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Orthogonal Discrimination among Functional Groups in Ullmann-Type C–O and C–N Couplings

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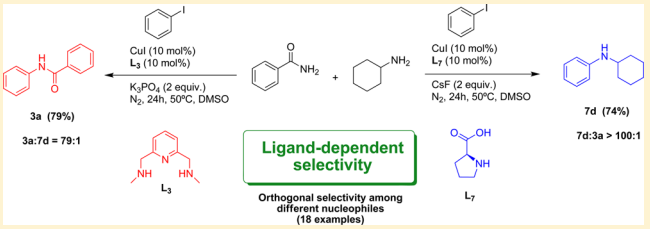
Supporting Information

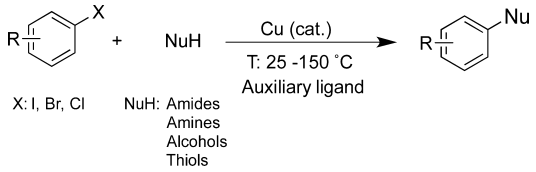
ABSTRACT: The copper-catalyzed arylation of nucleophiles has been established as an efficient methodology for the formation of C–C and C–heteroatom bonds. Considering the advances during the last two decades, the ligand choice plays a key role in such transformations and can strongly influence the catalytic efficiency. The applicability of these Ullmann-type coupling reactions regarding the orthogonal selectivity of different functional groups constitutes a challenging subject for current synthetic strategies. Herein, we report a useful toolkit of Cu-based catalysts for the chemoselective arylation of a wide-range of nucleophiles in competitive reactions using aryl iodides and bromides. We show in this work that the arylation of all kinds of amides can be orthogonal to that of amines (aliphatic or aromatic) and phenol derivatives. This high chemoselectivity can be governed by the use of different ligands, yielding the desired coupling products under mild conditions. The selectivity trends are maintained for electronically biased iodobenzene and bromobenzene electrophiles. Radical clock experiments discard the occurrence of radical-based mechanisms.



INTRODUCTION

Modern copper-catalyzed cross-coupling reactions have recently evolved into reliable and efficient methods for the formation of C–C and C–heteroatom bonds, which are present in a large number of natural and pharmaceutical products. Recent progress in modern catalytic Ullmann coupling reactions has led to the emergence of numerous methods to combine aryl halides (mainly iodides and bromides) with aliphatic amines, amino alcohols, amides, anilines, phenols, and other derivatives (Scheme 1).[1−7]

Scheme 1. Copper-Catalyzed Ullmann-Type C–Heteroatom Couplings



The first reports on Ullmann–Goldberg reactions originally required relatively harsh conditions such as high temperatures and sometimes the use of stoichiometric amounts of copper salts.[8−10] Interestingly, several "ligand-free" procedures have also been reported as effective catalytic systems for Ullmann-type reactions, taking advantage of the coordinating abilities of solvents such as DMF, DMP, and TEOS, albeit under high temperature conditions.[11−20] On the other hand, since the late 1990s, much effort has been devoted to the use of chelating ligands such as diamines, amino acids, phenanthroline derivatives, and β-diketones to perform coupling reactions under milder conditions while achieving enhanced yields.[3,7,21] Moreover, the employment of auxiliary ligands not only accelerates the reactions but also affords more reproducible and safer reactions in terms of operating conditions and residual toxicity.

In thermal-based Ullmann couplings the detection of intermediate species after the activation of the aryl halide, which is usually rate-limiting, is very limited, and most mechanistic proposals are derived from kinetic and computational studies.[22−26] The most invoked mechanism for Ullmann couplings is based on two-electron redox processes via a Cu^{I}/Cu^{III} catalytic cycle,[6] although some computational reports point toward one-electron redox processes through radical intermediates (Scheme 2)[22] and some MS studies suggest competing mechanisms.[27−30] On the other hand, Peters, Fu, and co-workers recently reported a photoinduced, nonthermal process involving a copper–carbazolide complex for promoting the radical-based C–N bond forming reaction.[31−36]

The ligand choice could play a determinant role in the selectivity of the arylation reaction as well as in the operative mechanism for such a transformation. Indeed, Buchwald and

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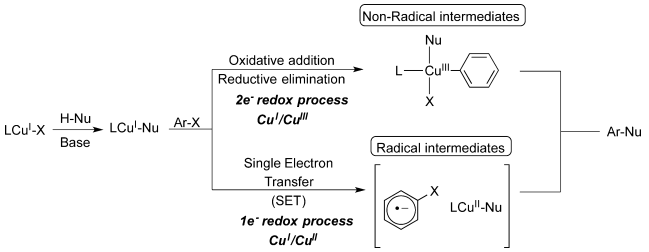
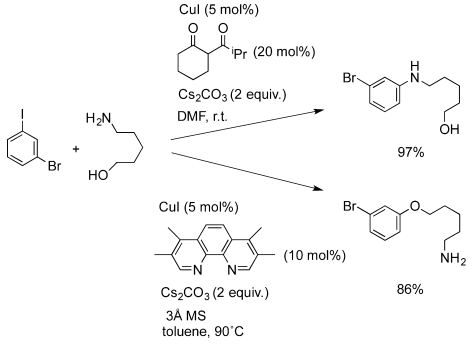
Scheme 2. Two Main Mechanistic Proposals for Ullmann-Type Couplings



co-workers reported the first example of chemoselective arylation of amino alcohols by using different auxiliary ligands.[37,38] While the β-diketone ligand promoted the formation of N-arylated product in DMF at room temperature, tetramethylphenanthroline ligand promoted selective O-arylation in toluene at 90 °C (Scheme 3).

Scheme 3. First Selective Ligand-Dependent Cu-Catalyzed Arylation of a Bifunctional Nucleophile Reported by Buchwald



Bearing in mind the importance of achieving selective reactivity among functional groups in current synthetic strategies, in this work we employed different well-known and available ligands coordinating to Cu^{I} with the aim of diverting the selective arylation of different nucleophiles at will. As a result, herein we disclose a useful toolkit of Cu-based catalytic systems for the highly chemoselective arylation of a wide range of nucleophiles in competitive reactions using aryl iodides and bromides.

RESULTS AND DISCUSSION

We recently described a practical ligand-free protocol for the N- and O-arylation of a wide range of amides, alcohols, and amines under common optimized reaction conditions.[20] Based on that experimental protocol and employing the base/solvent combination of K_3PO_4/DMSO with 10 mol % of CuI, in this work we explored the arylation of N- and O-nucleophiles using N,N-, N,O-, or O,O-bidentate or N,N,N-tridentate ligands ($\mathbf{L_1}$–$\mathbf{L_{10}}$) with aryl halides under mild conditions (Figure 1).[3,7] The K_3PO_4 base is substituted in selected cases by CsF or K_2CO_3 to further improve the yield of the desired products. We used this common experimental protocol for all kinds of nucleophiles to visualize the impact of the ligand nature.

First, iodobenzene (**1**) was subjected to N-arylation with different primary and secondary amides (**2**) (see Scheme 4 and Table S1). Aromatic primary amides (**2a** and **2f**; Table S1, entries 1 and 6) rendered good-to-excellent yields using di- or

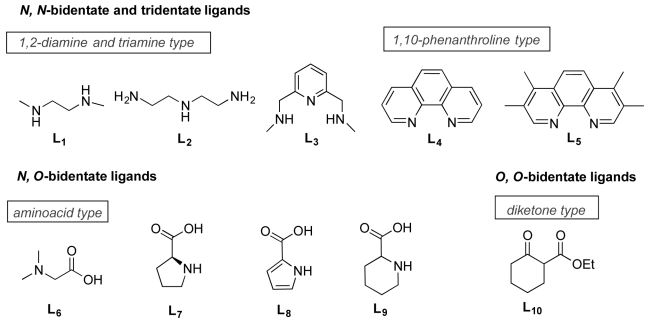


Figure 1. Bidentate and tridentate auxiliary ligands used in this work.

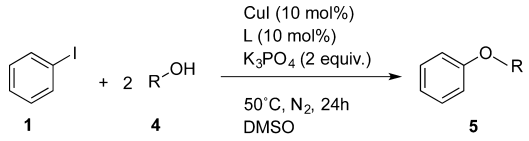
Scheme 4. Screening of Amides for N-Arylation with Iodobenzene

Preferred Auxiliary Ligands: $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_3}$ (for primary aromatic amides)
$\mathbf{L_7}$ (for primary aliphatic amides)
$\mathbf{L_4}$/130°C (for secondary amides)

triamine ligands ($\mathbf{L_1}$–$\mathbf{L_3}$). The use of *L*-proline ($\mathbf{L_7}$) was found to be the most suitable ligand for the arylation of the primary aliphatic amide **2g** in excellent yield at 80 °C (Table S1, entry 7). Due to the low reactivity of secondary amides, the use of 1,10-phenanthroline ($\mathbf{L_4}$) as a ligand at 130 °C was necessary to reach good performance in the arylation of aliphatic secondary amides (**3h** and **3j**; Table S1, entries 8 and 10). However, an exception was found for pyrrolidin-2-one (**2b**), a cyclic secondary amide, which afforded the N-arylated product **3b** in 80–91% using di- or triamine ligands ($\mathbf{L_1}$–$\mathbf{L_3}$) or 1,10-phenantholine ($\mathbf{L_4}$) under mild conditions (Table S1, entry 2).

Next, we explored the arylation of alcohols under the same reaction conditions (Scheme 5 and Table S2). As expected

Scheme 5. Mild O-Arylation of Alcohols with Iodobenzene



Preferred auxiliary ligand: $\mathbf{L_6}$

from previous studies, the O-arylation of phenols using dimethylglycine ($\mathbf{L_6}$) as a Cu-chelating ligand gave excellent coupling yields (82–97% **5a**, **5b**, **5c**, **5d**; Table S2, entries 1–4).[39,40] Phenols with electron-withdrawing groups and aliphatic alcohols gave poor yields irrespective of the auxiliary ligand used.

After screening the O-arylation of different alcohols, we were also interested in exploring the reactivity of amines as nucleophiles (Scheme 6 and Table S3). In line with the literature, the N,O-bidentate ligands such as proline ($\mathbf{L_7}$) or pyrrole-2-carboxylic acid ($\mathbf{L_8}$) were found to be the most suitable chelating moieties when the arylation of amines is targeted.[7,40–42,7,39–41] In addition, the employment of CsF as a

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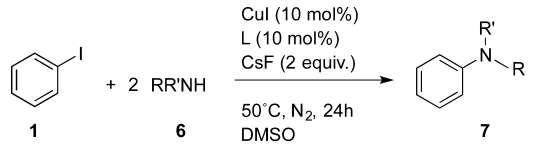
Scheme 6. Mild N-Arylation of Amines with Iodobenzene



base instead of K_3PO_4 rendered better results for these coupling reactions. In particular, the use of $\mathbf{L_8}$ for the N-arylation of aromatic amines afforded moderate to good yields (62−76%, **7a** and **7c**; Table S3, entries 1 and 3), while the N-arylated *p*-nitro-substituted aniline (**7b**) was obtained only in 22% yield (Table S3, entry 2). On the contrary, the N-arylation of primary aliphatic amines (**6d** and **6e**) was very effective using ligand $\mathbf{L_7}$, and excellent yields and conversions were observed (89−95%; Table S3, entries 4 and 5). Regarding secondary aliphatic amines, cyclic piperidine (**6g**) afforded the desired product **7g** in excellent yield (86% yield, Table S3, entry 7), while under the same reaction conditions, a very poor yield of the arylated product **7f** was observed (Table S3, entry 6). In contrast, conjugated N-heterocyclic secondary amine **6h** rendered the N-arylated product **7h** in excellent yield using $\mathbf{L_1}$ (96%; Table S3, entry 8). In particular, this latter product was also formed in excellent yields and conversions employing other ligands such as $\mathbf{L_2}$, $\mathbf{L_3}$, $\mathbf{L_4}$, or $\mathbf{L_6}$ or even working at rt with $\mathbf{L_1}$.

Eventually, we also examined the arylation of different N- and O-nucleophiles employing the aryl bromide as a substrate (Table S4). Excellent yields (88−100%) were obtained for aromatic alcohols (**5a** and **5c**; Table S4, entries 6 and 7), and moderate-to-good yields (50−80%) were found for aromatic and aliphatic amines (**7a**, **7c** and **7d**; Table S4, entries 8−10). Nevertheless, very poor reactivity was observed for the arylation of amides and only the use of pyrrole derivative $\mathbf{L_8}$ afforded the arylation of the cyclic amide pyrrolidin-2-one (**2b**) in 26% yield (Table S4, entries 1−5).

Ligand-Dependent Selectivities in Competition Reactions Using Iodobenzene. Considering the trends observed from the different ligands previously tested, we focused our attention on the study of the selective arylation of a wide-range of nucleophiles in competition reactions under mild conditions (50 °C). Thus, we performed competitive experiments combining amides, amines, and phenols under standard conditions (1 equiv of iodobenzene, 2 equiv of each nucleophile), aiming to find out the most suitable ligand for the arylation of each nucleophile in high selectivity and yield (Scheme 7).

In general trends, we have found that the arylation of aromatic amides is favored over that of phenols and amines when tridentated N-based auxiliary ligands and mild temperatures are used, with $\mathbf{L_1}$ and $\mathbf{L_3}$ being the best ones (Scheme 7, A−D). Owing to its well-known poor reactivity, the arylation of noncyclic aliphatic amides requires higher temperatures and is favored in front of the arylation of amines when $\mathbf{L_4}$ is used (Scheme 7, E−H). Moreover, noncyclic primary aliphatic amides can be slightly favored in front of the arylation of phenols with $\mathbf{L_4}$ (Scheme 7, L), but noncyclic secondary aliphatic amides cannot compete with phenols (Scheme 8, C). On the other hand, the arylation of cyclic aliphatic amides is sharply chemoselective in front of aliphatic amines, phenols and aromatic amides when $\mathbf{L_1}$ or $\mathbf{L_4}$ are used (Scheme 7, I, M, and Scheme 8, A). Moreover, the arylation of phenols is especially favored in competition with amines and amides when $\mathbf{L_6}$ is used (Scheme 7, A, J−M and Scheme S1). Finally, anilines are arylated selectively before phenols and amides (Scheme 7, B, F, G, J) when $\mathbf{L_8}$ is used. The product ratios are in general higher than 7 and in many cases above 20, showing an orthogonal selectivity in most of the competitions explored. The nonarylated nucleophile remained unconverted and could be recovered at the end of the reaction. Due to the low reactivity of aliphatic alcohols, no competition studies have been undertaken since those nucleophiles are clearly more challenging than the studied above (entries 6 and 7, Table S2).

Some nucleophiles present a strong preference toward arylation irrespective of the competing nucleophile or the auxiliary ligand used. Specifically, only minor changes in the selectivity could be achieved when the same family of nucleophiles is used, for example, the competitive reaction between two types of amides, benzamide (**2a**) and the cyclic amide pyrrolidin-2-one (**2b**) (Scheme 8, A). In this reaction, we were only able to set out conditions to render the N-arylation of **2b** in excellent yield and conversion using $\mathbf{L_4}$ at 50 °C (76% **3b**; **3b**/**3a** ratio = 8). Despite performing the reaction with other type of ligands such as $\mathbf{L_8}$, a very low yield of **3a** was obtained. Similarly, a competitive reaction of two types of amines (**6c** and **6d**) afforded the N-arylated cyclohexylamine **7d** as the major product in all cases tested (Scheme 8, B). Best results were observed by submitting proline ligand $\mathbf{L_7}$ as a ligand (78% **7d**; **7d**/**7c** ratio = 44). Along the same line, when the competition is performed between *N*-methylacetamide (**2h**) and *p*-methoxyphenol (**4c**) (Scheme 8, C, and Scheme S1), the O-arylated **5c** was successfully formed employing the glycine derivative $\mathbf{L_6}$ and K_2CO_3 in high yield and conversion at 50 °C (98% **5c**; **5c**/**3h** ratio >100). Additionally, the O,O-bidentate ligand $\mathbf{L_{10}}$ also led to the selective formation of **5c** under the same conditions. However, we were unable to find the appropriate conditions to tilt the balance in favor of the arylation of the secondary amide **2h**. Despite using the most suitable ligand for the formation of **3h** ($\mathbf{L_4}$), we found a very high selectivity for the O-arylated coupling product in all cases tested. The use of $\mathbf{L_1}$ with K_3PO_4 or CsF or $\mathbf{L_8}$ with K_2CO_3 at 50 °C significantly reduced the yield of the O-arylated product (37% and 57% yield, respectively); however, the reaction likewise proceeded in low yields for the formation *N*-arylacetamide **3h**. We rationalize that the facile arylation of phenol and the high temperatures that are required for achieving reactivity toward secondary amides prevent us from establishing suitable conditions for such competition reactions.

Ligand-Dependent Selectivities in Competition Reactions Using *Para*-Substituted Iodobenzenes. Additionally, in order to broaden the aryl iodide scope, we checked the effect of electron-donating and electron-withdrawing substituents at the *para* position. Thus, *p*-iodotoluene and *p*-nitroiodobenzene were selected as aryl halides in competition reactions analogous to Scheme 7, C (Scheme S2 and S3 in the SI). Regarding *p*-iodotoluene (Scheme S2), the arylation of benzamide **2a** was significantly suppressed using pincer ligand $\mathbf{L_3}$. On the contrary, the arylation of the same nucleophile using pyrrole derivative $\mathbf{L_8}$ was successfully improved up to 92% yield of **3n** as a single arylated product in complete conversion (**3n**/**7o** ratio = 92). On the other hand, the formation of the coupling product **7o** was also a bit suppressed when proline $\mathbf{L_7}$ was used; however, it was effectively formed as a unique

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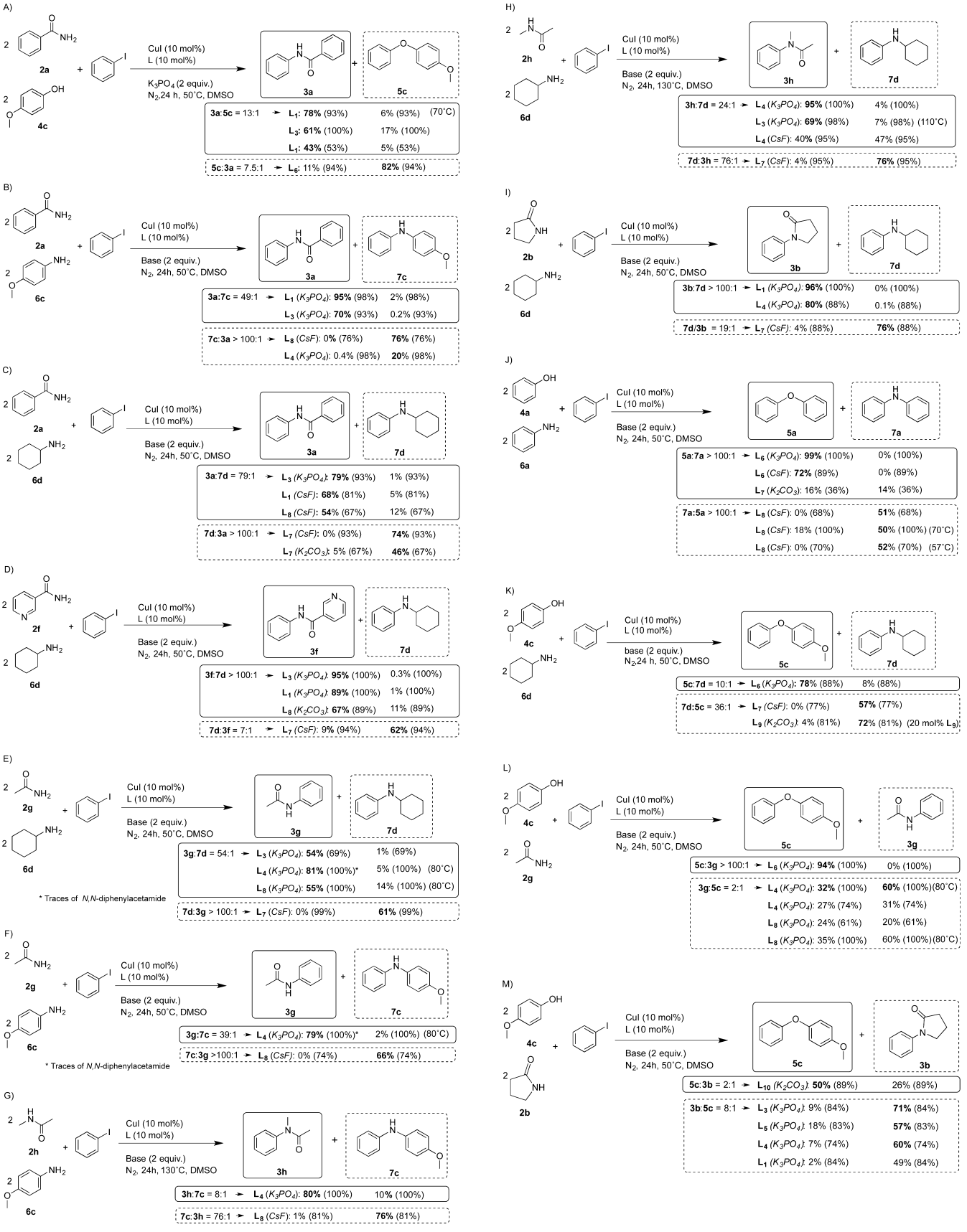
Scheme 7. Competition Reactions among Nucleophiles Using Iodobenzene with a Sharp Switch of Chemoselectivity[a]



[a]Conversions are given in parentheses; standard experimental conditions used.

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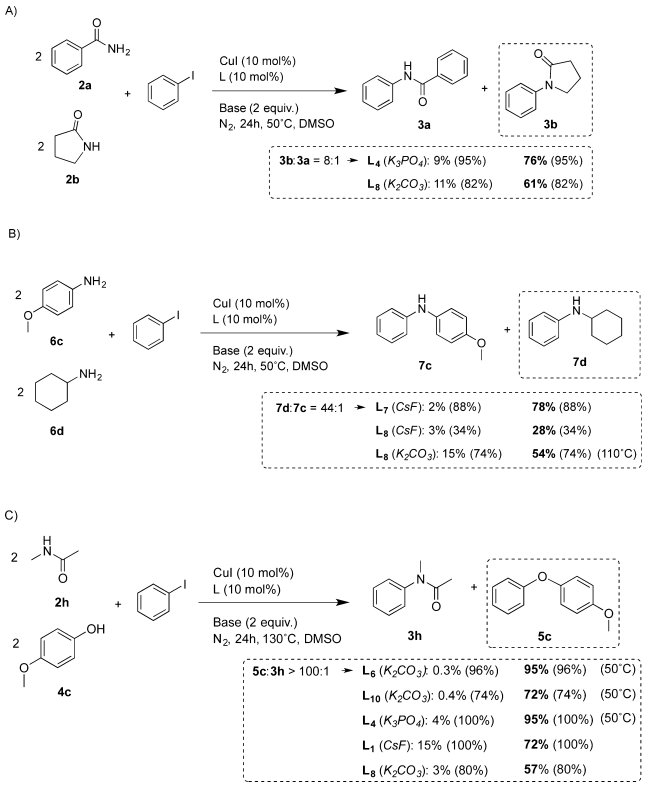
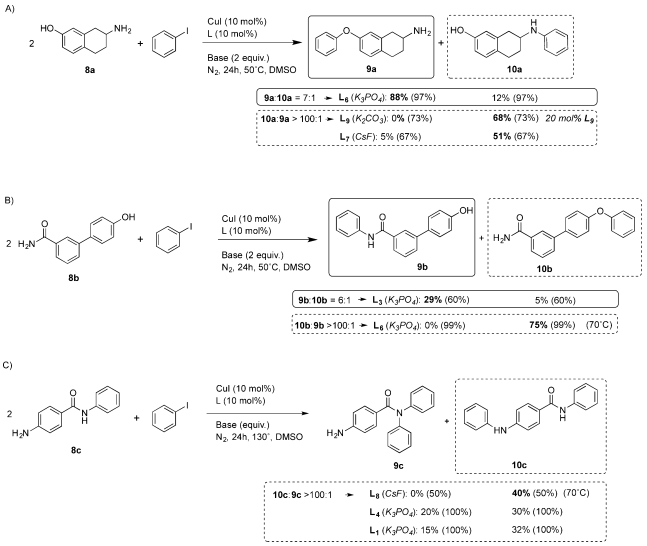
Scheme 8. Competition Reactions among Nucleophiles with Strong Arylation Preference for One Nucleophile Irrespective of the Auxiliary Ligand Used[a]



[a]Conversions are given in parentheses; standard experimental conditions used.

Scheme 9. Competition Reactions Using Bifunctional Nucleophiles 8a–8c[a]



[a]Conversions are given in parentheses; standard experimental conditions used.

product (55% **7o**, **7o**/**3n** ratio >100). When *p*-nitroiodobenzene was used as a substrate (Scheme S3), we observed a reactivity similar to that of the iodobenzene. It is noteworthy that pincer-type ligand L_3 improved the formation of **3l**, which was obtained almost as a single product in good yield (64% **3l**, **3l**/**7m** ratio = 32). Additionally, the employment of proline L_7 also gave rise to the coupling product **7m** as single product (66% **7m**, **7m**/**3l** ratio = 66). Therefore, both electron-rich and electron-deficient aryl iodides underwent arylation with excellent selectivities.

Ligand-Dependent Selectivities in Competition Reactions Using Bifunctional Nucleophiles and Iodobenzene. To further probe the orthogonality of our Cu-based catalytic systems, we next evaluated the selective arylation of different bifunctional nucleophiles (**8a**, **8b**, and **8c**) (Scheme 9). First, the aminophenol **8a** could be selectively O-arylated with dimethylglycine L_6 (Scheme 9, A) to give the coupling product **9a** in excellent yield and with high chemoselectivity (88% **9a**; **9a**/**10a** ratio = 7). On the other hand, the N-arylation of **8a** was highly favored when L_7 was used as a ligand and CsF as a base (**10a**, 51%). Very notably, running the same reaction with N,O-bidentate ligand L_9 (20 mol %) in combination with K_2CO_3 improved the formation of **10a** as a unique product up to 68% yield (**10a**/**9a** ratio >100). We also succeeded in the competition reaction between the bifunctional nucleophile **8b** (bearing aromatic amide and phenol functional groups) and iodobenzene (Scheme 9, B). Not surprisingly, the presence of the dimethylglycine L_6 at 70 °C led to the O-arylation of **8b**, yielding **10b** as a sole coupling product (75% **10b**; **10b**/**9b** ratio >100). On the contrary, this trend successfully switched to the formation of the N-arylated product **9b** in the presence of L_3, even though the yield was modest (29% **9b**; **9b**/**10b** ratio = 6). In the arylation reaction of 4-amino-*N*-phenylbenzamide (**8c**) with iodobenzene (Scheme 9, C), only the N-arylation of the amino group was observed as the major product, irrespective of the auxiliary ligand used. Compound **10c** was obtained as a single product in moderate yield and high selectivity when the pyrrole derivative ligand L_8 using CsF as a base (40% **10c**; **10c**/**9c** ratio >100) was used. Presumably, the arylation of the secondary amide was hampered by steric effects, and even when high temperatures (130 °C) together with L_1 or L_4 as ligands were used, the formation of **10c** was unavoidable in both cases tested.

Ligand-Dependent Selectivities in Competition Reactions Using Bromobenzene. With these good results in hand, we decided to conduct most of the competition reactions described above using bromobenzene. Because of the low reactivity of bromobenzene, reactions were undertaken at 110 or 130 °C. Among them and as shown in Scheme 10, competitions B′, H′, and I′ were those in which excellent selectivities and yields were observed. First, when the competitive reaction was run between benzamide (**2a**) and anisidine (**6c**) (Scheme 10, competition B′, equivalent to Scheme 7, B), we were very pleased to observe the single formation of *N*-arylamide **3a** in good yield using phenanthroline ligand L_4 at 130 °C (52% **3a**; **3a**/**7c** ratio >100). Remarkably, the selectivity was effectively turned to the unique arylation of **6c** in excellent yield when the pyrrole derivative L_8 (73% **7c**; **7c**/**3a** ratio >100) was employed. On the other hand, when the competitive reaction was run between *N*-methylacetamide (**2h**) and cyclohexylamine (**6d**) (Scheme 10, competition H′, equivalent to Scheme 7, H), the presence of DMEDA (L_1) at 110 °C yielded **3h** almost exclusively in remarkable yield and selectivity (68%, **3h**/**7d** ratio = 23). Surprisingly, all of the attempts using phenanthroline-type ligands (L_4 and L_5) aiming to promote the same coupling product failed. However, using proline as chelating ligand (L_7)

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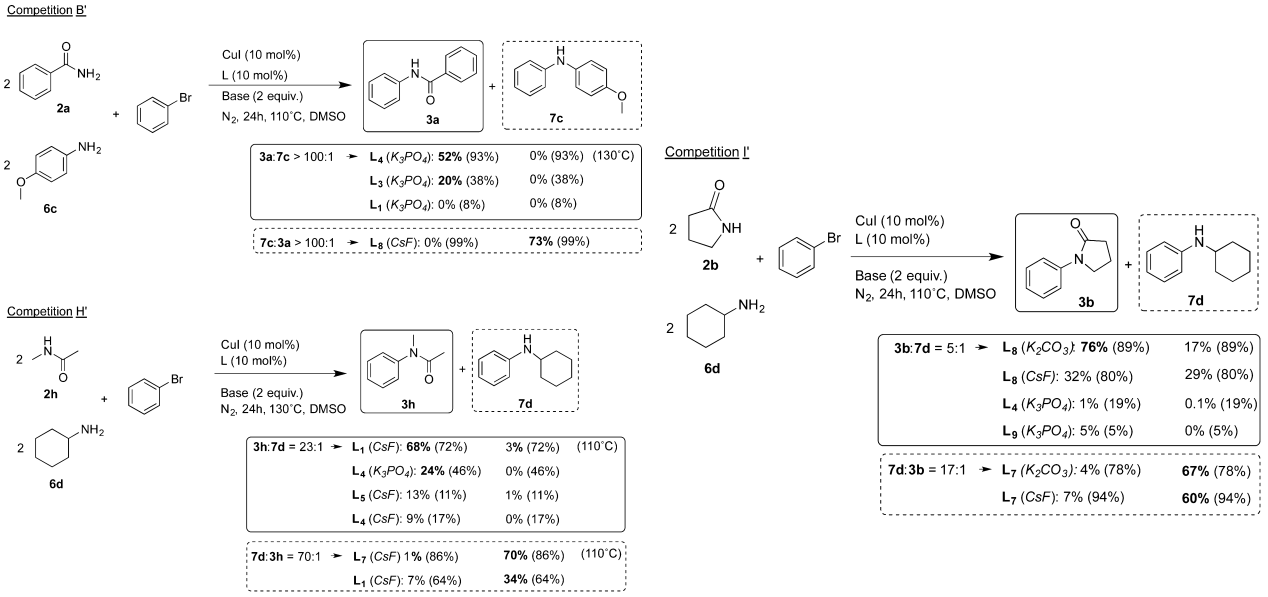
Scheme 10. Competition Reactions among Nucleophiles Using Bromobenzene with a Sharp Switch of Chemoselectivity[a]



[a]Conversions are given in parentheses.

at 110 °C successfully led to the almost exclusive formation of **7d** in 70% yield (**7d**/**3h** ratio = 70). In line with these results, we observed similar reactivity when facing the cyclic amide pyrrolidin-2-one (**2b**) and cyclohexylamine (**6d**) (Scheme 10, competition I′, equivalent to Scheme 7, I). While $\mathbf{L_7}$ provided the arylation of the aliphatic amine to yield **7d** in good yields (67% **7d**; **7d**/**3b** ratio = 17), the pyrrole derivative $\mathbf{L_8}$ using K_2CO_3 as a base favored the arylation of the cyclic amide in good yield and moderate selectivity (76% **3b**, **3b**/**7d** ratio = 5). We noticed an important base effect in the latter case, since the use of CsF as a base instead of K_2CO_3 prevented the chemoselectivity between both nucleophiles. Furthermore, competitive reactions A′, C′, D′, G′, and J′ and bifunctional **8a** employing bromobenzene also led to the selective arylation one of the nucleophiles, although most of them were in lower yields and moderate to good selectivities (Scheme S4, SI). Some unexpected effects were found, such as the fact that all reactions combining bromobenzene and aromatic amides **2a** and **2f** with $\mathbf{L_1}$ ligand completely failed in any competition tested (Scheme 10, competition B′, and Scheme S4, competitions A′, C′, and D′). Moreover, 1,10-phenathroline ($\mathbf{L_4}$) showed a chemoselective behavior with bromobenzene different from that with iodobenzene when facing primary amides and aliphatic or aromatic amines with other nucleophiles (competitions B/B′ and H/H′, Schemes 7 and 10).

Ligand-Dependent Selectivities in Competition Reactions Using Chlorobenzene. Several reactions were also attempted using chlorobenzene as arylating agent and several nucleophiles and auxiliary ligands; however, the reactivity was almost suppressed for all nucleophiles tested at 130 °C (Scheme S5, SI).

Practical Orthogonal Nucleophile Discrimination Summary. Table 1 summarizes the most important results of all tested competition reactions, and the best conditions found to achieve the arylation of a given nucleophile in the presence of another are highlighted. In general, highly selective arylation of any nucleophile can be performed under mild conditions in the presence of another nucleophile, provided careful selection of the auxiliary ligand and experimental conditions is made. Therefore, Table 1 is a practical recipe for mild and chemoselective C−O and C−N Ullmann-type couplings. Note that this high selectivity has also been successfully translated into bifunctional substrates (Scheme 10). However, the limitations of the methodology in terms of selectivity are shown in Table 2. The nonpreferred nucleophile in these competitions is arylated as a mixture with the arylation of the preferred nucleophile, so the corresponding reaction conditions are not included in Table 2.

Finally, to gain insight into the mechanism of the cross-coupling reactions with different auxiliary ligands, we have selected the most successful combinations of nucleophiles and ligands and used the radical clock 1-allyloxy-2-iodobenzene (**rc**) as substrate in the coupling reactions (Scheme 11). In all reactions, a significant amount of **rc-H** was observed, suggesting a protodecupration side reaction as previously observed by Cohen,[43] Hartwig,[25] and in the reactivity of well-defined model aryl-Cu^{III} complexes.[44] No traces were found of the cyclized coupling product, thus pointing toward a prototypical Cu^{I}/Cu^{III} mechanism for thermal-based Ullmann couplings and discarding a radical pathway. Given the fact that protodecupration product **rc-H** was found in important amounts when **rc** was used as a substrate, we wondered if this mechanism has also some contribution when iodobenzene is used. If so, benzene should be found as the product of a putative protodecupration. As suspected, low but significant amounts of benzene (from 4 to 8%) were found in several coupling reactions of anilines **6a**, **6b**, **6c**, and methylacetamide **2h**, indicating that the protodecupration pathway is generally spread as a side reaction in Ullmann couplings (see Scheme S6).

CONCLUSION

In light of the tremendous interest in finding a practical Cu-catalyzed methodology that allows orthogonal discrimination among N- or O-based functional groups, we have demonstrated that this is now possible with multiple combinations of

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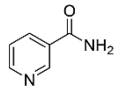
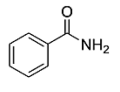
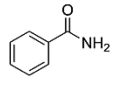
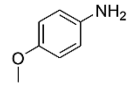
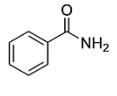
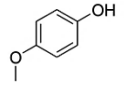
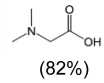
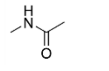
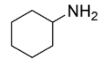
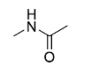
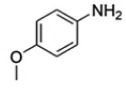
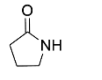
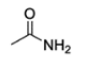
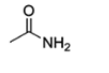
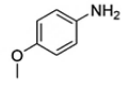
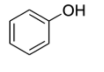
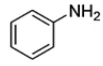
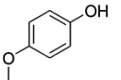
Table 1. Optimized Conditions for Ligand-Dependent Arylation of Nucleophiles (A or B) with Iodobenzene in Competition Reactions with Orthogonal Selectivity[a]

Conditions for A arylation	A	B	Conditions for B arylation
L_3 K_3PO_4 50°C (95%)			 L_7 CsF 50°C (62%)
L_3 K_3PO_4 50°C (79%)			 L_7 CsF 50°C (74%)
L_1 K_3PO_4 50°C (95%)			 L_8 CsF 50°C (76%)
L_1 K_3PO_4 50°C (78%)			 L_6 K_3PO_4 50°C (82%)
L_4 K_3PO_4 50°C (95%)			 L_7 CsF 50°C (76%)
L_4 K_3PO_4 50°C (80%)			 L_8 CsF 50°C (76%)
L_1 K_3PO_4 50°C (96%)			 L_7 CsF 50°C (76%)
L_4 K_3PO_4 80°C (39%)			 L_7 CsF 50°C (61%)
L_4 K_3PO_4 80°C (40%)			 L_8 CsF 50°C (66%)
L_6 K_3PO_4 50°C (99%)			 L_8 CsF 50°C (51%)
L_6 K_3PO_4 50°C (78%)			 L_7 CsF 50°C (57%)

[a]Standard reaction conditions: iodobenzene (0.88 mmol, 0.9 M), **A** and **B** (1.79 mmol), 24 h, DMSO under an inert atmosphere (yields given in parentheses).

nucleophiles using a common experimental methodology and a preferred auxiliary ligand for each nucleophile. The exact role of each auxiliary ligand in switching the selectivity requires already ongoing in-depth computational studies. So far, the precise, simple methodologies to be used for the arylation of any of the nucleophiles tested should be a precious practical guide in organic synthesis laboratories. Indeed, by means of using a radical clock substrate (**rc**), no signs of radical-mediated mechanism were found in any of the coupling reactions tested in this work, reinforcing the occurrence of a nonradical mechanism in the thermal-based copper-catalyzed cross-coupling reactions.

EXPERIMENTAL SECTION

General Methods. The reagents and solvents used were commercially available unless indicated otherwise. Solvents were purchased and were purified and dried by passing them through an activated alumina purification system. The preparation and handling of air-sensitive materials were performed in a N_2 drybox with O_2 and H_2O concentrations of <1 ppm. 4′-Hydroxy(1,1′-biphenyl)-3-carboxamide (**8b**) was synthesized following the published procedures.[45]

General Procedure for Catalytic Experiments. A vial was loaded with the base (1.8 mmol), the solid nucleophile (1.8 mmol), and the corresponding auxiliary ligand (10 mol %). Then, in an inert-atmosphere glovebox, copper(I) (10 mol %) in DMSO and the aryl iodide (0.9 mmol) were added. Liquid nucleophiles were added after

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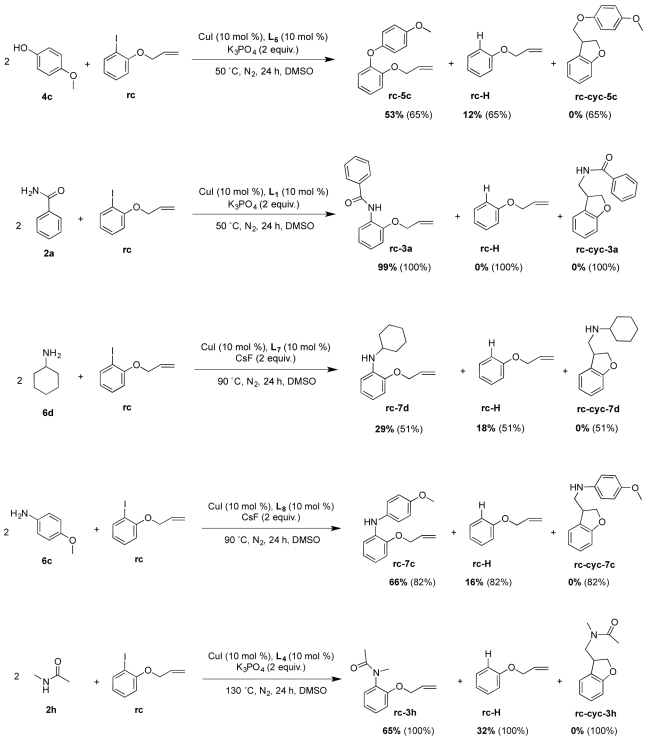
Table 2. Optimized Conditions for Ligand-Dependent Arylation of Nucleophiles with Iodobenzene in Competitive Reactions with High Selectivity for One of the Competing Nucleophiles (Column A)[a]

Conditions for A arylation	A	B
L_6 K_3PO_4 50°C (94%)		
L_6 K_3PO_4 50°C (95%)		
L_4 K_3PO_4 50°C (76%)		
L_3 K_3PO_4 50°C (71%)		
L_7 CsF 50°C (78%)		

[a]Standard reaction conditions: iodobenzene (0.88 mmol, 0.9 M), **A** and **B** (1.79 mmol), 24 h, DMSO under an inert atmosphere (yields are given in parentheses).

Scheme 11. Selected Coupling Reactions Using Radical Clock rc as Substrate



the aryl iodide. The vial was sealed, and the reaction mixture was kept under an inert atmosphere and placed in a preheated oil bath at the required temperature. After the reaction mixture was stirred for 24 h, 1,3,5-trimethoxybenzene (200 μL, 1.5 M in DMSO) as internal standard was added. Subsequently, the reaction was quenched by the addition of AcOEt (5 mL). The workup consisted of the filtration of 400 μL of the crude product through silica gel using AcOEt as eluent. All samples were analyzed by gas chromatography. The GC yields were obtained through calibration curves obtained with authentic sample of all products with 1,3,5-trimethoxybenzene as an internal standard.

Benzanilide (**3a**).[46,47] ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ (ppm): 7.17−7.23 (m, 1H), 7.43−7.48 (m, 2H), 7.60−7.72 (m, 3H), 7.86−7.89 (m, 2H), 8.03−8.07 (m, 2H), 10.34 (s, 1H, NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 120.3, 123.7, 127.6, 128.4, 128.6, 131.6, 134.9, 139.2, 165.5. HRMS (ESI-TOF (m/z)): calcd for $C_{13}H_{11}NONa$ 220.0733, found 220.0725, calcd for $(C_{13}H_{11}NO)_2Na$ 417.1573, found 417.1571.

1-Phenyl-2-pyrrolidone (**3b**).[46,47] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 2.14−2.22 (m, 2H), 2.59−2.65 (m, 2H), 3.87 (t, 2H, $^2J_{HH}$ = 6.9 Hz), 7.59−7.63 (m, 2H), 7.34−7.40 (m, 2H), 7.12−7.17 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 18.0, 32.7, 48.8, 119.9, 124.5, 128.8, 139.4, 174.2. HRMS (ESI-TOF (m/z)): calcd for $C_{10}H_{11}NONa$ 184.0733, found 184.0720, calcd $(C_{10}H_{11}NO)_2Na$ 345.1573, found 345.1559.

N-phenoxindole (**3c**).[48] ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ (ppm): 3.86 (s, 2H), 6.79−6.81 (m, 1H), 7.16 (td, 1H, $^2J_{HH}$ = 7.43 Hz, $^4J_{HH}$ = 1 Hz), 7.31 (td, 1H, $^2J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz), 7.44−7.46 (m, 1H), 7.50−7.58 (m, 3H), 7.64−7.70 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 35.9, 108.6, 122.4, 124.7, 124.8, 126.8, 127.5, 127.9, 129.6, 134.5, 144.8, 173.9. HRMS (ESI-TOF (m/z)): calcd for $C_{14}H_{11}NONa$ 232.0733, found 232.0726, calcd for $(C_{14}H_{11}NO)_2Na$ 441.1573, found 441.1577.

Salicylanilide (**3d**).[47] ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 7.04−7.09 (m, 2H), 7.22−7.26 (m, 1H), 7.45−7.50 (m, 2H) 7.52−7.56 (m, 1H), 7.79−7.82 (m, 2H), 8.06 (dd, 1H, $^2J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.4 Hz), 10.50 (s, 1H, NH), 11.90 (br s, 1H, OH). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 25 °C) δ (ppm): 117.2, 117.5, 119.0, 120.9, 124.2, 128.7, 129.0, 133.6, 138.1, 158.5, 166.6. HRMS (ESI-TOF (m/z)): calcd for $C_{13}H_{11}NO_2Na$ 236.0682, found 236.0679, calcd for $(C_{13}H_{11}NO_2)_2Na$ 419.1472, found 419.1471.

N-phenyl-4-hydroxybenzamide (**3e**).[47] ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ (ppm): 6.93−6.98 (m, 2H), 7.13−7.19 (m, 1H), 7.40−7.46 (m, 2H), 7.82.7.86 (m, 2H), 7.92−7.97 (m, 2H), 10.07 (s, 1H, NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 115.3, 120.6, 123.6, 125.7, 128.9, 130.1, 139.9, 160.9, 165.5. HRMS (ESI-TOF (m/z)): calcd for $C_{13}H_{11}NO_2Na$ 236.0682, found 236.0679, calcd for $(C_{13}H_{11}NO_2)_2Na$ 449.1472, found 449.1479.

Nicotinanilide (**3f**).[47] ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ (ppm): 7.20−7.26 (m, 1H), 7.44−7.50 (m, 2H), 7.67 (ddd, 1H, $^2J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 0.9 Hz), 7.85−7.89 (m, 2H), 8.39 (ddd, 1H, $^2J_{HH}$ = 8.03 Hz, $^3J_{HH}$ = 2.33 Hz, $^4J_{HH}$ = 1.73 Hz), 8.86 (dd, 1H, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.8 Hz), 9.20 (dd, 1H, $^3J_{HH}$ = 2.25 Hz, $^4J_{HH}$ = 0.75 Hz), 10.54 (s, 1H, NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 120.4, 123.5, 124.0, 128.7, 130.6, 135.5, 138.8, 148.7, 152.1, 164.1. HRMS (ESI-TOF (m/z)): calcd for $C_{12}H_{10}N_2ONa$ 221.0685, found 221.0674, calcd for $(C_{12}H_{10}N_2O)_2Na$ 419.1478, found 419.1464.

Acetanilide (**3g**).[46,47] ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ (ppm): 2.13 (s, 3H), 7.08−7.14 (m, 1H), 7.34−7.41 (m, 2H), 7.65−7.68 (m, 2H), 10.01 (s, 1H, NH). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 29.0, 118.9, 123.0, 128.7, 139.3, 168.3. HRMS (ESI-TOF (m/z)): calcd for C_8H_9NONa 158.0576, found 158.0566.

N-Methylacetanilide (**3h**).[49] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.87 (s, 3H), 3.27 (s, 3H), 7.18−7−21 (m, 2H), 7.31−7.36 (m, 1H), 7.39−7.45 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 22.4, 37.2, 127.1, 127.7, 129.7, 144.6, 170.6. HRMS (ESI-TOF (m/z)): calcd for $C_9H_{11}NONa$ 172.0733, found 172.0722, calcd for $(C_9H_{11}NO)_2Na$ 321.1573, found 321.1572.

N,N-Diphenylbenzamide (**3i**).[50] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.14−7.32 (m, 13H), 7.44−7.47 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 126.6, 127.7, 128.1, 129.4, 129.4, 130.4, 136.3, 144.3. HRMS (ESI-TOF (m/z)): calcd for

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$C_{19}H_{16}NO$ 274.1226, found 274.1234, calcd for $C_{19}H_{15}NONa$ 296.1046, found 296.1064, calcd for $(C_{19}H_{15}NO)_2Na$ 569.2199; found 569.2221.

*N,N-Ethylphenylacetamide (**3j**)*.[51] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.10 (t, 3H, $^2J_{HH}$ = 7.2 MHz), 1,82 (s, 3H), 3.75 (q, 3H, $^2J_{HH}$ = 7.2 MHz), 7.13−7.17 (m, 2H), 7.31−7.45 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 13.3, 23.1, 44.1, 128.1, 128.5, 129.9, 143.2, 170.2. HRMS (ESI-TOF (m/z)): calcd for $C_{10}H_{14}NO$ 164.1070, found 164.1067, calcd for $C_{10}H_{13}NONa$ 186.0889, found 186.0889, calcd for $(C_{10}H_{13}NO)_2Na$ 349.1886, found 349.1869.

*Diphenyl Ether (**5a**)*.[52] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.03−7.07 (m, 4H), 7.10−7.16 (m, 2H), 7.33−7.40 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 119.2, 123.5, 130.1, 157.6. GCMS: t_R 9.220. MS ($C_{12}H_{10}O$): 170.0.

*1-Methyl-4-phenoxybenzene (**5b**)*.[52] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 2.40 (s, 3H), 6.97−6.99 (m, 2H), 7.04−7.08 (m, 2H), 7.10−7.15 (m, 1H), 7.18−7.21 (m, 2H), 7.35−7−39 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 20.9, 118.5, 119.3, 122.9, 129.8, 130.5, 133.1, 154.9, 158.0. GCMS: t_R 10.584. MS ($C_{12}H_{12}O$): 184.0.

*1-Methoxy-4-phenoxybenzene (**5c**)*:[53] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.81 (s, 3H), 6.87−6.91 (m, 2H), 6.93−7.01 (m, 4H), 7.05 (t, 1H, J = 7.4 Hz), 7.28−7.33 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 55.9, 115.1, 117.8, 121.0, 122.6, 129.8, 150.3, 156.1, 158.7. GCMS: t_R 12.359. MS ($C_{13}H_{12}O_2$): 200.1.

*1,3-Dimethyl-5-phenoxybenzene (**5d**)*.[54] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 2.29 (s, 6H), 6.64−6.65 (m, 2H), 6.76 (sept, 1H, $^4J_{HH}$ = 0.7 MHz), 6.99−7.03 (m, 2H), 7.07−7.12 (m, 1H), 7.30−7.37 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 21.6, 116.8, 119.1, 123.2, 124.2, 129.9, 139.8, 157.4, 157.7. GCMS: t_R 11.596. MS ($C_{12}H_{12}O$): 198.1.

*1-(4-Nitrophenoxy)benzene (**5e**)*.[53] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.00−7.06 (m, 2H), 7.09−7.14 (m, 2H), 7.22−7.32 (m, 1H), 7.43−7.51 (m, 2H), 8.20−8.25 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 117.3, 120.8, 125.7, 126.2, 130.6, 154.9, 163.6. GCMS: t_R 14.180. MS ($C_{12}H_{12}O$): 215.0.

*Ethoxybenzene (**5f**)*.[55] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.4 (t, 3H), 4.02 (q, 2H), 6.87−6.93 (m, 3H), 7.30−7.34 (m, 2H). GCMS: t_R 3.76. MS ($C_8H_{10}O$): 122.0.

*N,N-Diphenylamine (**7a**)*.[41,56] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 5.71 (s, 1H, NH), 6.96 (tt, 2H), 7.08−7.12 (m, 4H), 7.27−7.32 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 117.9, 121.0, 129.4, 143.2. HRMS (ESI-TOF (m/z)): calcd for $C_{12}H_{12}N$ 170.0964, found 170.0948.

*p-Nitro-N-phenylaniline (**7b**)*.[57] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 6.33 (s, 1H, NH), 6.92−6.97 (m, 2H), 7.14−7.26 (m, 3H), 7.35−7.42 (m, 2H), 8.09−8.11 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6, 25 °C) δ (ppm): 113.9, 122.2, 124.9, 126.5, 130.0, 139.7, 140.0, 150.4. HRMS (ESI-TOF (m/z)): calcd for $C_{12}H_{11}N_2O_2$ 215.0815, found 215.0813.

*p-Methoxy-N-phenylaniline (**7c**)*.[57,58] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.80 (s, 3H), 5.46 (s, 1H, NH) 6.81−6.92 (m, 5H), 7.05−7.09 (m, 2H), 7.18−7.23 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 55.8, 114.9, 115.9, 119.8, 122.5, 129.5, 139.7, 140.0, 150.4. HRMS (ESI-TOF (m/z)): calcd for $C_{13}H_{14}NO$ 200.1070, found 200.1059.

*N-Cyclohexylaniline (**7d**)*.[57] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.16−1.50 (m, $5H^{aliphatic}$), 1.68−1.75 (m, $1H^{aliphatic}$), 1.80−1.85 (m, $2H^{aliphatic}$), 2.10−2.14 (m, $2H^{aliphatic}$), 3.28−3.35 (m, 1H), 3.55 (m, 1H, NH), 6.63−6.66 (m, 2H), 6.72 (t, 1H, $^2J_{HH}$ = 7.2 Hz $^4J_{HH}$ = 0.93 Hz), 7.19−7.24 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 25.2, 26.1, 33.7, 51.8, 113.3, 117.0, 129.4, 147.6. HRMS (ESI-TOF (m/z)): calcd for $C_{12}H_{18}N$ 176.1434, found 176.1406, calcd for $C_{12}H_{17}NNa$ 198.1253, found 198.1226.

*N-Propylaniline (**7e**)*.[59] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.03 (t, 3H, $^2J_{HH}$ = 7.39 Hz), 1.67 (q, 2H, $^2J_{HH}$ = 7.28 Hz), 3.11 (t, 2H, $^2J_{HH}$ = 7.01 Hz), 3.64 (s, 1H, NH), 6.61−6.65 (m, 2H), 6.72 (tt, 1H, $^2J_{HH}$ = 14.71 Hz, $^3J_{HH}$ = 7.24 Hz, $^4J_{HH}$ = 1.07 Hz,), 7.17−7.24 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 11.7, 22.8, 45.9, 112.7, 117.1, 129.2, 148.6. HRMS (ESI-TOF (m/z)): calcd for $C_9H_{14}N$ 136.1121, found 136.1126.

*N,N-Diethylaniline (**7f**)*.[60] This compound was obtained in a low yield. It was detected by GCMS: t_R 6.834. MS ($C_{10}H_{15}N$): 149.1.

*1-Phenylpiperidine (**7g**)*.[58] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.55−1.62 (m, 2H), 1.68−1.75 (m, 4H), 3.14−3.17 (m, 4 H), 6.79−6.85 (m, 1H), 6.92−6.97 (m, 2H), 7.21−7.28 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 24.3, 25.9, 50.7, 116.5, 119.2, 129.0, 152.3. HRMS (ESI-TOF (m/z)): calcd for $C_{11}H_{16}N$ 162.1277, found 162.1265.

*1-Phenyl-1H-imidazole (**7h**)*.[61] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.21 (s, 1H), 7.29 (s, 1H), 7.35−7.41 (m, 3H), 7.47−7.52 (m, 2H), 7.86 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 118.1, 121.2, 127.3, 129.6, 130.1, 135.3, 137.1. HRMS (ESI-TOF (m/z)): calcd for $C_9H_9N_2$ 145.0760, found 145.0771, calcd for $C_9H_8N_2Na$ 167.0580, found 167.0580, calcd for $(C_9H_8N_2)_2Na$ 311.1267, found 311.1262.

*7-Phenoxy-1,2,3,4-tetrahydronaphthalen-2-amine (**9a**)*. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.56 (s, 2H, NH), 1.60−1.66 (m, 1H, H^i or H^j), 1.97−2.04 (m, 1H, H^i or H^j), 2.53 (dd, $^2J_{HH}$ = 16.22 Hz, $^3J_{HH}$= 9.41 Hz, 1H, H^f or H^g), 2.80−2.85 (m, 2H, H^k and H^l), 2.94 (dd, $^2J_{HH}$ = 16.41 Hz, $^3J_{HH}$ = 5.14 Hz, 1H, H^f or H^g), 3.15−3.24 (m, 1H, Hh), 6.73 (d, $^4J_{HH}$ = 2.54 Hz, 1H, H^d), 6.78 (dd, $^3J_{HH}$ = 8.29 Hz, $^4J_{HH}$ = 2.63 Hz, 1H, H^e), 6.99 (dt, $^4J_{HH}$ = 7.64, 1.12 Hz, 2H, H^a), 7.05 (dt, $^3J_{HH}$ = 7.69 Hz, $^4J_{HH}$ = 1.12 Hz, 2H, H^c and H^d), 7.31 (dd, $^3J_{HH}$ = 7.52 Hz, $^4J_{HH}$ = 1.28 Hz, 2H, H^b). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 27.4 (C_8), 29.7 (C_{11}), 31.0 (C_{10}), 52.9 (C_9), 117.1 (C_{13}), 118.4 (C_1), 119.4 (C_6), 122.9 (C_3), 129.6 (C_2), 19.8 (C_{14}), 131.0 (C_{12}), 136.0 (C_7), 155.1 (C_5) and 157.8 (C_4). HRMS (ESI-TOF (m/z)): calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1395, calcd for $(C_{16}H_{17}NO)_2H$ 479.2693, found 479.2708.

*7-(Phenylamino)-5,6,7,8-tetrahydronaphthalen-2-ol (**10a**)*. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.77 (m, 1H, H^e or H^f), 2.16 (m, 1H, H^e or H^f), 2.64 (ddd, $^2J_{HH}$ = 16.58 Hz, $^3J_{HH}$ = 8.34 Hz, 1H, H^h or H^i), 2.83 (m, 2H, H^d), 3.15 (ddd, $^2J_{HH}$ = 16.54 Hz, $^3J_{HH}$ = 4.86 Hz, 1H, H^i or H^h), 3.75 (m, 1H, H^g), 4.58 (m, 1H, NH), 6.55 (d, $^4J_{HH}$ = 2.62 Hz, 1H, H^a), 6.64 (dd, $^3J_{HH}$ = 8.66 Hz, $^4J_{HH}$ = 1.06 Hz, 3H, H^b and H^j), 6.70 (tt, $^3J_{HH}$ = 7.93 Hz, $^4J_{HH}$ = 1.07 Hz, 1H, H^l), 6.98 (d, $^3J_{HH}$ = 8.41 Hz, 1H, H^c), 7.18 (dd, $^3J_{HH}$ = 7.39 Hz, $^4J_{HH}$ = 1.2 Hz, 2H, H^k). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 26.6 (C_6), 29.3 (C_7), 36.6 (C_9), 48.5 (C_8), 113.5 (C_3 and C_{12}), 115.6 (C_1), 117.8 (C_{14}), 128.4 (C_5 or C_{10}), 129.3 (C_{13}), 129.9 (C_4), 136.0 (C_5 or C_{10}), 147.1 (C_{11}) and 153.6 (C_2). HRMS (ESI-TOF (m/z)): calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1378, calcd for $(C_{16}H_{17}NO)_2Na$ 501.2515, found 501.2507.

*4′-Hydroxy-N-phenyl(1,1′-biphenyl)-3-carboxamide (**9b**)*. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 6.90 (d, $^3J_{HH}$ = 8.61 Hz, 2H, Hi), 7.12 (t, $^3J_{HH}$ = 7.40 Hz, $^4J_{HH}$ = 1.12 Hz, 1H, H^a), 7.37 (t, $^3J_{HH}$ = 7.40 Hz, 2H, H^b), 7.57 (t, $^3J_{HH}$ = 7.68 Hz, 1H, H^f), 7.61 (dd, $^3J_{HH}$ = 8.70 Hz, 2H, H^h), 7.79 (d, $^3J_{HH}$ = 8.61 Hz, $^4J_{HH}$ = 1.17 Hz, 3H, H^c and H^g), 7.85 (dt, $^3J_{HH}$ = 7.68 Hz, $^4J_{HH}$ = 1.49 Hz, 1H, H^e), 8.14 (t, J = 3.32, $^4J_{HH}$ = 1.67 Hz, 1H, H^d), 9.66 (s, 1H, OH) and 10.31 (s, 1H, NH). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, 25 °C) δ (ppm): 116.3 (C_{14}), 120.9 (C_3), 124.2 (C_1), 125.5 (C_7), 126.2 (C_8), 128.5 (C_{13}), 129.1 (C_2), 129.4 (C_9 and C_{10}), 130.7 (C_{12}), 136 (C_6), 139.6 (C_4), 140.8 (C_{11}), 157.9 (C_{15}) and 166.1 (C_5). HRMS (ESI-TOF (m/z)): Positive mode (+): calcd for $C_{19}H_{15}NO_2Na$ 312.0995, found 312.0994; Negative mode (−): calcd for $C_{19}H_{14}NO_2$ 288.1025, found 288.1002, calcd for $(C_{19}H_{14}NO_2)(C_{19}H_{15}NO_2)$ 577.2127, found 577.2110.

*4′-Phenoxy(1,1′-biphenyl)-3-carboxamide (**10b**)*. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 5.73 (s, 1H, NH), 6.17 (s, 1H, NH), 7.07−7.13 (m, 4H, H^f and H^g), 7.16 (tt, $^3J_{HH}$ = 7.42, $^4J_{HH}$ = 1.15 Hz, 1H, H^i), 7.37−7.42 (m, 2H, H^h), 7.54 (t, $^3J_{HH}$ = 8.00 Hz, $^4J_{HH}$ = 0.61 Hz 1H, H^c), 7.60 (dt, $^3J_{HH}$ = 8.85 Hz, $^4J_{HH}$ = 2.18 Hz, 2H, H^e), 7.76 (dt, $^3J_{HH}$ = 7.77 Hz, $^4J_{HH}$ = 1.80 Hz, 2H, H^a and H^d) and 8.06 (t, $^3J_{HH}$ = 3.75 Hz, $^4J_{HH}$ = 1.92 Hz, 1H, H^b). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 119.1 (C_{10}), 119.2 (C_{13}), 123.6 (C_{15}), 125.7

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(C_6), 126.1 (C_4), 128.5 (C_9), 129.1 (C_5), 129.9 (C_{14}), 130.4 (C_1), 133.9 (C_2), 135.1 (C_8), 141.2 (C_7), 156.9 (C_{12}), 157.4 (C_{11}) and 169.2 (C_3). HRMS (ESI-TOF (m/z)): calcd for $C_{19}H_{15}NO_2Na$ 312.1000, found 312.0993, calcd for $(C_{19}H_{15}NO_2)_2Na$ 601.2103, found 601.2078, calcd for $(C_{19}H_{15}NO_2)_3Na$ 890.3206, found 890.3186.

*4-Amino-N,N-diphenylbenzamide (**9c**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.78−3.92 (m, 2H, NH), 6.44 (d, $^3J_{HH}$ = 8.71 Hz, 2H, H^b), 7.11−7.19 (m, 6H, H^c or H^d and H^e), 7.23−7.33 (dd, $^3J_{HH}$ = 7.87 Hz, $^4J_{HH}$ = 2.05 Hz, 6H, H^a and H^c or H^d). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 113.6 (C_4), 125.2 (C_2), 125.9 (C_9), 127.4 (C_7 or C_8), 129.1 (C_7 or C_8), 131.8 (C_3), 144.7 (C_6), 148.6 (C_5), 170.7 (C_1). (ESI-TOF (m/z)): calcd for $C_{19}H_{17}N_2O$ 289.1335, found 289.1335, calcd for $C_{19}H_{16}N_2ONa$ 311.1155, found 311.1163, calcd for $(C_{19}H_{16}N_2O)_2Na$ 599.2417, found 599.2420.

*N-Phenyl-4-(phenylamino)benzamide (**10c**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 6.07 (s, 1H, NHamine), 7.04 (d, $^3J_{HH}$ = 8.65 Hz, 2H, H^b), 7.07 (d, $^3J_{HH}$ = 7.20 Hz, 1H, H^e), 7.13 (t, $^3J_{HH}$ = 7.46 Hz, $^4J_{HH}$ = 1.04 Hz, 1H, H^h), 7.16 (d, $^3J_{HH}$ = 7.72 Hz, $^4J_{HH}$ = 1.18 Hz, 2H, H^c), 7.35 (dt, $^3J_{HH}$ = 7.74 Hz, 4H, H^d and H^g), 7.63 (d, $^3J_{HH}$ = 8.60 Hz, 2H, H^f), 7.77 (d, $^3J_{HH}$ = 8.54 Hz, 2H, H^a), 7.80 (s, 1H, NH_{amide}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 115.2 (C_4), 120.1 (C_7 and C_{11}), 122.9 (C_9), 124.2 (C_{13}), 125.7 (C_2), 128.8 (C_8 or C_{12}), 129.0 (C_3), 129.5 (C_8 or C_{12}), 138.2 (C_{10}), 141.1 (C_6), 147.2 (C_5), 165.5 (C_1). HRMS (ESI-TOF (m/z)): calcd for $C_{19}H_{16}N_2ONa$ 311.1155, found 311.1149, calcd for $(C_{19}H_{16}N_2O)_2Na$ 599.2417, found 599.2407.

*1-(Allyloxy)-2-iodobenzene (**rc**).* **rc** was synthesized following published procedures.[36] The characterization of **rc-H** was performed by comparison to a commercially available sample.

*1-(Allyloxy)-2-(4-methoxyphenoxy)benzene (**rc-5c**).* ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.81 (s, 3H), 4.62 (dt, $^3J_{HH}$ = 5.23 Hz, $^4J_{HH}$ = 1.55 Hz, 2H), 5.24 (ddd, $^2J_{HH}$ = 10.50 Hz, $^3J_{HH}$ = 3.21 Hz, $^4J_{HH}$ = 1.64 Hz, 1H), 5.34 (ddd, $^2J_{HH}$ = 17.25 Hz, $^3J_{HH}$ = 3.65 Hz, $^4J_{HH}$ = 1.72 Hz, 1H), 5.94- 6.08 (m, 1H), 6.84- 6.97 (m, 6H), 7.01-7.09 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 55.6, 69.9, 114.6, 114.9, 117.5, 119.1, 119.9, 121.4, 123.8, 133.2, 146.9, 149.8, 151.3, 155.2. HRMS (ESI-TOF (m/z)): calcd for $C_{16}H_{16}O_3Na$ 279.0992, found 279.0999, calcd for $(C_{16}H_{16}O_3)_2Na$ 535.2091, found 535.2084.

*N-(2-(Allyloxy)phenyl)benzamide (**rc-3a**).* ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 4.68 (dt, $^3J_{HH}$ = 5.28 Hz, $^4J_{HH}$ = 1.44 Hz, 2H), 5.37 (ddd, $^2J_{HH}$ = 10.50 Hz, $^3J_{HH}$ = 3.17 Hz, $^4J_{HH}$ = 1.32 Hz, 1H), 5.46 (ddd, $^2J_{HH}$ = 17.29 Hz, $^3J_{HH}$ = 3.47 Hz, $^4J_{HH}$ = 1.61 Hz, 1H),6.05-6.12 (m, 1H), 6.95 (dd, $^3J_{HH}$ = 7.25 Hz, $^4J_{HH}$ = 2.37 Hz, 1H), 7.05-7.09 (m, 2H), 7.50- 7.58 (m, 3H), 7.92 (dd, $^3J_{HH}$ = 8.28 Hz, $^4J_{HH}$ = 1.76 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 25 °C) δ (ppm): 69.6, 111.5, 118.2, 119.9, 121.5, 123.8, 127.0, 128.1, 128.8, 131.7, 132.8, 135.7, 147.1, 165.2. HRMS (ESI-TOF (m/z)): calcd for $C_{16}H_{15}NO_2Na$ 276.0995, found 276.0991, calcd for $(C_{16}H_{15}NO_2)_2Na$ 529.2098, found 529.2083.

*2-(Allyloxy)-N-cyclohexylaniline (**rc-7d**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.15−1.31 (m, 3H), 1.31- 1.48 (m, 3H), 1.61−1.73 (m, 1H), 1.73- 1.86 (m, 2H), 2.09 (d, $^3J_{HH}$ = 12.18 Hz, 2H), 3.22- 3.34 (m, 1H), 4.19 (s, 1H, NH), 4.57 (dt, $^3J_{HH}$ = 5.23 Hz, $^4J_{HH}$ = 1.51 Hz, 2H), 5.30 (ddd, $^2J_{HH}$ = 10.50 Hz, $^3J_{HH}$ = 3.21 Hz, $^4J_{HH}$ = 1.64 Hz, 1H), 5.42 (ddd, $^2J_{HH}$ = 17.23 Hz, $^3J_{HH}$ = 3.55 Hz, $^4J_{HH}$ = 1.58 Hz, 1H), 6.04- 6.18 (m, 1H), 6.63 (dd, $^2J_{HH}$ = 10.50 Hz, $^3J_{HH}$ = 8.17 Hz, $^4J_{HH}$ = 1.44 Hz, 2H), 6.79 (dd, $^3J_{HH}$ = 8.04 Hz, $^4J_{HH}$ = 1.41 Hz, 1H), (ddt, $^2J_{HH}$ = 15.35 Hz, $^3J_{HH}$ = 7.69 Hz, $^4J_{HH}$ = 1.31 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 25.1, 26.0, 33.5, 51.4, 69.3, 110.5, 111.3, 115.7, 117.3, 121.5, 133.7, 137.7, 145.7. HRMS (ESI-TOF (m/z)): calcd for $C_{15}H_{22}NO$ 232.1696, found 232.1705, calcd for $C_{15}H_{21}NONa$ 254.1515, found 254.1514.

*2-(Allyloxy)-N-(4-methoxyphenyl)aniline (**rc-7c**).* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.83 (s, 3H), 4.64 (dt, $^3J_{HH}$ = 5.45 Hz, $^4J_{HH}$ = 1.34 Hz, 2H), 5.33 (ddd, $^2J_{HH}$ = 10.46 Hz, $^3J_{HH}$ = 3.33 Hz, $^4J_{HH}$ = 1.40 Hz, 1H), 5.45 (ddd, $^2J_{HH}$ = 17.26 Hz, $^3J_{HH}$ = 3.59 Hz, $^4J_{HH}$ = 1.59 Hz, 1H), 6.03 (s, 1H, NH), 6.07−6.20 (m, 1H), 6.77 (td, $^3J_{HH}$ = 7.69 Hz, $^4J_{HH}$ = 1.73 Hz, 2H), 6.82−6.92 (m, 3H), 7.07 (dd, $^3J_{HH}$ = 7.79 Hz, $^4J_{HH}$ = 1.74 Hz, 2H) 7.17 (d, $^3J_{HH}$ = 8.91 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, *CDCl*$_3$, 25 °C) δ (ppm): 55.6, 69.5, 111.8, 112.8, 114.6, 117.8, 118.4, 121.3, 123.0, 133.4, 135.4, 146.3, 155.4. HRMS (ESI-TOF (m/z)): calcd for $C_{16}H_{17}NO_2Na$ 278.1151, found 278.1161.

*N-(2-(Allyloxy)phenyl)-N-methylacetamide (**rc-3h**).* ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ (ppm): 1.84 (s, 3H), 3.21 (s, 3H), 4.60 (dt, $^3J_{HH}$ = 4.98 Hz, $^4J_{HH}$ = 1.65 Hz, 2H), 5.30 (ddd, $^2J_{HH}$ = 10.57 Hz, $^3J_{HH}$ = 4.36 Hz, $^4J_{HH}$ = 1.50 Hz, 1H), 5.41 (ddd, $^2J_{HH}$ = 17.27 Hz, $^3J_{HH}$ = 4.90 Hz, $^4J_{HH}$ = 1.68 Hz, 1H), 5.96- 6.08 (m, 1H), 6.96- 7.02 (m, 2H), 7.19 (dd, $^3J_{HH}$ = 7.68 Hz, $^4J_{HH}$ = 1.68 Hz, 1H) 7.85 (td, $^3J_{HH}$ = 8.91 Hz, $^4J_{HH}$ = 1.79 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, *CDCl*$_3$, 25 °C) δ (ppm): 21.6, 35.8, 68.6, 113.2, 117.6, 121.2, 129.0, 129.2, 132.5, 154.0, 171.4. (ESI-TOF (m/z)): calcd for $C_{12}H_{15}NO_2Na$ 228.0995, found 228.0993, calcd for $(C_{12}H_{15}NO_2)_2Na$ 433.2098, found 433.2095.

Synthesis of Auxiliary Ligand L_3. *N,N′-Dimethyl-2,6-bis-(aminomethyl)pyridine as HCl Salt (L_3·(HCl)$_2$).* 2,6-Bis-(chloromethyl)pyridine (1 g, 5.6 mmol) was added to aqueous methylamine (40%) (30 mL, 350 mmol) in a round-bottom flask, and the mixture was stirred at room temperature for 2−3 days. The reaction was monitored by ^{1}H NMR. Next, NaOH (0.470 g) was added, and the mixture was concentrated under reduced pressure. The crude was extracted with CH_2Cl_2, and the combined organic layers were dried with anhydrous $MgSO_4$. Finally, the solvent was evaporated under reduced pressure, obtaining L_3 as a yellow oil (0.920 g, 90% yield). Since the product is highly hygroscopic, the hydrochloric salt L_3·$(HCl)_2$ was prepared by dissolving the oil in $CHCl_3$ (1 mL) and hydrochloric acid 36.5% (0.85 mL). The aqueous phase was dried under vacuum to dryness, and the crystallization was performed with a mixture of MeOH and Et_2O (0.660 g, 55% yield). L_3·$(HCl)_2$ salt: ^{1}H NMR (400 MHz, D_2O, 25 °C) δ (ppm): 2.83 (s, 6 H), 4.43 (s, 4 H), 7.46 (d, 2 H), 7.93 (t, 1 H). HRMS (ESI-TOF (m/z)): calcd for $C_9H_{16}N_3$ 166.1339, found 166.1345. Anal. Calcd for ($C_9H_{17}N_3Cl_2$·1.15 H_2O): C, 41.76; H, 7.51; N, 16.23. Found: C, 41.78; H, 7.37; N, 16.10.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01035.

Experimental details; full characterization of chemical compounds; supplementary methods; supplementary schemes, figures, and tables (PDF)

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Notes

The authors declare no competing financial interest.

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