Enabling Room-Temperature Copper Cross-Coupling Reactions of Anilines with Aryl Bromides

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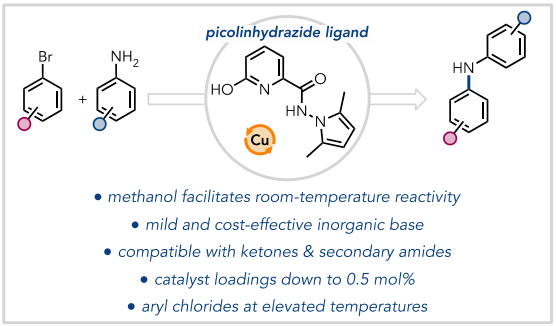
TOC graphics



ABSTRACT: Biaryl amines are essential structural motifs prevalent in agrochemicals, pharmaceuticals, and materials. Herein, we present a novel copper-catalyzed method for aniline cross-couplings promoted by a 6-hydroxy picolinhydrazide ligand. The method achieves room-temperature reactivity with aryl bromides, enabled by a methanol/ethanol solvent mixture and a mild, functional group-compatible base, with catalyst loadings as low as 0.5 mol%. The use of industrially preferred bases and solvents, as well as the high catalytic activity, offers a significant advancement in the practicality and scalability of industrial processes. Furthermore, the approach extends to the cross-coupling of aryl chlorides under elevated temperatures and demonstrates compatibility with additional nucleophile classes.

KEYWORDS: Copper, Catalysis, Cross-Coupling, Aniline, 6-Hydroxy Picolinhydrazide, Room-Temperature

INTRODUCTION

Biaryl amines represent valuable structural motifs with significance in drug discovery, crop protection agents, and materials science.[1–13] As such, developing catalytic systems that enable their efficient and mild synthesis is of considerable interest to academic and industrial chemists. While palladium-catalyzed transformations have undergone extensive research and optimization in recent decades,[14–22] the development of alternative catalysts based on cost-effective earth-abundant metals is highly sought after. Such catalysts must not only exhibit high catalytic efficiency but should ideally comply with permissible residual metal concentrations, allowing their use in the late-stage synthesis of active pharmaceutical ingredients (APIs) without necessitating cost-intensive downstream metal removal processes. Copper, with an extensive history in cross-coupling reactions, namely Ullmann[23] and Ullmann-type reactions[24–33], and a residual metal tolerance thirty times higher than that of palladium,[34] emerges as an ideal candidate to meet these requirements.

In the recent past, Ullmann-type reactions have undergone enormous improvements, initiated by the establishment of powerful anionic oxalamide ligands by Ma and co-workers,[33] enabling a new generation of highly effective copper catalysts for the cross-coupling of various nucleophiles with aryl bromides and chlorides at progressively lower catalyst loadings and milder conditions.[35–48]

In the context of Ullmann-type aniline cross-coupling reactions utilizing second-generation and related ligands,[42,49–53] Ma and co-workers reported in 2017 that *N*,*N*′-bis(furan-2-ylmethyl)oxalamide **L1** represents a highly active oxalamide ligand for mild cross-coupling reactions of aryl bromides at 80 °C (Figure 1, A).[52] In a following study, the substrate scope could be extended by employing a related ligand **L2**, requiring elevated temperatures and an alkoxide base (Figure 1, B).[42] Singer and co-workers reported picolinamide **L3** as a privileged ligand for broad aniline cross-couplings using DMSO as the solvent (Figure 1, C).[53–55] More recently, Buchwald achieved a significant breakthrough by overcoming the previously unattainable reactivity of copper catalysts in cross-coupling reactions with aryl bromides at room temperature (Figure 1, D).[51,56,57] This was accomplished through the introduction of novel N^1,N^2-diarylbenzene-1,2-diamine ligands, which enabled the cross-coupling of alkyl amines[56] and aliphatic alcohols[57] with electronically and sterically challenging electrophiles. Notably, the aniline-derived ligand proved ineffective for aniline coupling under their standard conditions, which relied on alkoxide bases.[56] In these conditions, the presence of aromatic amino functionalities even suppressed the otherwise highly efficient aliphatic amine cross-coupling. To address this limitation, Buchwald and co-workers introduced sodium trimethylsilanolate, a milder yet significantly more expensive alternative to alkoxides. This adjustment facilitated the coupling of selected anilines at 50 °C in DMSO.[51]

Despite the need for highly active copper catalysts, operating at low temperatures, factors such as solvent selection, base choice, and the complexity of ligand synthesis are equally critical considerations, when holistically assessing these catalytic methods for industrial adoption.[34] Solvent selection is particularly significant, as solvents constitute approximately 60% of the materials used in pharmaceutical processes.[58] Commonly employed solvents in copper-catalyzed cross-coupling reactions,[59] such as DMSO, are categorized as problematic within the pharmaceutical industry, in part due to the associated potential safety risks and high boiling point.[60–65] In contrast, alcoholic solvents are recommended alternatives; however, they frequently fail to deliver optimal activity in cross-coupling methodologies. Furthermore, the choice of base must be carefully evaluated. For example, even the use of cost-effective, mild K_3PO_4 can lead to eutrophication of natural water bodies if the wastewater is not adequately treated,[66] thereby increasing overall process costs.[34] Viable alternatives include sodium or potassium carbonate and hydroxide, which offer compelling benefits in terms of cost and environmental sustainability.[34]

Building on the recent advancements in the development of highly efficient copper catalysts for aniline cross-coupling, alongside careful consideration of the remaining reaction parameters, we set out to develop a copper-catalyzed cross-coupling methodology enabling the coupling of anilines with aryl bromides for the first time operating at room-temperature. Our approach prioritizes the use of industrially preferred solvents and bases to enhance the practicality and scalability of the process.

Herein, we report the use of a new 6-hydroxy picolinhydrazide ligand[67,68] for the copper-catalyzed cross-coupling of aryl bromides with anilines at room-temperature. A solvent mixture of industrially preferred MeOH and EtOH is key to achieving high catalytic efficiency with K_2CO_3 as a mild inorganic base, tolerating acidic functional groups that can inhibit catalysis with stronger alkoxide bases. Additionally, aryl chloride cross-coupling, as well

as different exemplary C–X (N-, O-, S- and P-centered nucleophiles) cross-couplings could be achieved, demonstrating the nucleophile compatibility of **L5** when utilized at elevated temperatures.

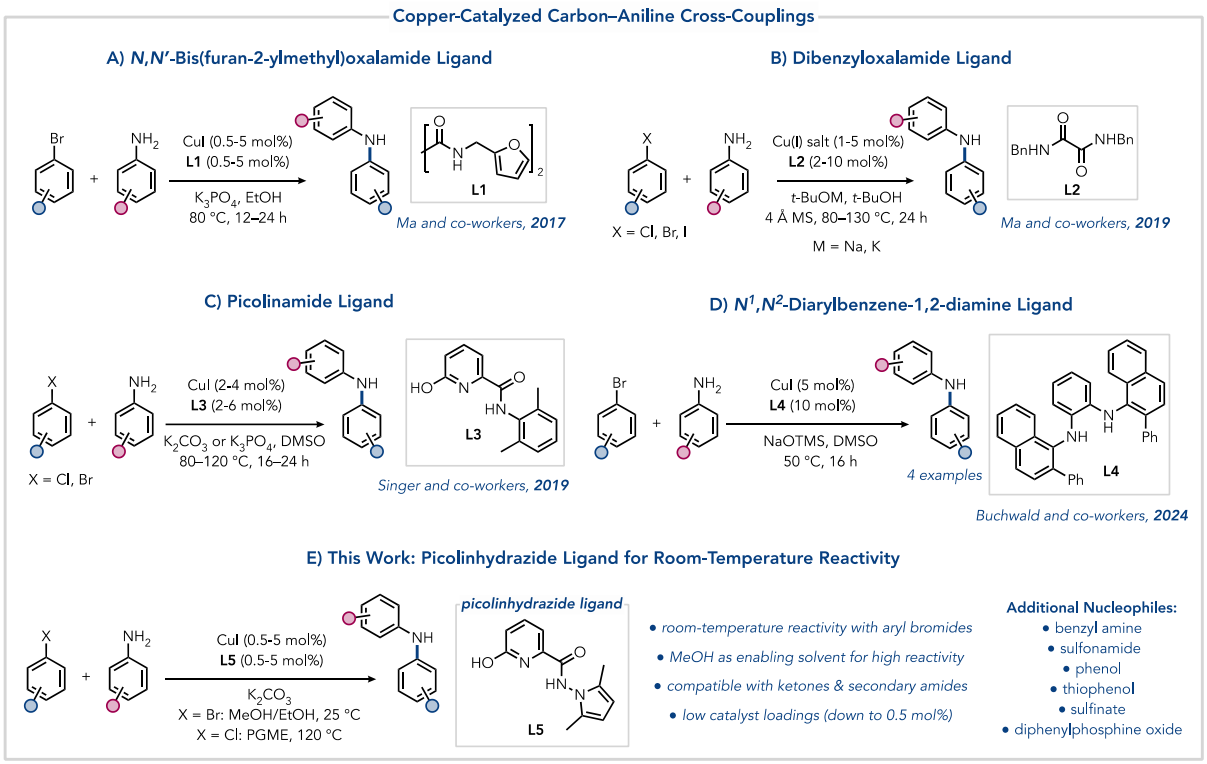


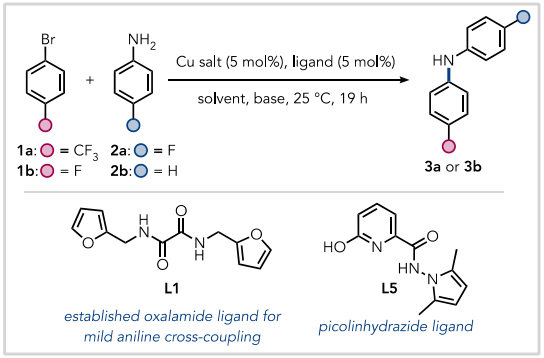
Figure 1. Overview of copper-catalyzed aniline cross-coupling using second-generation and related ligands.

RESULTS AND DISCUSSION

We started our investigation by probing the reactivity of furfurylamine-derived oxalamide **L1** as a benchmark, considering that it represents the most active ligand reported for mild aniline cross-couplings using an industrially preferred solvent (EtOH) and a cost-effective mild base (K_3PO_4).[52] Interestingly, when the reported reaction was performed with increased catalyst loadings at room-temperature, no significant conversion could be observed (Table 1, entry 1). Subsequently, we carried out the reaction using the novel picolinhydrazide ligand **L5**, which integrates structural elements from two of the most active ligands for Ullmann-type cross-coupling of anilines[53] and phenols.[36] To our delight, the reaction furnished the desired biaryl amine in 87% yield (Table 1, entry 2). To assess the method's compatibility with more electron-rich aryl bromides, we tested the cross-coupling of *p*-fluorobromobenzene with aniline (Table 1, entry 3). Although effective, a considerable decrease of 16% yield was observed, motivating further investigation. Changing the base to the more desirable option of K_2CO_3 led to a reduction in yield, even with the more activated aryl bromide **1a** (Table 1, entry 4). Given the limited solubility of carbonates in alcoholic solvents,[69] we explored whether using MeOH could enhance the reaction's conversion. Notably, a substantial improvement in conversion was observed with K_2CO_3 and MeOH. However, this condition also led to the formation of methanol-coupled byproducts in significant amounts (14–16%) for both aryl bromides (**1a** and **1b**) (Table 1, entries 5 and 6). Consequently, we attempted to reduce methanol coupling while maintaining the methanol-induced reactivity enhancement by utilizing a 1:1 mixture of EtOH and MeOH. Fortunately, the reaction furnished the desired product in 96% yield for the more activated aryl bromide **1a** and 88% for *p*-fluorobromobenzene (**1b**) after 19 h with 9% aryl bromide remaining (Table 1, entries 7 and 8). Performing the reaction with K_3PO_4 and the new solvent mixture did not lead to comparable results (Table 1, entry 9). Control experiments highlight the necessity of both copper and the ligand for effective catalysis (Table 1, entries 10 and 11). Intriguingly, DMSO, a privileged solvent in copper catalysis, led to low conversions to the desired product **3a** (Table 1, entry 12), highlighting that base solubility cannot be the singular factor improving catalytic efficiency with MeOH. Lastly, we wanted to probe if the methanol-induced reactivity enhancement is limited to picolinhydrazide **L5**. Therefore, we subjected oxalamide **L1** to the novel reaction conditions (Table 1, entry 13), leading to a significant reactivity improvement when compared to K_3PO_4 and EtOH (Table 1, entry 1), although not reaching the reactivity of picolinhydrazide **L5** (Table 1, entry 7). These results underscore the broader potential

of MeOH as an effective solvent for achieving mild Ullmann-type cross-couplings, along with the high activity achieved with picolinylhydrazide **L5**.

Table 1. Optimization of room-temperature aniline cross-coupling.



entry	substrates	Cu salt	ligand	base	solvent/s	3 [%]
1	a	CuI	**L1**	K_3PO_4	EtOH	3
2	a	CuI	**L5**	K_3PO_4	EtOH	87
3	b	CuI	**L5**	K_3PO_4	EtOH	71
4	a	CuI	**L5**	K_2CO_3	EtOH	63
5	a	CuI	**L5**	K_2CO_3	MeOH	82 (16)[a]
6	b	CuI	**L5**	K_2CO_3	MeOH	77 (14)[a]
7	a	CuI	**L5**	K_2CO_3	MeOH/EtOH (1:1)	96 (2)[a]
8	b	CuI	**L5**	K_2CO_3	MeOH/EtOH (1:1)	88
9	a	CuI	**L5**	K_3PO_4	MeOH/EtOH (1:1)	68 (21)[a]
10	a	-	**L5**	K_2CO_3	MeOH/EtOH (1:1)	0
11	a	CuI	-	K_2CO_3	MeOH/EtOH (1:1)	0
12	a	CuI	**L5**	K_2CO_3	DMSO	17%
13	a	CuI	**L1**	K_2CO_3	MeOH/EtOH (1:1)	19 (4)[a]

Reactions performed under nitrogen atmosphere with aryl bromide (1.0 mmol, 1.0 equiv), aniline (1.3 mmol, 1.3 equiv), and base (1.5 mmol, 1.5 equiv) in the respective solvent/s (1.0 M). [a]Yields in brackets correspond to the methanol-coupled byproduct. Yields were determined by ^{19}F-NMR with either fluorobenzene or trifluorotoluene as internal standard.

With optimized reaction conditions in hand, we explored the synthetic utility of the method (Figure 2). For anilines with varying electronic structure (**3**–**5**), very good to excellent isolated yields were obtained. An *ortho*-disubstituted aniline underwent the reaction successfully, furnishing biaryl amine **6** in good yield. Even though longer reaction times were required for the more challenging *para*-methoxybromobenzene as the electrophile, product **7** still formed in very good yield at room-temperature. Next, we investigated functional groups reported as challenging in previous room-temperature protocols, likely due to the reliance on strong alkoxide bases.[55] To our delight, the mild conditions allowed for cross-coupling of enolizable ketones (**8** and **9**) and a secondary amide (**10**) in excellent isolated yields. Moreover, heterocycles are tolerated well, although requiring elevated temperatures to achieve 90% yield for the coupling of 3-bromopyridine (**11**), whereas room-temperature reactivity can be maintained to furnish quinoline **12** in very good yield. This showcases a prominent trend in copper catalysis, where pyridine moieties in the absence of proximal steric hindrance often decrease catalytic activity, possibly due to catalyst deactivation. To evaluate the method's efficiency, we scaled up the reactions and attempted cross-coupling reactions with reduced catalyst loadings. Fortunately, the reactions still work reliably with 1 mol% and 0.5 mol% of catalyst loadings as demonstrated with enolizable ketone **13** and more electron-rich fluorobenzene **14**. We want to emphasize that copper, ligand **L5**, the substrates, and the base could all be weighed in under ambient atmosphere and still lead to efficient catalysis even at low catalyst loadings. While 79% yield was obtained for product **14** at room-temperature, quantitative conversion to the desired product was observed at 60 °C with

shorter reaction times. This highlights the potential for further reducing catalyst loadings when the reaction temperature is elevated.

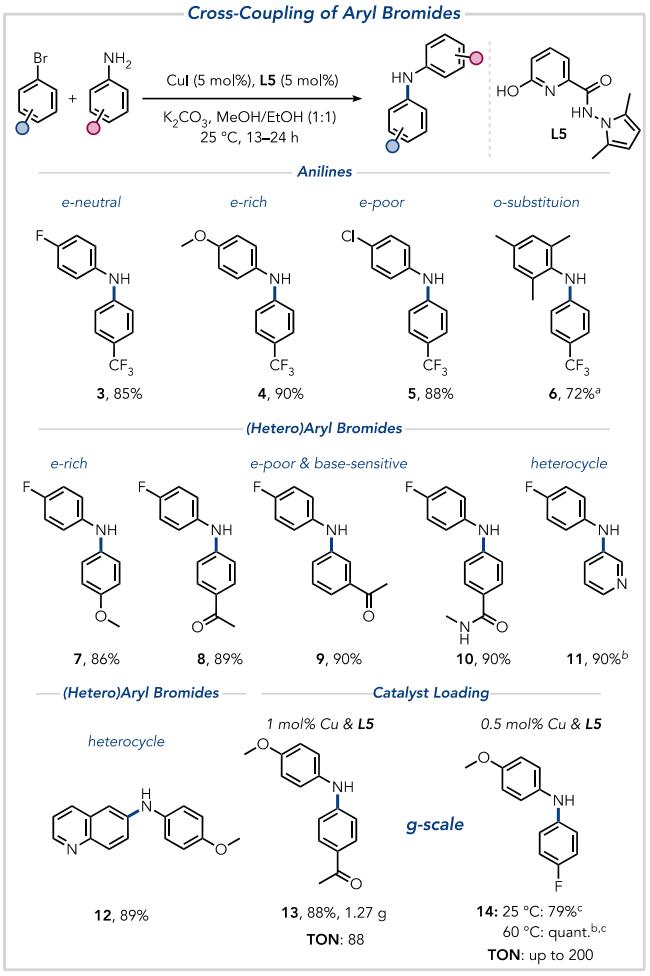


Figure 2: Scope of aniline cross-coupling with aryl bromides. Reactions performed under nitrogen atmosphere with aryl bromide (1.0 mmol, 1.0 equiv), aniline (1.3 mmol, 1.3 equiv), and K_2CO_3 (1.5 mmol, 1.5 equiv) in MeOH/EtOH (1:1) (1.0 M). [a]50 °C, [b]60 °C. [c]Yield determined by ^{19}F-NMR with trifluorotoluene as internal standard. Please see supporting information for experimental details of the upscaling of biarylamine **13** and **14**.

With good activity at room-temperature for aryl bromides, we sought to investigate aryl chloride couplings at elevated temperatures (Figure 3). Considering the limited boiling point of MeOH, we opted for 1-methoxy-2-propanol (PGME) as an alternative alcohol solvent. Again, anilines of varying electronic structures are well tolerated (**3**, **7**, and **15**) with very good to excellent yields. Sterical hinderance is tolerated, although providing a slightly reduced yield for aryl amine **6**. Enolizable ketones (**8** and **13**), as well as quinoline **16** provide no exception and can be obtained in excellent yields.

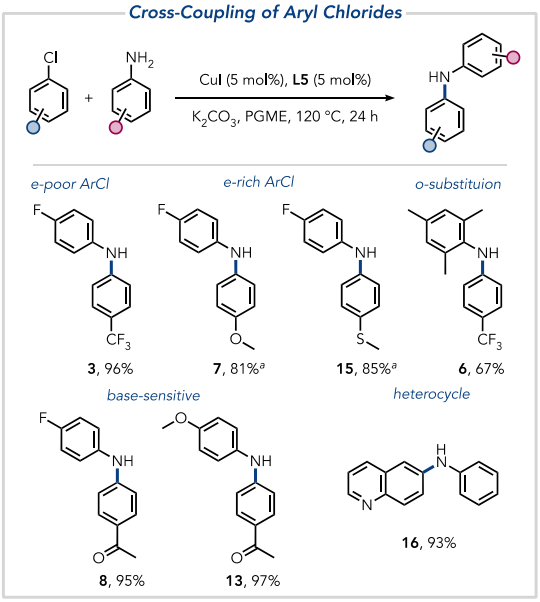


Figure 3: Scope of aniline cross-coupling with aryl chlorides. Reactions performed under nitrogen atmosphere with aryl chloride (1.0 mmol, 1.0 equiv), aniline (1.3 mmol, 1.3 equiv), and K_2CO_3 (1.5 mmol, 1.5 equiv) in PGME (2.0 M). [a]CuI (8 mol%), **L5** (10 mol%).

Taking into consideration that copper-catalyzed cross-coupling reactions often rely on a distinct ligand motif, we explored various exemplary carbon–heteroatom bond forming reactions with picolinhydrazide **L5** (Figure 4). Besides anilines, alkyl amines and sulfonamides are common nucleophiles for C–N cross-coupling reactions.[70] As such, *p*-toluenesulfonamide and benzylamine were taken as model substrates and underwent successful coupling to form the corresponding products **17** and **18** with 77% and 90% isolated yield, respectively. Moreover, phenols represent an attractive nucleophile class due to the prevalence of their coupling products in biologically relevant molecules.[71] Fortunately, aryl ether **19** could be obtained in 70% isolated yield. Hydroxylation was observed as a byproduct and could be decreased by the use of molecular sieves. Additionally, C–P bond formation using diphenylphosphine oxide as the nucleophile effectively formed the triarylated phosphine oxide **20**. Lastly, C–S cross-coupling reactions with an aromatic thiol, as well as methane sulfinate could be achieved to furnish the corresponding thioether **21** and sulfone **22** in excellent isolated yields. Intriguingly, for the cross-coupling of diphenylphosphine oxide and thiophenol, non-ideal DMSO proved beneficial over PGME.

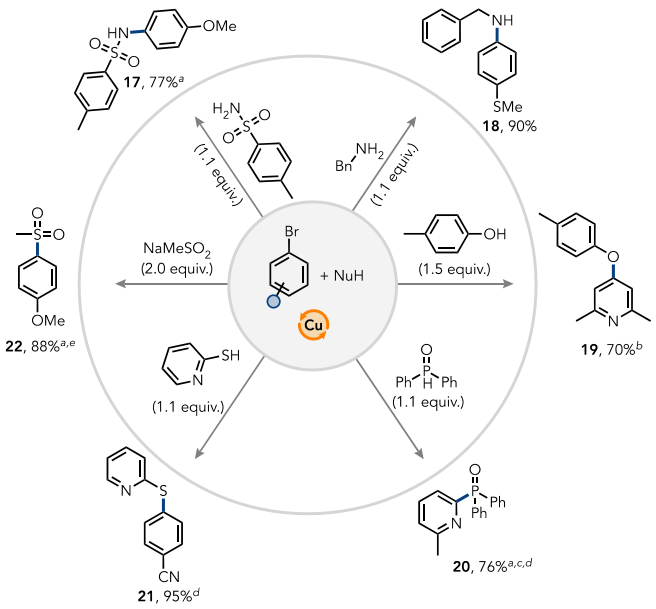


Figure 4: Scope of additional nucleophiles. The reactions were performed on 3.0 mmol scale with aryl bromide (1.0 equiv), nucleophile (1.1–2.0 equiv), CuCl (5 mol%), **L5** (6 mol%), 1-methoxy-2-propanol (2.0M), and K_3PO_4 (1.5 equiv) at 80 °C for 20–24 h. [a]120 °C, [b]3 Å molecular sieves added, [c]sodium ascorbate (5 mol%) added, [d]DMSO (2.0M), [e]K_2CO_3 (1.5 equiv).

Lastly, a critical factor for the industrial adoption of catalytic methods is the complexity of the ligand. Often, ligands with lower activity have to be used when the synthesis of highly active ligands is too time- or cost-intensive.[34] To address this, a straightforward synthetic route using commercially available starting materials to access picolinhydrazide **L5** in three steps was developed. Notably, the first two steps can be executed in one-pot.

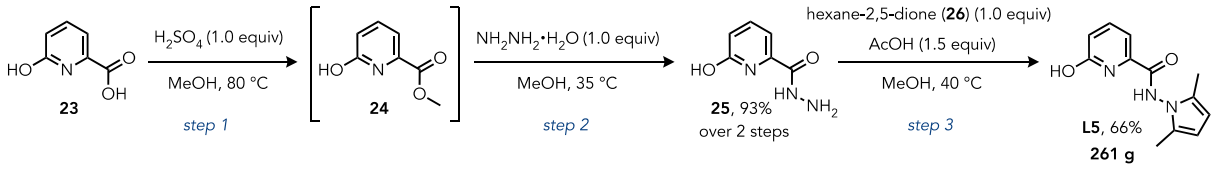


Figure 5: Optimized synthesis of 6-hydroxy picolinhydrazide **L5**.

Specifically, esterification of picolinic acid **23** under acidic conditions yields ester **24**. Subsequent addition of hydrazine hydrate results in the formation of hydrazide **25** in excellent isolated yield. Finally, condensation with diketone **26** produces the desired picolinhydrazide **L5**, yielding 261 g of the product.

CONCLUSIONS

In summary, we have developed a novel method for copper-catalyzed cross-coupling of anilines with aryl bromides at room-temperature utilizing a 6-hydroxypicolinhydrazide ligand. The method demonstrates broad compatibility with structurally diverse coupling partners and achieves efficient coupling with minimal catalyst loadings of just 0.5 mol%. Importantly, the use of an industrially preferred base and solvents makes this method highly amenable to large-scale applications. In this context, copper-based methodologies stand out as particularly advantageous due to the permissible residual metal concentrations of copper in API development, combined with its abundance and cost-effectiveness. The observed beneficial effects of methanol as a solvent in copper catalysis are anticipated to inspire further exploration of related protocols that could benefit similarly from such solvent effects. Furthermore, the reaction conditions are adaptable to the coupling of aryl chlorides using an alternative alcohol solvent, as well as to other nucleophile classes, with only minor modifications to the solvent and base systems. Taken together, we believe that 6-hydroxy picolinhydrazides represent a promising class of ligands with the potential to advance various Ullmann-type reactions of significant interest to both academic and industrial chemists.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details and characterization data of the isolated products can be found in the supporting information (PDF).

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Author Contributions

‡These authors contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Jonas Düker, Nele Petersen, Noah Richter, Teresa Faber, Niklas Hölter, Niklas Kehl, Jan Oboril, Julian Strippel, Nicolas Guimond, Sherif J. Kaldas, Maximilian Lübbesmeyer, Giulio Volpin, and Julius Hillenbrand are employees of Bayer AG, a life-science company operating in the healthcare and agriculture sectors.

Moreover, a patent has been filed for the use of the described ligand (PCT/EP2024/075573).

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