(PPh ₃) ₃]	70
7	[CuCl(SIMes)]	>5	18	[CuI(PPh ₃) ₃]	86
8	{Cu[P(OPh) ₃] ₂ }	43	19	[CuCl(PPh ₃)]	49
9	{CuBr[PPh(OMe) ₂]}	55	20	[CuBr(PPh ₃)]	38
10	{CuBr[PPh(OPh) ₂]}	64	21	[CuI(PPh ₃)]	38
11	{CuBr[PPh(OPh-2-OMe) ₂]}	51	22	CuI	25

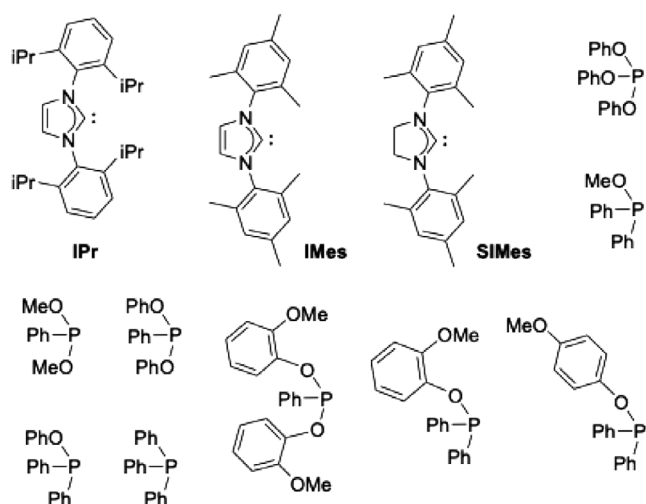
^{a)} Reaction conditions: **1a** (0.5 mmol), 4-iodoanisole (0.75 mmol), *t*-BuOLi (1.25 mmol), [Cu] (5 mol%), DMF (1 mL), 140 °C, 18 h.
^{b)} ¹H NMR yields are the average of at least two independent experiments.

ingly, only a signal corresponding to triphenylphosphine oxide was observed in the ³¹P NMR spectrum of the slurry at the end of the reaction before any work-up.^[18]

It is important to note that the reaction without a copper(I) source led to no reaction, whereas only 25% of **2a** was formed when using 5 mol% of CuI under these conditions. This is significantly lower than the range of yields reported by Ackermann for similar substrates; however, not only was the copper loading halved, but also the reaction conditions are slightly different

with air and moisture present in our experiments. Furthermore, our system did not benefit from inert conditions (dry DMF, N₂ atmosphere) since a lower yield of 46% in **2a** was obtained in the absence of air and moisture.

The effect of the temperature was next examined, but yields in triazole **2a** quickly decreased as the temperature was lowered (62% at 120 °C and 22% at 100 °C). Different additives/ligands that had previously been shown to be beneficial in related reactions were also tested (Table 2). Amino acids, such



Scheme 2. Ligands employed in this work.

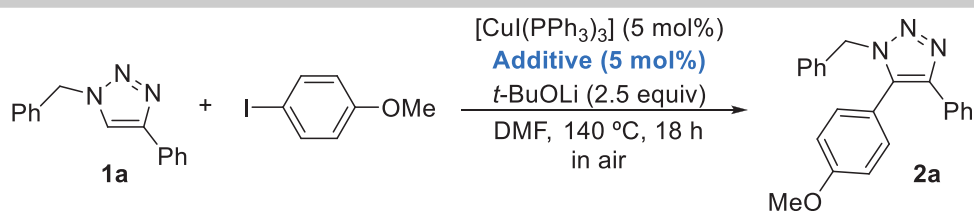
as L-proline, are established ligands for copper-mediated cross-coupling reactions,^[19] and phenanthroline has been used in the copper-catalysed direct arylation of 1,3,4-oxadiazoles and 1,2,4-triazoles.^[20] However, in this case, both additives decreased the overall yield of trisubstituted triazole **2a**, as did the use of additional PPh₃ (overall Cu/PPh₃ = 1:4)^[21] (Table 2, entries 2, 3, and 5). In terms of copper loading, slightly higher loadings (i.e. 6 and 7 mol%) led to comparable results, whereas the yield of **2a** quickly decreased with lower loadings (Table 2, entries 6–10).

Alternative solvents were then considered in efforts to achieve complete conversion of the initial triazole, however, other traditional high boiling solvents only led to average conversions (Table 3, entries 2–5). The use of polar aprotic solvents, such as DMF, is problematic since these are very high concern

substances that might be soon restricted in industrial applications. Hence, we also screened safer and more sustainable alternatives such as a deep eutectic solvent (choline chloride/urea, 1:2),^[22] cyrene,^[23] and *N*-butylpyrrolidinone (NBP).^[24] The first two options only led to the recovery of the starting triazole **1a**, whereas only 39% yield was obtained with NBP (Table 3, entries 6–8). While a replacement for DMF could not be found, comparable results were obtained at either 1.0 or 0.5 M, reducing the overall amount of DMF needed in these reactions (Table 3, entries 1 and 10). The reaction efficiency dropped significantly at either higher or lower concentrations (Table 3, entries 9, 11, and 12).

Similarly, other bases screened were ineffective in the model arylation reaction (Table 3). The strong influence of the counterion of the base is of note as both sodium and potassium *tert*-butoxides led to disappointing results compared to the optimized lithium derivative (Table 3, entries 10–12). Furthermore, the reaction appeared to be very sensitive to the base loading and the original 2.5 equiv of *t*-BuOLi appeared to be ideal for the formation of **2a** under these conditions (Table 3, entries 13 and 19–21).

Overall, none of the conditions tested significantly improved the efficiency of the model reaction; nevertheless, we studied the scope of the reaction using a 1 M concentration to minimize the amount of DMF waste generated (Scheme 1). Also, it is noteworthy that under these conditions no reaction was observed with bromotoluene or a triflate derivative. In terms of scope, fair to good conversions to the desired trisubstituted triazoles were observed in general, however, most triazoles **2** had very similar R_f values to the starting triazoles **1**, making the chromatographic separation challenging (Scheme 3). Gratifyingly, despite the forcing reaction conditions, a number of functional groups were well tolerated, such as halogens, nitriles, or ethers. Decom-

Table 2. Further optimisation reactions.^{a)}

Entry	Additive	[Cu] (mol%)	Yield (%) ^{b)}
1	None	5	86
2	L-Proline	5	61
3	1,10-Phenanthroline	5	58
4	Pyridine	5	60
5	PPh ₃	5	64
6	None	7	81
7	None	6	80
8	None	4	72
9	None	3	56
10	None	2	46

^a) Reaction conditions: **1a** (0.5 mmol), 4-iodoanisole (0.75 mmol), *t*-BuOLi (1.25 mmol), [CuI(PPh₃)₃] (5 mol%), DMF (1 mL), 140 °C, 18 h.

b) ^1H NMR yields are the average of at least two independent experiments.

Table 3. Solvent and base optimisation.^{a)}

Base: <i>t</i> -BuOLi (2.5 equiv)				Solvent: DMF (0.5 M)			
Entry	Solvent	Conc (M)	Yield (%) ^{b)}	Entry	Base	Loading (equiv)	Yield (%) ^{b)}
1	DMF	0.5	86	13	<i>t</i> -BuOLi	2.5	86
2	DMSO	0.5	25	14	<i>t</i> -BuONa	2.5	8
3	DMAc	0.5	47	15	<i>t</i> -BuOK	2.5	15
4	Diglyme	0.5	40	16	K ₃ PO ₄	2.5	>5
5	<i>p</i> -Xylene	0.5	27	17	NaH	2.5	>5
6	DES	0.5	>5	18	KOH	2.5	>5
7	Cyrene	0.5	>5	19	<i>t</i> -BuOLi	3	60
8	NBP	0.5	39	20	<i>t</i> -BuOLi	2	30
9	DMF	2.0	68	21	<i>t</i> -BuOLi	1.5	14
10	DMF	1.0	90				
11	DMF	0.25	61				
12	DMF	0.10	21				

^{a)} Reaction conditions: **1a** (0.5 mmol), 4-iodoanisole (0.75 mmol), [CuI(PPh₃)₃] (5 mol%), 140 °C, 18 h.
^{b)} ¹H NMR yields are the average of at least two independent experiments.

position was observed in several instances, which was attributed to the combination of high reaction temperatures and the nature of the base. When both starting materials were heated at 140 °C in DMF overnight in the absence of base, they were recovered quantitatively. However, when different 1,4-disubstituted triazoles were treated overnight under catalytic conditions in the absence of an aryl iodide, different degrees of decomposition were observed. 1-Benzyltriazoles were relatively stable and 70% recovery was achieved with a 4-phenyl substituent. In contrast, 1-phenyltriazoles were completely converted into a complex mixture of compounds under identical conditions. This can be attributed to the fragmentation of intermediate 5-lithio-1-phenyl-1,2,3-triazoles, a reaction that readily takes place at room temperature.^[25] In consequence, attempts of arylation of 1-phenyltriazoles were unsuccessful and only traces of the desired products were observed at best. Despite the forcing conditions, the only by-product that was isolated was a phenol analogue of **2a**, consistent with demethylation. Only 3% of this by-product was isolated after column chromatography, and its identity was confirmed by HRMS. No similar by-products were observed in other reactions with 4-iodoanisole (Supporting Information).

Among the 1,4-disubstituted triazoles screened, those bearing a pyridyl substituent on C4 displayed an increased reactivity, and a range of compounds with both heterocyclic motifs could be isolated in good to high yields. Both 2- and 3-pyridyl substituents worked well, and this activating effect allowed the use of iodoarenes with electron withdrawing substituents (Scheme 3, **2n**, **2o**, and **2r**). On the other hand, significantly lower conversions were observed when the pyridyl group was

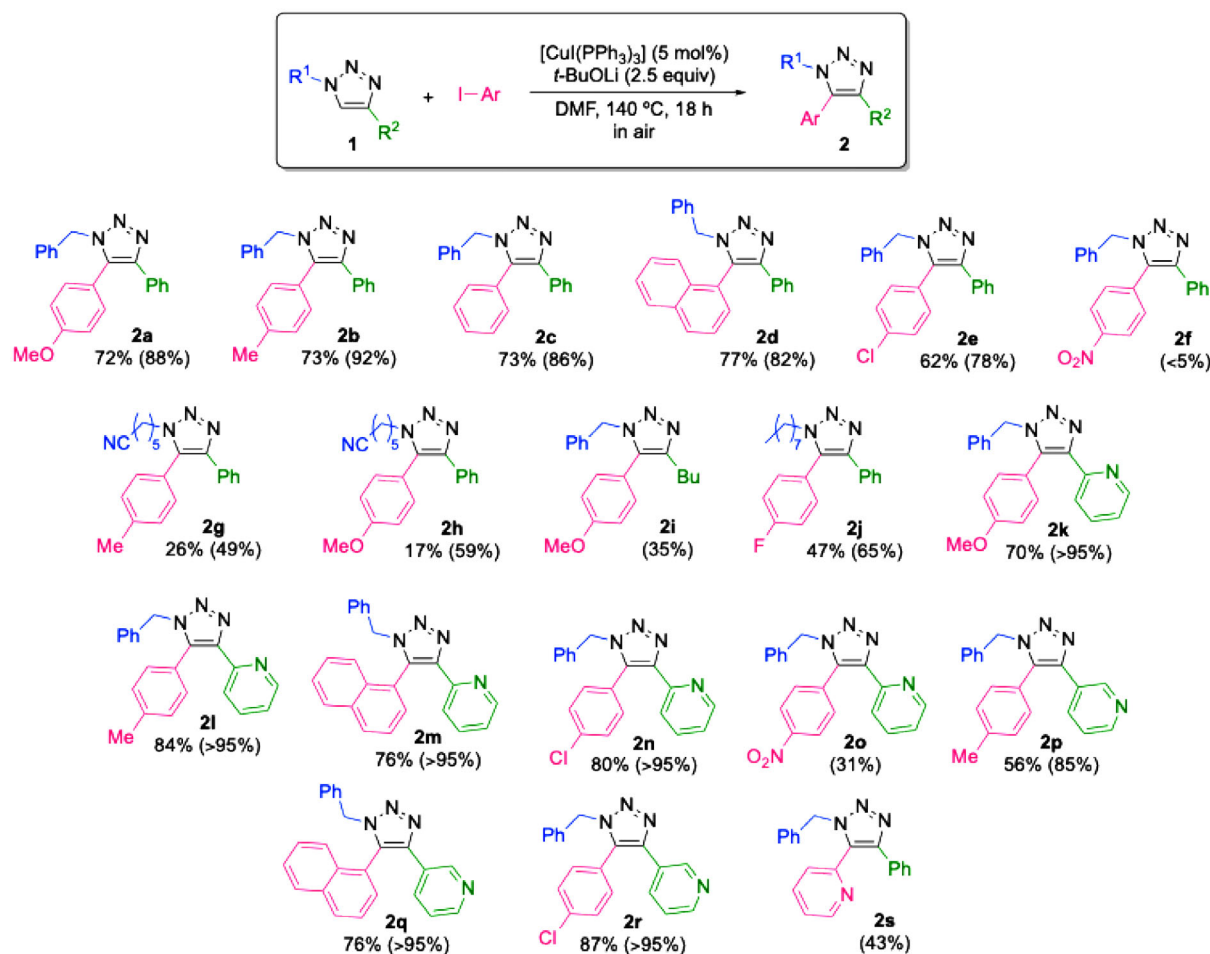
introduced through the arylating agent (Scheme 3, **2s**). These results are particularly relevant since pyridine-containing 1,2,3-triazoles are popular motifs that have shown great promise in several fields such as metal coordination and activity modulation,^[26] supramolecular chemistry,^[27] and biologically active compounds.^[28]

3. Conclusions

Different series of copper(I) complexes were screened in the arylation of 1,4-disubstituted triazoles to identify [CuI(PPh₃)₃] as the most promising catalyst. Optimized reaction conditions are quite forcing, in line with literature precedents. Nevertheless, the present system is compatible with the presence of air and moisture, and the amount of DMF used is minimized. Due to the high temperatures and the base used, decomposition of the starting triazoles can be an issue, but gratifyingly a range of fully substituted triazoles could be isolated in pure form, including important pyridyl-containing triazoles.

4. Experimental Section

General considerations: All reactions were carried out in air using technical solvents without any precautions to exclude moisture or oxygen. Commercially available reagents were used as received without further purification. Column chromatography and TLC were performed on silica gel (Kieselgel 60), using UV light and phosphomolybdic acid or KMnO₄ dip to visualise the compounds. Melting points (uncorrected) were determined on an Electrothermal Gallen-



Scheme 3. Scope of $[\text{CuI}(\text{PPh}_3)_3]$ -catalysed arylation reactions. Reaction conditions: **1** (0.5 mmol), iodoarene (0.75 mmol), *t*-BuOLi (1.25 mmol), $[\text{CuI}(\text{PPh}_3)_3]$ (5 mol%), DMF (0.5 mL), 140 °C, 18 h. Isolated yields (^1H NMR yields) are the average of at least two independent experiments.

hamp and a Cole-Parmer MP-400D Stuart apparatus. NMR spectra were recorded in CDCl_3 on Bruker AVANCE 400 spectrometers (^1H : 400 MHz and ^{13}C : 100 MHz) at room temperature. Chemical shifts, δ , are given in ppm relative to tetramethylsilane (0.00 ppm), CDCl_3 (77.0 ppm). The multiplicity is given as br, s, d, t, q, and m for broad, singlet, doublet, triplet, quartet, and multiplet, respectively. Assignments of some ^1H and ^{13}C NMR signals rely on COSY, HSQC, HMBC, and/or DEPT experiments. Mass spectra were recorded on either a Micromass Autospec Premier, Micromass LCT Premier or a VG Platform II spectrometer using ESI at the Mass Spectrometry Service of Imperial College London. $[\text{CuI}(\text{PPh}_3)_3]$ was prepared using a reported procedure^[29] and kept in a vial in air.

General procedure for $[\text{CuI}(\text{PPh}_3)_3]$ -catalysed arylation of triazoles: In a vial fitted with a screw cap and a magnetic stirrer bar, 1,4-disubstituted triazole (0.5 mmol), aryl iodide (0.75 mmol), *t*-BuOLi (1.25 mmol), $[\text{CuI}(\text{PPh}_3)_3]$ (25 mg, 5 mol%), and DMF (0.5 mL) were introduced. After stirring for 18 h at 140 °C, the reaction slurry was cooled to room temperature and water was added. The resulting mixture was extracted with ethyl acetate. The combined organic phases were washed with saturated ammonium chloride solution, water, and brine, then dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography. Reported yields are isolated yields and are the average of at least two independent experiments.

1-Benzyl-5-(4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole (2a): Using the general procedure from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole

(0.118 g, 0.5 mmol) and 4-iodoanisole (0.178 g, 0.75 mmol), the title compound was isolated by column chromatography (petroleum ether/EtOAc = 7:3) as a light yellow solid (0.122 g, 72%). The obtained spectroscopic data for **2a** are consistent with the literature.^[30,13c] *R*_f = 0.51 (hexanes/EtOAc, 1:2); mp 104–106 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.60–7.54 (m, 2H, H^{Ar}), 7.30–7.20 (m, 6H, H^{Ar}), 7.08–7.01 (m, 4H, H^{Ar}), 6.93 (d, 2H, J = 7.6 Hz, H^{Ar}), 5.39 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.5 (C^{Ar}), 144.4 (NC = C-Ph), 135.5 (C^{Ar}), 133.7 (C^{Ar}), 131.3 (CH^{Ar}), 131.0 (C^{Ar}), 128.6 (CH^{Ar}), 128.4 (CH^{Ar}), 128.1 (CH^{Ar}), 127.5 (CH^{Ar}), 127.4 (CH^{Ar}), 126.6 (CH^{Ar}), 119.6 (NC-*p*-anisyl), 114.6 (CH^{Ar}), 55.3 (CH_3), 51.8 (CH_2) ppm; LRMS (ESI): *m/z* 341 $[(\text{M}+\text{H})^+]$, 6), 235 (19), 222 (44), 206 (66), 116 (94), 91 (100).

Supporting Information

Supporting information includes experimental procedures, characterisation data for the prepared compounds and copies of their ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

FAIR data including primary NMR FID files and computational data can be accessed at Imperial College Research Services Data Repository, DOI: 10.14469/hpc/14893.^[31]

Keywords: Arylation · C–H activations · Copper · Phosphine · Triazole

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