SOCIETY FOR NATURAL SCIENCES STUDENT JOURNAL

Technical report

Sustainable Copper-Catalysed Arylations for Chemical Manufacture

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Abstract – Functionalised aromatic compounds are the backbone to most pharmaceutical and biologically active molecules, their synthesis heavily reliant on TM-catalysed arylation reactions. Pd dominates this field, but its scarcity and toxicity has motivated scientists to look for alternatives. This report demonstrates a more environmentally-friendly approach to Cu-catalysed Ullmann-type coupling through the development and application of a small library of structurally diverse picolinamide ligands, synthesised via T3P-mediated amide coupling. The ligands were prepared in good yield and subsequently evaluated in Cu-catalysed C–N and C–O coupling reactions under mild conditions, employing K_3PO_4 and i-PrOAc as more sustainable alternatives to conventional bases and solvents. Where successful coupling was achieved, yield varied depending on the ligand used, highlighting the importance of ligand structure in achieving efficient reactivity. Overall, this work demonstrates that Ullmann-type couplings can be achieved under more sustainable conditions, providing insight into the development of greener and more practical arylation methodologies.

Abbreviations

C – carbon; $CDCl_3$ – chloroform; Cs – caesium; Cs_2CO_3 – caesium carbonate; Cu – copper; CuI – copper (I) iodide; Et_3N – triethylamine; EtOAc – ethyl acetate; F – fluorine; i-PrOAc – isopropyl acetate; K – potassium; K_3PO_4 – potassium phosphate; $MgSO_4$ – magnesium sulphate; N – Nitrogen; NH_4OH – ammonium hydroxide solution; O – Oxygen; Pd – palladium; RBF – round bottomed flask; S – Sulfur; T3P – propylphosphoric anhydride; THF – tetrahydrofuran; TM – transition metal; ^1H NMR – proton nuclear magnetic resonance spectroscopy

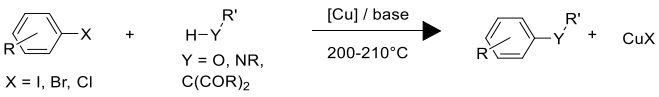
Introduction

Arylation reactions are fundamental organic transformations that enable the formation of C-C and C-heteroatom (e.g., C-N, C-O, C-S) bonds, taking a central focus in modern synthetic chemistry. Crucially, they provide efficient routes to structurally diverse molecules which underpin the syntheses of many pharmaceutical, agrochemical and functional materials. TM-catalysed cross-coupling reactions, typically involving the substitution of an aryl halide with a nucleophile to enable new C-heteroatom bonds, encompass the most widely adopted methods for achieving such transformations, owing to their versatility and reliability. (1)

Pd-based methodologies, recognised by the 2010 Nobel Prize in Chemistry, have long dominated this field due to their high efficiency and broad substrate scope. (2) However, the reliance on Pd presents several limitations, including low natural abundance, high cost, toxicity, and associated environmental concerns. Moreover, many Pd-catalysed processes require complex ligands and employ unsustainable solvents and harsh bases, further exacerbating their environmental impact. (3)

As a result, attention has recently been directed towards the development of alternative catalytic systems based on more abundant and less toxic metals. (4)

The father to TM-catalysed cross-couplings, Cu-based Ullmann-couplings (Scheme 1), have re-emerged as an attractive alternative, owing to Cu's high natural abundance, low cost, low toxicity, and complementary reactivity to Pd. However, classical Ullmann-type chemistry required harsh conditions, specifically high temperatures, strong bases and high catalyst loadings, which limited practicality and led to poor functional group tolerance. Resultantly, these methodologies were largely superseded by Pd-catalysis for a long time. More recently, advances in ligand design have enabled these reactions to proceed under significantly milder conditions, (5) with the development of bidentate ligands particularly enhancing catalytic efficiency and expanding the substrate scope of these transformations. Among them, picolinamide ligands have emerged as an effective class for promoting Ullmann-type couplings, particularly in the formation of aryl ethers and amines. (6)

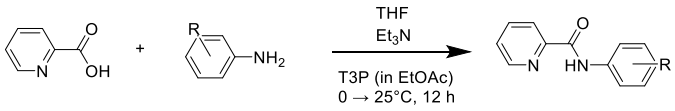


Scheme 1 – generic Ullmann-type coupling

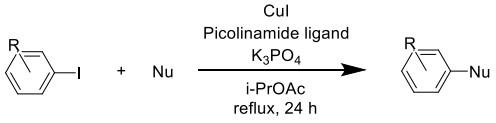
Picolinamide ligands, having been identified as able to coordinate to a metal centre via various modes, (9) are ideal subjects for structure-activity relationship studies. Herein, a small library of picolinamide ligands, varying in substitution at the N-phenyl ring, are synthesised, and their subsequent performance in Cu-catalysed arylation reactions are studied.

Alongside catalyst developments, improving the sustainability of chemical processes is a growing priority in line with rising concerns regarding humans' environmental impact and waste management. A particularly good target area to improve the sustainability of a process is solvent usage, as solvents account for 50-60% of the material used for a typical process. (7) Consequently, the replacement of traditional polar aprotic and volatile organic solvents with more sustainable alternatives is one leading strategy in green chemistry. Similarly, the use of milder and less hazardous bases is desirable to reduce toxic waste and improve process safety. (8)

All of this in mind, this project focussed on (i) using a more sustainable amide coupling methodology to synthesise the ligands (Scheme 2), and (ii) subsequent screening of their performance in various arylations between aryl halides and ester-, phenol-, imine- functionalised nucleophiles under mild conditions, where i-PrOAc and K_3PO_4 were employed as a sustainable solvent and mild base (Scheme 3).



Scheme 2 – sustainable amide coupling for picolinamide ligand synthesis



Scheme 3 – Picolinamide ligand-assisted Cu-catalysed coupling between an aryl halide and a nucleophile (Nu). Nu = sulfonamide, imidazole, aminopyridine, phenol.

Results and discussion

Synthesis of picolinamide ligands

The use of T3P proved advantageous due to its ability to promote amide bond formation cleanly, generating water-soluble by-products, thereby enabling a simple aqueous work-up. This method is an optimisation on the literature method (9), where triphenyl phosphite and pyridine were used, which require more intensive purification and generate waste products which are less environmentally friendly. However, further

investigation would be necessary to establish whether this method would still be successful on the equivalent multigram scale reported by the literature method.

Within the group, a small library of four picolinamide ligands varying in structure of the N-heterocyclic ring (Figure 1) was successfully synthesised (one per member), yielding >60% of each desired product as crystalline solids (Table 1). The ^{1}H NMR spectrum of L1 is shown in Figure 2. A downfield singlet at δ 10.37 ppm was assigned to the amidic NH proton. Resonances between δ 8.64–6.53 ppm were assigned to the aromatic protons of both the picolinamide and substituted phenyl rings. Notably, singlets at δ 3.94 and 3.82 ppm, each integrating to three protons, were assigned to the methoxy substituents. The chemical shifts and integrations of these signals were consistent with the expected structure. Moreover, no signals corresponding to the starting materials were observed, and no significant impurity peaks were detected, indicating that the desired product was obtained in good purity.

Figure 1 – structures of picolinamide ligands synthesised. L1 was synthesised by Grace Assheton.

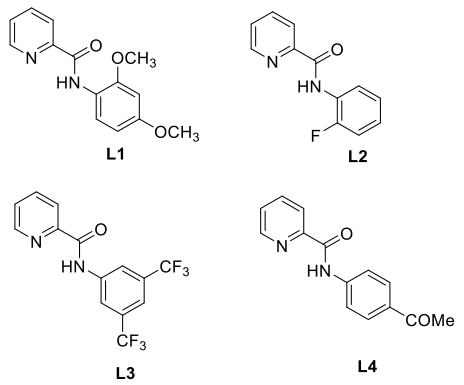
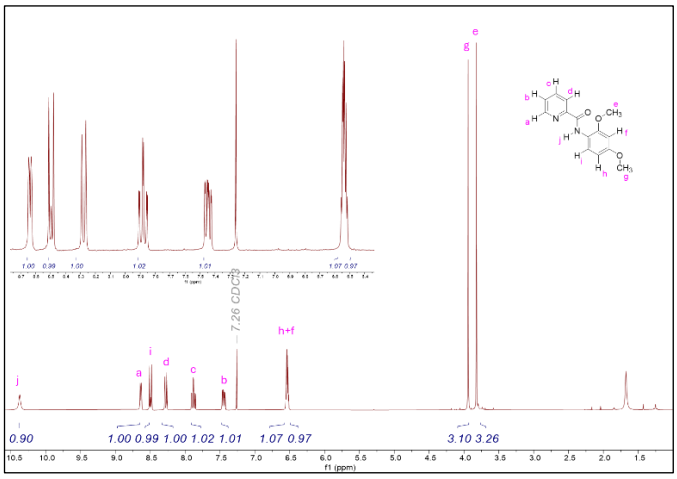


Table 1 – results of ligand syntheses via sustainable T3P coupling. Results marked with * were completed by Grace Assheton.

Ligand	Yield (%), (g)	Physical appearance
L1*	94%, 1.19 g*	Black crystalline solid*
L2	62%, 0.653 g	White crystalline solid
L3	unknown	White crystalline solid
L4	97%, 1.13g	White crystalline solid

Figure 2 – ^{1}H NMR spectra of L1 product. Protons are alphabetically labelled corresponding to their posotion on L1 (structure on right). An expansion of the aromatic region is shown to highlight splitting.



In contrast to the white appearance of the remaining ligands, L1 appeared black. Given the clean NMR, the black appearance was most likely caused by a trace oxidised impurity that is below NMR detection. The 2,4-dimethoxy substitution of both the precursor to L1 and L1 itself makes the compound uniquely electron rich, priming it to oxidation, which would likely give a black material. Even <1% of the oxidised material can make the entire solid look black, which is consistent with it being in insufficient quantity to show up by NMR. The remaining ligands comprise electron-withdrawing or neutral substituents, which resist oxidation, hence their white appearance.

Reaction scope was demonstrated through the use of anilines bearing a range of substituents, including electron-donating groups (e.g., methoxy, L1) and electron-withdrawing groups (e.g., fluoro, L2). No difficulties were encountered during syntheses, and all yields were comparable, suggesting that this method is tolerant to a variety of electronic environments.

Catalytic screening

A series of catalytic experiments were conducted within the group to evaluate the performance of L1-L4 at assisting in Cu-catalysed Ullmann coupling reactions. Table 2 shows the substrates tested.

Varying the nucleophile. Cross-couplings (I-III) investigated the performance of the ligands to assist Cu-catalysed coupling between various nucleophiles and 4-iodoanisole. The procedure for cross-coupling (I) involved filtration through celite for the work-up, which resulted in poor mass recovery of the crude material and necessitated additional filtration prior to NMR analysis due to the persistence of insoluble Cu-salts coming through into the crude material. The ^{1}H NMR of the crude material obtained after work-up contained dominant signals closely matched to those expected for 4-iodoanisole, (10) as well as signals which matched those found for the ligand (Figure 2). Moreover, signals did not appear around shifts expected for the desired product, nor the benzenesulfonamide substrate. Being slightly acidic, it is possible that the benzenesulfonamide formed a salt with the base, which would have precipitated and stuck to the celite during filtration, hence not present in the final crude material. Acidic substrates were not used in the remaining cross couplings, so not likely to have the same issue. However, a more critical issue with this work-up was the difficult removal of Cu. Consequently, an aqueous work-up was adopted for subsequent reactions, to improve mass recovery and Cu removal.

The adapted work-up, an aqueous extraction, was employed in cross-couplings (II-III). Once again, insignificant formation of the desired products was observed, however, mass recovery was significantly improved. Therefore, aqueous extraction was used for the remainder of the reactions as a more suitable work-up procedure.

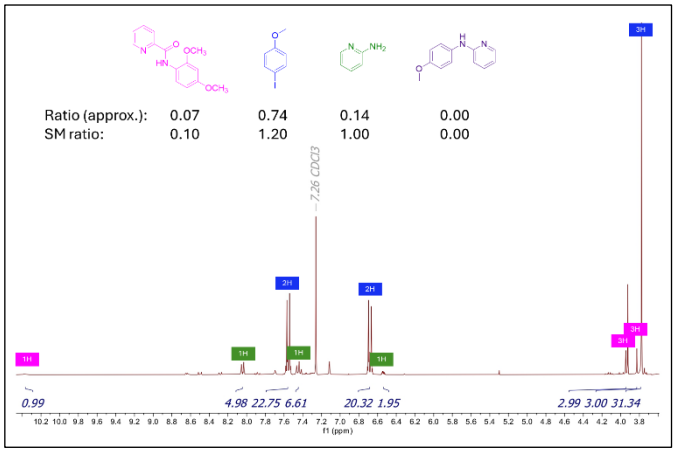
Cross-couplings (I-III) with L1 yielded a black crystalline crude material, the colour likely due to coloured impurities from the ligand remaining inthe crude material. None of the ligand/nucleophile combinations resulted in significant product formation detectable by ^{1}H NMR, the spectra largely dominated by signals corresponding to the starting materials. To illustrate this fact, the ^{1}H NMR spectrum of cross-coupling (III) is shown (Figure 3). The signals

Table 2 – substrates tested in cross-couplings

Experiment reference	Nucleophile	Electrophile	Work-up
Cross-coupling I	Benzenesulfonamide	4-iodoanisole	Filtration through celite
Cross-coupling II	Imidazole	4-iodoanisole	Aqueous
Cross-coupling III	2-aminopyridine	4-iodoanisole	Aqueous
Cross-coupling IV	3,5-dimethylphenol	4-iodoanisole	Aqueous
Cross-coupling V	3’-hydroxyacetophenone	4-iodoanisole	Aqueous
Cross-coupling VI	3,5-dimethylphenol	3-iodobenzonitrile	Aqueous

corresponding to each substrate have been identified and their relative integrations compared to those of the initial reaction mixture. While the relative amounts of 4-iodoanisole and ligand are comparable between the starting and crude materials, a significant decrease in the signals corresponding to 4-aminopyridine is observed, likely resulting from extractive loss during work-up. The absence of product signals in the ^{1}H spectrum makes it highly unlikely that the 4-aminopyridine was consumed in productive coupling. Instead, the partial solubility of 4-aminopyridine in the aqueous phase likely resulted in its extraction from the organic layer during separation.

Figure 3 – ^{1}H NMR spectrum of cross-coupling III product. Proton signals are colour coded to match their corresponding structure. Approximate ratios of reactants and product are shown.



Benchmark reaction. The investigated couplings up to this point of the study had not been reported in the literature under the same conditions. In previous work, Sambiagio demonstrated successful ligand-assisted coupling between 4-iodoanisole and 2,4-dimethoxyphenol using picolinamide ligands. (9) To assess the effectiveness of the ligands L1-L4, coupling IV was performed as a benchmark reaction based on this literature work. In contrast to the successful reports in the literature, no significant formation of the desired product was observed by ^{1}H NMR spectra for any of ligands L1-4. Consistent with that seen in the previous cross-couplings, a black crystalline solid crude material was obtained, and the ^{1}H NMR spectrum showed dominant peaks indicative of unreacted starting materials.

The unsuccessful reproduction of this benchmark reaction led to the conclusion that there was an issue with one or more of the reaction materials, most likely the 4-iodoanisole. Analysis of the ^{1}H NMR spectrum of the isolated 4-iodoanisole appeared consistent with the expected structure. (10) However, trace impurities that are not detectable by the NMR instrument used or an NMR inactive contaminant could be present. Presence of such impurities could inhibit catalytic activity, which would explain why various coupling reactions have not worked with this substrate, despite literature success.

Varying the electrophile. To further probe the system, cross-coupling VI investigated varying the aryl iodide, replacing 4-iodoanisole with 3-iodobenzonitrile. Under otherwise identical conditions, this modification resulted in significant conversion, with clear evidence of product formation observed from the emergence of new aromatic signals consistent with the expected product, alongside a corresponding decrease in starting material signals in the ^{1}H NMR spectra. All four ligands (L1-4) were evaluated in this coupling, following the same general procedure.

Successful coupling was observed with three of the four ligands, although the extent of conversion was different for each ligand (Table 3). Cross-coupling VI using L3 gave the highest conversion rate. Analysis of the corresponding ^{1}H NMR spectrum is shown in Figure 4. Comparison of starting stoichiometries with signal integrations after reaction reflects a clear change in the relative composition of materials. A remarkably comparable 0.47 equivalent integration of coupled product and reduction of 0.47 equivalents in integration of nucleophile suggests that consumption of the nucleophile is largely accounted for by the intended coupling. This contrasts with reactions using 4-iodoanisole, in

Table 3 – results of cross-coupling VI. Results marked with * were completed by Grace Assheton.

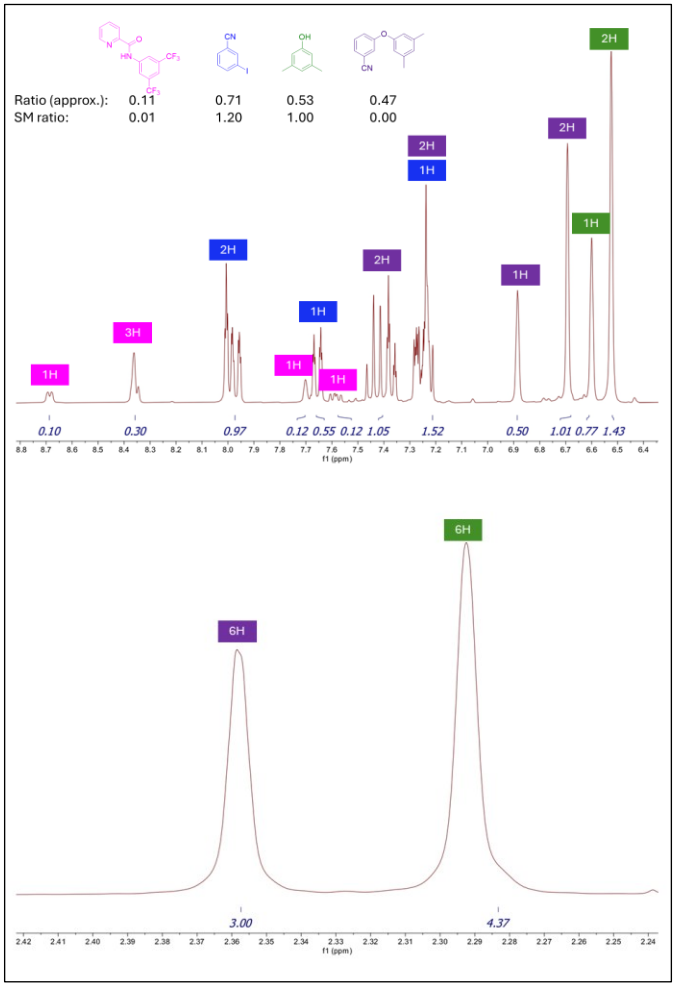
Ligand	Coupling reagents	Solvent	Base	Conversion** (%)
L1*	3-iodobenzonitrile + 3,5-dimethyl phenol	i-PrOAc	K_3PO_4	12%*
L2				0%
L3				47%
L4				42%

**Conversion values are ratios of product to starting material by ^{1}H NMR analysis of the crude reaction mixture; values are used as a proxy for conversion and do not represent isolated yields.

which nucleophile consumption did not correlate with any product formation. Incomplete consumption of both reaction substrates indicates that the reaction did not proceed to full conversion, perhaps due to limited catalytic activity. Additionally, a 10% increase in ligand signal intensity was observed. This would suggest some loss of other components of the reaction mixture during work-up, resulting in the ligand appearing proportionally more abundant in the crude material.

Replacing 4-iodoanisole with 3-iodobenzonitrile resulted in coupling success under otherwise identical conditions. This result provided a strong support for the interpretation that there was an underlying issue with the specific batch of 4-iodoanisole used in the preceding experiments. To further support this interpretation, a repeat of one or more of cross-couplings I-IV using a different batch of 4-iodoanisole would need to be performed, followed by subsequent analysis of the products ^{1}H NMR spectrum. If this resulted in observable desired product, then an issue with the batch of 4-iodoanisole used in cross-couplings I-IV could be concluded with high confidence. Nonetheless, without such data, an issue with the batch of 4-iodoanisole was concluded with reasonable confidence.

Figure 4 – ^{1}H NMR spectrum of cross-coupling VI using L3. Proton signals are colour coded to match their corresponding structure. Approximate ratios of reactants and product are shown. Reaction completed by a colleague.



Structure-activity relationships - *N*-phenyl Substitution

The variation in catalytic performance observed across the ligand series was likely the result of both electronic and steric effects coming from varying substitution at the *N*-phenyl ring. One identified mode of coordination between a picolinamide ligand and Cu is anionic, (9,11) requiring the amide to be deprotonated. Consequently, the acidity (pK_a) of the amide N-H is a key determining factor of the concentration of the active, anionic ligand. Under the mildly basic conditions employed (K_3PO_4), the acidity of the amide is expected to show a more pronounced effect on catalytic performance. Conversely, if a stronger base were used, the acid/base equilibrium for the amide would favour the deprotonated form regardless of the pK_a of the ligand. Hence, pK_a is expected to have a greater impact on catalytic activity under the conditions employed. Ligands bearing electron-withdrawing substituents are expected to lower the pK_a of the amide, thereby facilitating deprotonation, increasing the extent of metal-ligand binding and, in turn, catalytic activity.

L3, bearing two strongly electron-withdrawing *meta*-trifluoromethyl (*m*-CF_3) substituents, illustrates this effect. The *m*-CF_3 substituents exert a powerful inductive effect, withdrawing electron density from the aromatic ring, which indirectly withdraws electron density from the amide N, thus stabilising the conjugate base. Importantly, the effects of the two substituents are additive, leading to a substantial decrease in pK_a, promoting ligand-Cu coordination. This is consistent with the high relative conversion observed for L3.

L4, bearing a *para*-acetyl (*p*-OAc) substituent, also demonstrated high relative catalytic activity. Being *para*, the acetyl group is perfectly positioned for effective pi-conjugation with the amide through the aromatic ring (a resonance effect). This provides a direct pathway for delocalisation of electron density away from the amide, thus stabilising the conjugate base and lowering pK_a. Alone, this resonance withdrawal is stronger than the inductive withdrawal from one *m*-CF_3 group. However, L3 benefits from the cumulative inductive effect of two *m*-CF_3 groups, which ultimately exerts a stronger electron-withdrawing influence. This trend is consistent with Hammett substituent constants, (12) where more positive σ values correlate with greater stabilisation of charge in the conjugate base. The larger cumulative σ for *m*-CF_3 di-substitution relative to *p*-OAc mono-substitution would predict a greater decrease in pK_a, thereby more effective deprotonation and coordination. This likely contributes to the higher activity of L3 relative to L4.

Additionally, steric factors play a likely role in explaining why only a relatively small difference in activity was observed between L3 and L4, despite a large pK_a difference. In L4, substitution is *para*, which exerts minimal steric hindrance, thereby enabling unobstructed approach of L4 to Cu. In L3, substitution is *meta*, exerting a higher degree of steric hindrance. Optimal ligand performance hence appears to reflect a balance between pK_a value and steric hindrance.

In contrast, L2, bearing an *ortho*-fluoro (*o*-F) substituent, exhibits lower catalytic activity. Although F is electron-withdrawing, it is significantly less so than a CF_3 group, and there is only one substituent in L2. Thus, the reduction in pK_a is expected to be less than for L3, leading to less deprotonation and reduced potential for ligand-Cu coordination. Additionally, the *ortho* positioning of F introduces steric hindrance close to the coordination site. However, as F is not much larger than H, any effect of this is likely small.

Finally, L1, bearing electron-donating *ortho/para*-methoxy (*o/p*-OMe) substituents, displayed negligible catalytic activity. As a result of increasing electron density of the *N*-phenyl ring, these substituents would increase the pK_a of the amide. Therefore, under the mildly basic

conditions employed (K_3PO_4), only a low concentration of amide would likely be deprotonated. Resultantly, less ligand-Cu coordination would be expected. Additionally, substitution at an *ortho* position introduces steric hindrance in close proximity to the coordination site. These two factors are therefore likely to act in combination to suppress catalytic activity in L1.

Solvent/base system

Crucially, these reactions were performed employed using K_3PO_4 as a mild base i-PrOAc as a green solvent, representing sustainability-driven progress over commonly reported systems which report using Cs_2CO_3 and polar aprotic solvents such as THF or acetonitrile. (6) Successful employment of K_3PO_4 demonstrates that Cs_2CO_3 is not required for effective catalysis. As Cs is a scarce element with recognised supply risks and environmentally constrained extraction, (13) its use is inherently unsustainable. In contrast, K is an abundant element, and salts such as K_3PO_4 are inexpensive and readily available, offering a more practical and sustainable alternative.

In green solvents selection guides, acetates rank second only to water, reflecting their favourable environmental profile, whereas polar aprotic solvents such as THF and acetonitrile are classified as “hazardous”, so excluding these from industrial scale processes is a priority. (14,15) The effectiveness of i-PrOAc in this system therefore demonstrates that greener solvent choices can be implemented without compromising catalytic performance, thereby improving both the environmental profile and potential scalability of Ullmann-type methodologies.

Conclusion

A small library of picolinamide ligands was successfully synthesised in high yield (62-97%) using T3P-mediated amide coupling, providing a more sustainable and practical alternative to previously reported methods. (8) Initially, the ligands were evaluated in Ullmann-type couplings with 4-iodoanisole as the electrophilic substrate, which gave negligible conversion. However, replacing this substrate with 3-iodobenzonitrile resulted in successful coupling for three of the four ligands tested. The contrasting results between these substrates, despite literature success for both, (8) suggests that the 4-iodoanisole was impure. Differences in catalytic activity across the ligand series indicated that both ligand acidity and steric accessibility (at the coordinating N atom) are important factors in promoting efficient Cu-ligand coordination, with electron-withdrawing substituents enhancing activity and steric hindrance reducing it. Importantly, these reactions were performed using K_3PO_4 and i-PrOAc as greener alternative base and solvent to previous reports, demonstrating that effective Ullmann-type coupling can be achieved under more sustainable conditions. Overall, this work highlights the importance of ligand design and substrate selection in developing practical and environmentally friendly Ullmann-type arylation methodologies.

Experimental section

All reactions were conducted in a fume hood under an ambient atmosphere unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker AV3 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm and referred to the solvent signal ($CDCl_3$: 7.26 ppm).

Synthesis of picolinamide ligands

General procedure A: the appropriate aniline (5.12 mmol, 1.05 equiv) and Et_3N (9.74 mmol, 1.36 mL, 2.00 equiv) were added to a solution of picolinic acid (4.88 mmol, 0.6 g, 1.00 equiv) in anhydrous THF (14.0 mL) under N_2 atmosphere. The solution was cooled to 0°C in an ice bath, and T3P (6.82 mmol, 4.0 mL, 1.40 equiv) was added dropwise over ~10 min. The solution was allowed to warm to room temperature and stirred overnight. The mixture was diluted with pure water (~140 mL),

and the product was collected by vacuum filtration, washed with pure water (x2) and dried under vacuum for ~5 minutes.

***N*-(2,4-Dimethoxyphenyl)picolinamide (L1):** prepared according to General Procedure A using 2,4-dimethoxyaniline (0.78 g, 5.12 mmol). The reaction proceeded to give L1 as a black crystalline solid. Yield: 1.19g. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.37 (1 H, s), 8.64 (1 H, d, *J*=4.7), 8.50 (1 H, t, *J*=9.5), 8.28 (1 H, d, *J*=7.8), 7.88 (1 H, td, *J*=7.7, 1.7), 7.45 (1 H, ddd, *J*=7.6, 4.8, 1.3), 6.53 (1 H, d, *J*=5.1), 6.53 (1 H, t, *J*=4.8), 3.94 (3 H, s), 3.82 (3 H, s).

***N*-(2-Fluorophenyl)picolinamide (L2):** prepared by colleagues according to General Procedure A using 2-fluoroaniline.

***N*-(3,5-Bis(trifluoromethyl)phenyl)picolinamide (L3):** prepared by colleagues according to General Procedure A using 3,5-di(trifluoromethyl)aniline.

***N*-(4-Acetylphenyl)picolinamide (L4):** prepared by colleagues according to General Procedure A using 4-aminoacetophenone.

Copper-catalysed coupling reactions

General procedure B: an oven-dried flask and magnetic stir-bar was charged with the relevant aryl iodide (1.0 mmol), the relevant pro-nucleophile (1.2 mmol), K_3PO_4 (424 mg, 2.0 mmol), CuI (20 mg, 0.1 mmol) and L1 (0.1 mmol). iPrOAc (2.0 mL) was added, and the reaction mixture was heated to reflux (~100°C) for 24 h under air. After cooling to room temperature, the reaction mixture was transferred to a separating funnel and diluted with EtOAc (40 mL). Pure water (30 mL) and NH_4OH (~5 mL) were added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure in a pre-weighed RBF. The crystallised product was weighed and analysed by ^{1}H NMR. Each cross-coupling was performed by colleagues following general procedure B, but with each of L2-4 in place of L1.

Cross-coupling I:

Attempted synthesis of *N*-(4-methoxyphenyl)benzenesulfonamide: using 4-iodoanisole (234 mg) as the aryl iodide and benzenesulfonamide (189 mg) as the pro-nucleophile, reactions were performed according to general procedure B, except that after cooling to room temperature, the reaction mixture was diluted with isopropyl acetate (~50 mL) and filtered through celite. This step replaced the aqueous work-up described in general procedure B.

Cross-coupling II:

Attempted synthesis of *N*-(4-methoxyphenyl)imidazole: using 4-iodoanisole (234 mg) as the aryl iodide and imidazole (81.7 mg) as the pro-nucleophile, reactions were performed according to general procedure B.

Cross-coupling III:

Attempted synthesis of *N*-(4-methoxyphenyl)pyridin-2-amine: using 4-iodoanisole (234 mg) as the aryl iodide and 2-aminopyridine (112.9 mg) as the pro-nucleophile, reactions were performed according to general procedure B.

Cross-coupling IV:

Attempted synthesis of 1-(3,5-dimethylphenoxy)-4-methoxybenzene: using 4-iodoanisole (234 mg) as the aryl iodide and 3,5-dimethylphenol (146.4 mg) as the pro-nucleophile, reactions were performed according to general procedure B.

Cross-coupling V:

Attempted synthesis of 3'-(4-methoxyphenoxy)acetophenone: using 4-iodoanisole (234 mg) as the aryl iodide and 3'-Hydroxyacetophenone (166.0 mg) as the pro-nucleophile, reactions were performed according to general procedure B.

Cross-coupling VI:

Attempted synthesis of 3'-hydroxy-4-methoxybiphenyl-3-acetophenone: using 3-Iodobenzonitrile as the aryl iodide and 3,5-dimethylphenol (146.4 mg) as the pro-nucleophile, reactions were performed according to general procedure B.

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