N,N′-(Phenylmethylene)diacetamide Analogues as Economical and Efficient Ligands in Copper-Catalyzed Arylation of Aromatic Nitrogen-Containing Heterocycles

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Abstract: *N,N′*-(Phenylmethylene)diacetamide analogues which were simply prepared from the condensation reaction of an aldehyde with an amide or urea were found to be efficient ligands in copper-catalyzed coupling reaction of aryl halides with various azole nucleophiles. The newly developed ligand showed broad application scope in this conversion. Compounds including imidazoles, benzoimidazoles, pyrrole, indole, and benzotriazole were successfully arylated with diversified aromatic halides to give corresponding products in moderate to excellent yields.

Key words: *N,N′*-(phenylmethylene)diacetamide, economical, ligand, copper, arylation

Aryl-functionalized N-heterocyclic moieties are of considerable interest to the chemical community due to their occurrence in biological scaffolds, natural products, as well as functional materials.[1] N-Arylation reaction has been recognized as one of the most practical methods in synthesizing arylated N-heterocyclic compounds. This classical C–N bond-forming reaction was originally achieved by the well-known Ullmann reaction which involved the use of stoichiometric amount of copper catalyst, high temperature, and long reaction time.[2] During the past decade, a large number of improved strategies have been developed to achieve this arylation reaction more efficiently. Typical examples are the palladium-catalyzed protocol developed by Buchwald[3] and Hartwig,[1c,d,4] as well as the modified Ullmann reaction which uses copper salts, for instance, CuI as the metal source.[5] As an economical metal of vast abundance, copper has attracted great research interest as a catalyst in N-arylation reaction.[6]

Most frequently, ligand is a necessary component in copper-catalyzed N-arylation reaction, and a good ligand can promote the reaction at much higher efficacy under less drastic conditions. Therefore, developing simple and practical ligands for these coupling reactions consists of a main direction on the improvement. To date, significant advance has been achieved in developing novel and efficient ligands to practically assist the desired arylation of various azoles since the discovery of Buchwald's diamine ligand.[7] Typical examples including diamines,[7] amino acids,[8] diimines,[9] and phosphoric moieties.[10] Besides these classical ligands, there are also many novel scaffolds that have been reported as excellent ligands for the copper-catalyzed arylation. For example, *N*-hydroxy-imides,[11] benzotriazole,[12] hydroxyquinoline,[13] 4,7-dimethoxy-1,10-phenanthroline,[14] 2-oxocyclohexane-carboxylate,[15] 2-aminopyrimidine-4,6-diol,[16] hydrazone,[17] and pyrrolidinylmethylimidazole derivatives[18] have been recently claimed as efficient ligands. Based on the great success achieved in the nitrogen-containing ligands, we envisaged that the compounds having 1,1-diamide motif (Figure 1) could possibly serve as ligands in the arylation conversion even though their functions as ligands have not been claimed previously.[19]

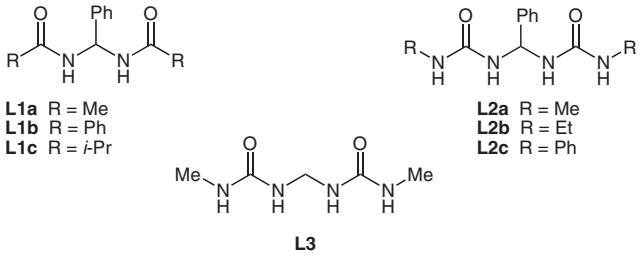

Figure 1 Ligands screened for the N-phenylation reaction

Initially, we synthesized a series of the analogous compounds as showed in Figure 1 to investigate their function as ligands in copper-catalyzed arylation reaction. The reaction of imidazole **2a** with iodobenzene (**1a**) was selected as a model reaction and was carried out in the presence of 10 mol% CuI, 2 equivalents Cs_2CO_3 and 20 mol% of the ligand at 110 °C. After 12 hours in DMSO, the yields of target product **3a** obtained in the presence of different ligands were tabulated in Figure 2.

It could be easily found that ligands of the **L1** type were more efficient than ligands of type **L2** and type **L3**. The best result was given by ligand **L1a** (65%). Moreover, in ligands of type **L1**, electronic deficiency in the ligand structure led to poorer result (**L1b**), and the steric hindrance also showed remarkable influence on this arylation reaction as implied in the result obtained from ligand **L1c**. Hence, we optimized other parameters of the same model reaction by employing **L1a** as the ligand.

To further optimize the reaction conditions, the base, solvent, and temperature effects were screened in the pres-

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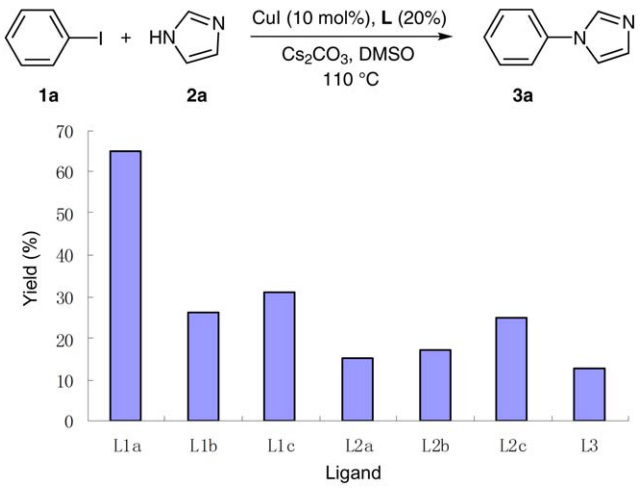


Figure 2 Effect of ligands on the N-arylation of imidazole

ence of the 20 mol% of ligand and 10 mol% of CuI (Table 1). As displayed in entries 1–4, lower temperature was inefficient for this reaction, and DMSO was found to be the ideal solvent among the examined candidates. In addition, K_2CO_3 and K_3PO_4 turned out to be poor base additives as compared to Cs_2CO_3. As previous work have disclosed that organic base such as sodium methanolate was able to serve as highly efficient base additive in CuI-catalyzed N-arylation,[11] we then employed sodium methanolate as the base to check if the yield could be improved. To our delight, higher yield was obtained when sodium methanolate was used (entry 7). Encouraged by the improved yield in the presence of sodium methanolate, we further changed the amounts of CuI/ligands as well as the temperature used in the reaction in order to acquire further improvement on the yield. As shown in entries 8–11, it was found at 120 ° that the yield of *N*-phenyl imidazole could be further increased to 75% from 70% at 110 °C. While a smaller amount of CuI led to inferior results, however, 10 mol% of ligand furnished 85% yield of the product, which was apparently higher than the result given by 20 mol% ligand. Finally, we further prolonged the reaction time and increased the reaction temperature, but no observable improvement was obtained (entries 12 and 13).

After optimization of the general reaction conditions, we then subjected various N-heterocyclic aromatic compounds as well as aromatic halides to investigate the application scope of the catalytic system. As expected, aryl iodide was found having generally good reactivity to various azole partners (Table 2, entries 1–9)[19] to yield corresponding arylated azoles in moderate to good yields. Meanwhile, aryl bromides were less reactive. When bromobenzene was subjected to react with imidazole at 130 °C for 12 hours, only trace amount of **3a** was observed. However, some functionalized aryl bromides were able to react with azoles at 130 °C, and the target products were generally furnished in moderate yields after 12 hours (entries 10–12). Previous studies have disclosed that activation of aryl chlorides is a practical approach to achieve arylation

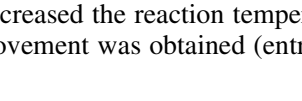
Table 1 Optimization of the N-Arylation of Imidazole with Iodobenzene in the Presence of Ligand **L1a**[a]

Entry	Solvent/base	CuI/ligand (mol%)	Temp (°C)	Yield (%)[b]
1	DMSO/Cs_2CO_3	10/20	100	35
2	DMSO/Cs_2CO_3	10/20	110	65
3[c]	DMSO + H_2O/Cs_2CO_3	10/20	110	<5
4	DMF/Cs_2CO_3	10/20	110	11
5	DMSO/K_2CO_3	10/20	110	Trace
6	DMSO/K_3PO_4	10/20	110	Trace
7	DMSO/NaOMe	10/20	110	70
8	DMSO/NaOMe	10/20	120	75
9	DMSO/NaOMe	5/20	120	63
10	DMSO/NaOMe	10/10	120	85
11	DMSO/NaOMe	5/10	120	35
12	DMSO/NaOMe	10/10	130	80
13[d]	DMSO/NaOMe	10/10	120	82

[a] Conditions: Reagents (0.5 mmol), base (2 equiv), DMSO (1.5 mL), 12 h.
[b] Isolated yield.
[c] DMSO (1 mL) mixed with H_2O (0.5 mL).
[d] The reaction time was 24 h.

of azoles via easily available aryl chlorides, we therefore selected several aryl chloride candidates to examine their reactions in our system. The results obtained from these reactions were satisfactory as these functionalized aryl chlorides also displayed good reactivity with other N-heterocyclic compounds such as imidazole, benzoimidazole, pyrrole, indole, benzotriazole, as well as their related derivatives.

Table 2 N-Arylation of Nitrogen Heterocycles with Different Carbon Aromatic Halides[a]



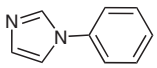
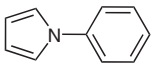
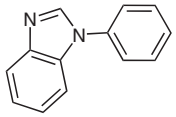
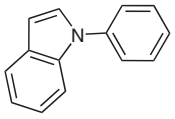
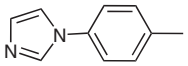
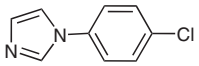
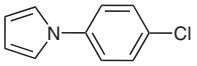
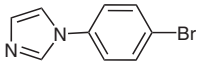
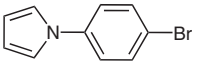
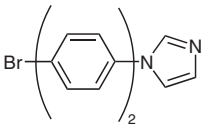
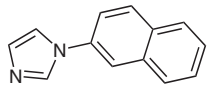
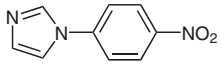
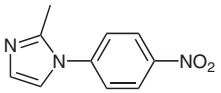
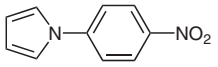
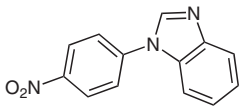
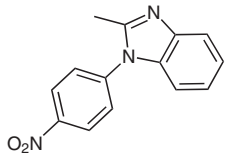
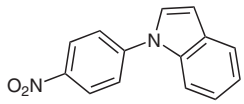
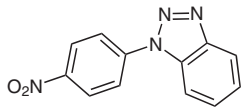
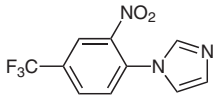
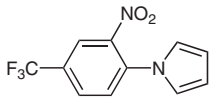
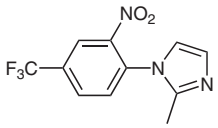
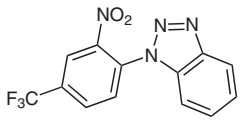
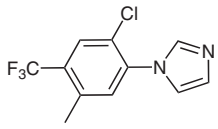
Entry	ArX	Product	Yield (%)[b]
1	PhI **1a**	 **3a**	85
2	**1a**	 **3b**	69
3	**1a**	 **3c**	52

Table 2 N-Arylation of Nitrogen Heterocycles with Different Carbon Aromatic Halides[a] (continued)

ArX (1) + HetNH (2) —CuI (10 mol%), L (10 mol%), NaOMe (2 equiv), DMSO→ HetNAr (3)

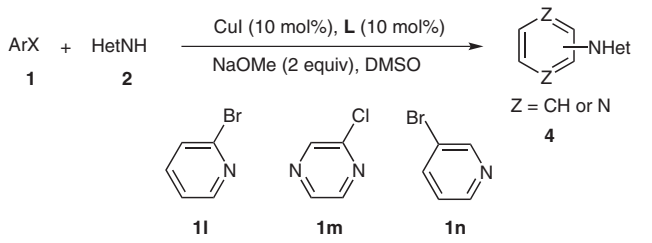
Entry	ArX	Product	Yield (%)[b]
4	**1a**	 **3d**	65
5	4-MeC_6H_4I **1b**	 **3e**	48
6	4-ClC_6H_4I **1c**	 **3f**	87
7	**1c**	 **3g**	83
8	4-BrC_6H_4I **1d**	 **3h**	76
9	**1d**	 **3i**	68
10	1,4-$Br_2C_6H_4$ **1e**	**3h**	43
11	4-(4-BrC_6H_4)-C_6H_4Br **1f**	 **3j**	40
12[c]	2-Naph-Br **1g**	 **3k**	48
13	4-$ClC_6H_4NO_2$ **1h**	 **3l**	91
14	**1h**	 **3m**	76
15	**1h**	 **3n**	93
16	**1h**	 **3o**	85
17	**1h**	 **3p**	50
18	**1h**	 **3q**	57
19	**1h**	 **3r**	65
20	2-NO_2-4-$F_3CC_6H_3Cl$ **1i**	 **3s**	90
21	**1i**	 **3t**	86
22	**1i**	 **3u**	67
23	**1i**	 **3v**	95
24	1,2-Cl_2-4-CF_3-5-MeC_6H_2 **1j**	 **3w**	50

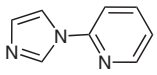
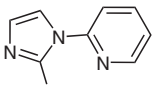
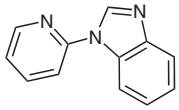
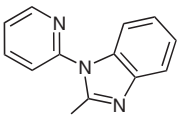
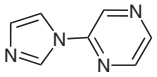
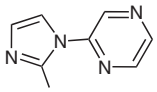
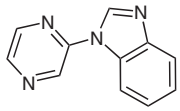
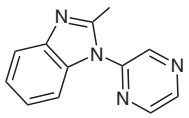
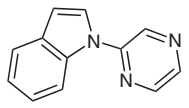
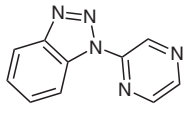
[a] Conditions: Reagents (0.5 mmol), DMSO (1.5 mL), 12 h (unless specified otherwise), 120 °C (entries 1–3), 90 °C (entries 4 and 18), 130 °C (entries 5–12, 14, 16, 17, 19–24), 110 °C (entries 13 and 15).
[b] Isolated yield.
[c] The reaction time was 24 h.

After the study on the reaction of aryl halide, we successively turned our attention to the reaction of heteroaromatic halides with azole compounds (Table 3).[19] In general, nitrogen-containing heteroaromatic compounds having halide functionality at *ortho* position such as 2-bromopy-

ridine (**1l**) and 2-chloropyrazine (**1m**) showed better efficiency on arylation. However, other regioisomers such as 3-bromopyridine provided only trace conversion, which implied that the activation of heteroatom on the aromatic ring was important for their arylation efficiency.

Table 3 N-Arylation of Nitrogen Heterocycles with Heteroaromatic Halides[a]



Entry	ArX	Product[b]	Yield (%)[c]
1	**1l**		92
2	**1l**		82
3	**1l**		90
4	**1l**		88
5	**1m**		86
6	**1m**		85
7	**1m**		66
8	**1m**		66
9[d]	**1m**		70
10	**1m**		94
11	**1n**	–	Trace

[a] Conditions: Reagents (0.5 mmol), DMSO (1.5 mL), 130 °C, 12 h.
[b] The products of entries 1–10 were numbered as **4a–j**, in that order.
[c] Isolated yield.
[d] The reaction was carried out at 90 °C.

In conclusion, easily accessible compound *N*,*N*′-(phenylmethylene)diacetamides which possess a 1,1-diamine subunit has been found as efficient ligands in arylation reaction of diversified azoles and aromatic halides. This marks the first example on the application of such ligands in N-arylation reactions. Application of this kind of readily available, inexpensive compounds provided a new ligand choice in the azole arylation reaction.

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(19) **Preparation of Ligands L1a–c**
Benzaldehyde (10 mmol) and the corresponding amide (20 mmol) were added to the vessel with 5 mL MeCN (5 mL), and TMSCl (30 mol%) was applied as catalyst. The mixture was refluxed for 8 h. The crude product precipitated from the solution. The analytical pure product was obtained in 94%, 78%, and 92% yield, respectively, by washing with MeCN (3 mL).
Ligand **L1a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.50 (d, 2 H), 7.38–7.27 (m, 5 H), 6.52 (t, 1 H), 1.86 (s, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.5, 141.5, 129.2, 128.4, 127.3, 58.2, 23.4. ESI-MS: *m/z* = 229 [M + Na]$^+$.
Preparation of L2a–2c
Benzaldehyde (10 mmol) and substituted urea (20 mmol) were mixed with MeCN (5 mL) and stirred at r.t. for 5 h. The corresponding product were furnished in quantitative yield after removal of solvent.
Ligand **L2a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.31 (s, 4 H), 7.24 (s, 1 H), 6.63 (d, 2 H), 6.17 (s, 1 H), 5.96 (s, 2 H), 2.55 (s, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.6, 143.8, 129.0, 127.9, 127.0, 60.3, 27.2. ESI-MS: 259 [M + Na]$^+$.
Preparation of L3
Paraformaldehyde (0.6 g) and acetamide (20 mmol) were mixed in MeCN (5 mL), the mixture was refluxed at 110 °C for 10 h to give **L3** in 75% yield.
Ligand **L3**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.44 (t, 2 H), 5.94 (s, 2 H), 4.22 (t, 2 H), 2.53 (d, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.8, 47.0, 27.4. ESI-MS: 183 [M + Na]$^+$.
General Experimental Procedure for the Arylation of Azole
Azole (0.5 mmol), aromatic halide (0.5 mmol), CuI (10 mol%), ligand (10 mol%) and NaOMe (1 mmol) were located in a flask with DMSO (1.5 mL). The mixture was heated at the corresponding temperature for 12 h. The reaction mixture was filtrated by SiO_2 and extracted with EtOAc (3 × 8 mL). The combined organic was concentrated and subjected to SiO_2 column to give target products.
Compound **3j**: mp 247–250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.59 (d, 2 H), 7.52 (d, 2 H), 7.41–7.37 (m, 4 H), 7.27 (s, 1 H), 7.19 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.7, 138.8, 136.8, 135.7, 132.3, 130.2, 128.8, 128.6, 122.4, 122.1, 118.6. ESI-MS: 299 [M + H]$^+$.
Compound **4c**(liquid): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60–8.57 (m, 2 H), 8.06 (t, 1 H), 7.88–7.85 (m, 2 H), 7.55 (d, 1 H), 7.38–7.35 (m, 2 H), 7.29–7.26 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.0, 149.6, 144.8, 141.5, 139.1, 132.3, 124.4, 123.5, 122.0, 120.8, 114.5, 112.8. ESI-MS: 196 [M + H]$^+$.