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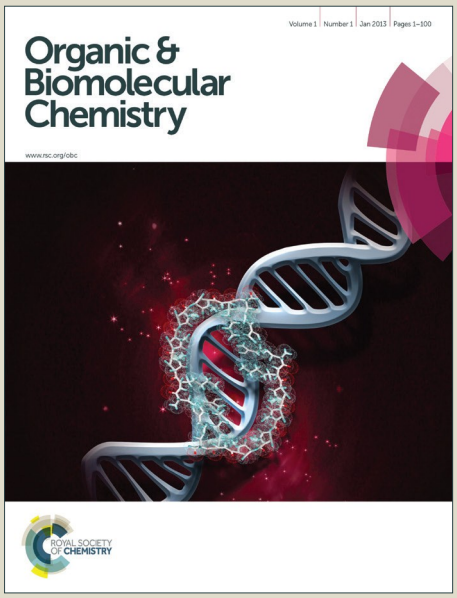

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N-(1-Oxy-2-picolyl)oxalamic Acids as New Type of *O*,*O*-Ligands for the Cu-Catalyzed *N*-Arylation of Azoles with Aryl Halides in Water or Organic Solvent

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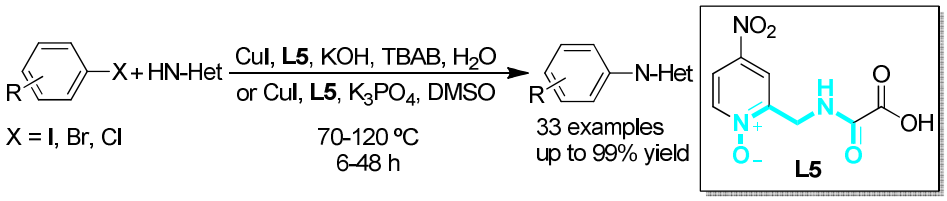

Abstract

N-(1-Oxy-pyridin-2-ylmethyl)oxalamic acids (**L3-L5)** were identified as novel efficient ligands for copper-catalyzed C-N cross-coupling of azoles and aryl halides in water. The *N*-arylation of imidazoles, indoles and pyrazoles proceeded with moderate to excellent yields and complete selectivity over aromatic amines and phenols. Moreover, **L5**, which is also efficient in organic solvent with low catalyst loading, can be used to promote the *N*-arylation reactions with water-sensitive materials. The catalytic mechanism was proposed based on the results of several verification experiments which indicated that the ligands as new-type chelators may coordinate to

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Cu(I) with two oxygen atoms of *N*-oxide and amide in the coupling process.

Introduction

N-arylazoles are found in many bioactive compounds, natural products and chemical materials for the synthesis of ionic liquids or *N*-heterocyclic carbenes.[1] Conventional preparation protocols of these moieties, including nucleophilic substitution of activated aryl halides with azoles and traditional Cu-catalyzed Ullmann C-N cross couplings, have several apparent drawbacks which limited their applications. Strongly electronic-withdrawing substitutes are necessary to activate the aryl halides in the former case. However, both of them suffer from harsh conditions and narrow functional group tolerance.[2] So far, great effort has been made to overcome these problems. For example, *N*-arylation of azoles can be accomplished using aryllead triacetate, arylboronic acid, triarylbismuth, diaryl iodonium salt, and arylstannane reagents with low loading of copper salt under mild conditions, but these methods generally require toxic, expensive or unusual reagents which are difficult to obtain.[3]

The most attractive and efficient methods for the preparation of *N*-aryl azoles involve copper-catalyzed Ullmann-type coupling reactions. The coupling can be catalyzed by ligand-free or ligand-assisted copper catalyst while Cu-ligands were applied to decrease the amount of catalyst, increase the functional group tolerance and avoid harsh conditions.[4] Since several *N*,*N*-and *N*,*O*-based chelators were developed as efficient Cu-ligands used to facilitate the *N*-arylation of azoles by Buchwald et al.[5] and Ma et al.[6] respectively, a series of novel copper/ligand systems have been reported.[3f,7] Eco-friendly Cu/ligand systems, performed with low loading of catalysts, at mild conditions and/or in water, appeared in recent years.[8] Aqueous-phase

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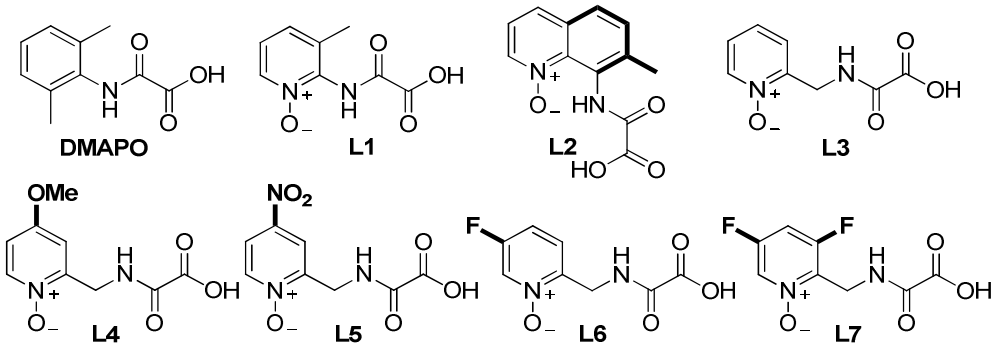
reaction is particularly attractive owing to the fact that water is the most economic and eco-friendly material.[8c,d]

. In our previous report, *N*-(2,6-dimethylphenyl)oxalamic acid (**DMAPO**) was shown to be a powerful ligand to enable copper-catalyzed reactions of aryl halides with primary/secondary amines to take place under relatively mild conditions.[9] We found that **DMAPO** can also slightly facilitate the Cu-catalyzed *N*-arylation of azoles in water. On this basis, we designed and synthesized a series of oxalamic acid-type ligands (**L1**-**L7**). These ligands were reconstructed from **DMAPO** with *N*-oxide strategy which has been used in the design of Cu-ligand for Ullmann reaction.[10] Intensive research of the substituent effect on the catalytic efficiencies of the ligands furnished several new and efficient Cu-ligands. Herein, we describe a full account of our recent work about novel *O*,*O*-ligands which can efficiently promote the copper-catalyzed coupling of azoles with aryl halides in aqueous-phase and organic solvent.

Results and Discussion

Figure 1. Structures of DMAPO and the designed Ligands



The structures of **DMAPO** and the designed ligands were shown in figure 1. **L1**-**L7** with *N*-oxide groups are stable and easily synthesized from different materials in high yields. Firstly,

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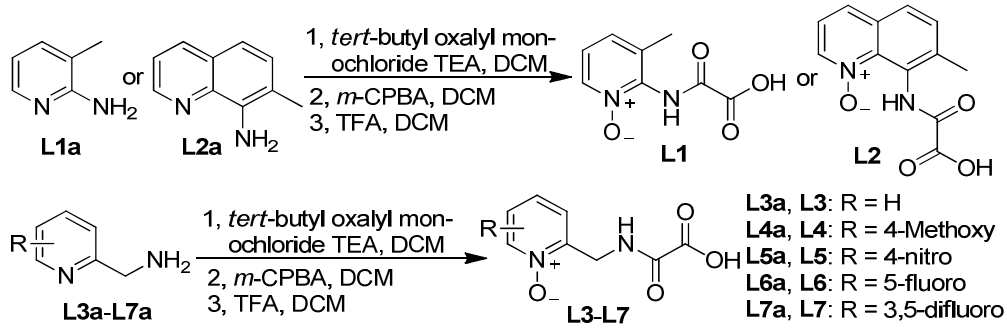
we obtained substituted 2-picolylamines/arylamines (**L1a-L7a**) through different methods.[11] Treatment of amines with *tert*-butyl oxalyl monochloride afforded **L1b-L7b**, followed by treatment with 3-chloroperbenzoic acid to yield pyridine *N*-oxides (**L1c-L7c)**. Finally, the ligands (**L1**-**L7**) were obtained after the *tert*-butyl groups were removed by trifluoroacetic acid (Scheme 1).

Scheme 1. Synthesis of the Designed Ligands Containing Pyridine *N*-Oxide Groups (L1-L7)



4-Bromoanisole and imidazole were chosen as model substrates to screen the efficiencies of these ligands in the *N*-arylation reactions in water. The standardized protocol was carried out with 4-bromoanisole (1.0 mmol), imidazole (1.4 mmol), CuI (5.0 mol %), **L**igand (10 mol %) and TBAB (0.2 eq) at 100 °C in water (1 mL). As shown in table 1, **DMAPO** can slightly promote the model reaction while **L1** and **L2**, which were directly reconstructed from **DMAPO** with pyridine *O*-oxide strategy, showed better activities (entries 1-3). **L2** was reasonably simplified through removing an aromatic ring to afford **L3** which efficiently promote the coupling with excellent yield (entry 4). **L4**-**L7** as analogues of **L3** were equipped with different substitutes on the pyridine rings to examine the effect of the substitutes to their activities. The results showed that the

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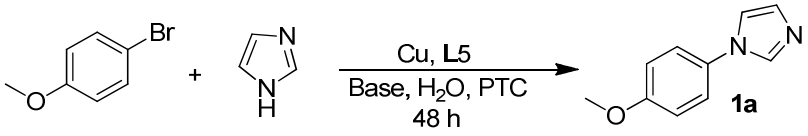
efficiencies of the ligands were maintained when the substitutes were added to the 4-position of the pyridine ring (entries 5-8).

By using **L5** as the ligand, the coupling of 4-bromoanisole and imidazole was selected as the model reaction to optimize the catalytic conditions in water, including optimization of the bases, copper sources, additives and temperature. Reactions employing different bases, including K_3PO_4, Cs_2CO_3 and KOH, at 90 °C were explored. The efforts showed that three inorganic bases provided almost the same yield (entries 9-11); however, KOH was the cheapest one and of practical application in this coupling reaction. The reactions with different copper sources showed that CuI promote the highest yielding reaction (70%) although other copper salts can be utilized in this coupling (entries 12-14). TBAB as phase transfer catalyst was found to be the most favorable additive for the catalytic reaction and the amount can be reduced to 0.1 equiv without significant decrease in yield (entries 15-19). The isolated yield of the coupling with 0.1 eq TBAB increased to 95% when the temperature was raised to 100 °C (entry 20). However, the optimal conditions for the coupling of 4-bromoanisole and imidazole in water involves the application of 5 mol % of CuI, 10 mol % of L5, 0.1 equiv of TBAB and 2.0 equiv KOH at 100 °C. Under the optimized conditions, 4-iodoanisole furnished the same product in satisfactory yield (90 %) when performed with imidazole at 70 °C (entry 21).

Table 1. DMAPO and Designed Ligands for Copper-catalyzed N-Arylation of Imidazole with 4-Bromoanisole in Water[a]



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Entry	Copper salt	**L**igand	Base	PTC(mol%)	Temp(°C)	Yield[%][b]
1	CuI	**DMAPO**	KOH	TBAB(20)	100	18
2	CuI	**L1**	KOH	TBAB(20)	100	36
3	CuI	**L2**	KOH	TBAB(20)	100	78
4	CuI	**L3**	KOH	TBAB(20)	100	97
5	CuI	**L4**	KOH	TBAB(20)	100	96
6	CuI	**L5**	KOH	TBAB(20)	100	98
7	CuI	**L6**	KOH	TBAB(20)	100	85
8	CuI	**L7**	KOH	TBAB(20)	100	82
9	CuI	**L5**	KOH	TBAB(20)	90	70
10	CuI	**L5**	K_3PO_4	TBAB(20)	90	71
11	CuI	**L5**	Cs_2CO_3	TBAB(20)	90	73
12	Cu_2O[c]	**L5**	KOH	TBAB(20)	90	54
13	$CuBr_2$	**L5**	KOH	TBAB(20)	90	58
14	$CuSO_4$	**L5**	KOH	TBAB(20)	90	55
15	CuI	**L5**	KOH	TEBA(20)	90	10
16	CuI	**L5**	KOH	TEAC(20)	90	Trace
17	CuI	**L5**	KOH	PEG-400(20)	90	6
18	CuI	**L5**	KOH	TBAB(10)	90	67
19	CuI	**L5**	KOH	--	90	4
20	CuI	**L5**	KOH	TBAB(10)	100	95
21	CuI	**L5**	KOH	TBAB(10)	70	90[d]

[a]Unless otherwise noted, the reactions were carried out with 4-bromoanisole (1.00 mmol), imidazole (1.40 mmol), Copper salt (5.0 mol %), **L**igand (10 mol %), base (2.00 mmol), PTC and H_2O (1.0 mL) under N_2-atmosphere for 48 h in schlenk tube; [b]Isolated yield; [c]2.5 mol % Cu_2O was applied; [d]4-iodoanisole instead of 4-bromoanisole.

TEBA: Benzyltriethylamonium·Chloride; TEAC: Tetraethylammonium chloride.

When the temperature dropped to 90 °C and the solvent was changed into organic solvent (DMSO), only **L5** afforded satisfactory yield (96%) with low loading of catalyst (2.5 mol % CuI and 5.0 mol % **L**) as shown in table 2. This result indicated that strong electronic-withdrawing group at the 4-position of the pyridine drastically increase the activity of the catalyst. Finally, **L5** was chosen as the ligand to examine the robustness of the reaction due to the applicability of **L5** to aqueous and organic solvent.

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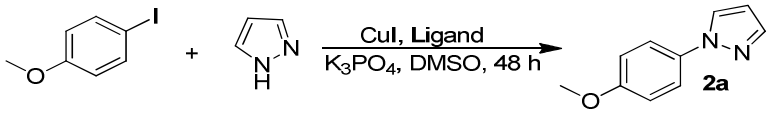
Table 2. DMAPO and Designed Ligands for Copper-catalyzed N-Arylation of Pyrazole with 4-Iodoanisole in DMSO[a]

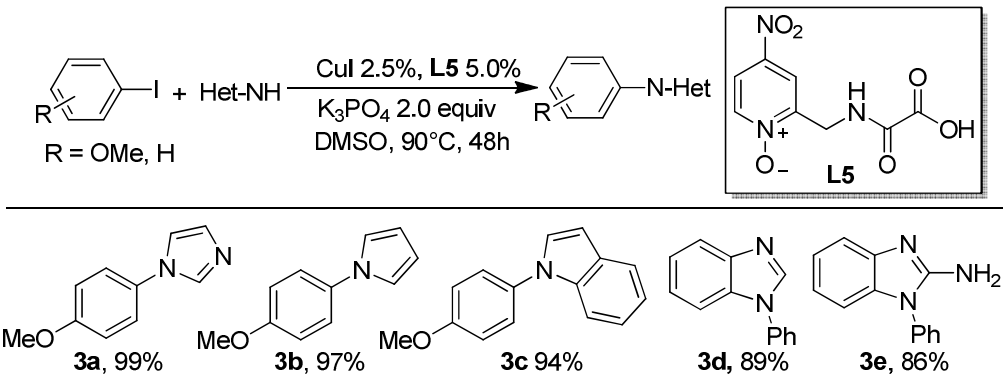


Ligand	None	DMAPO	L1	L2	L3	L4	L5	L6	L7
Yield[%][b]	14	26	30	45	54	61	**96**	41	20

[a]Unless otherwise noted, the reactions were carried out with 4-iodoanisole (1.00 mmol), pyrazole (1.40 mmol), CuI (2.5 mol %), **L** (5.0 mol %), K_3PO_4 (2.00 mmol) and DMSO (1.0 mL) at 90 °C for 48 h in reaction tube under N_2 atmosphere; [b]Isolated yield.

In DMSO, a wide variety of functional azoles successfully coupled with aryl iodides when the reactions were operated with low loading of catalysts (2.5 mol % CuI and 5.0 mol % **L5**) and K_3PO_4 (2.0 eq) at 90 °C for 48 h (table 2). Imidazole, pyrazole, pyrrole, indole and benzimidazoles exclusively provided the corresponding products with excellent isolated yields even performed with aryl iodides possess electron-donating groups.

Table 3. CuI-Catalyzed Couplings of Azoles with Aryl Iodides in DMSO[a,b]



[a]Unless otherwise noted, the reactions were carried out with aryl iodides (1.00 mmol), azole (1.40 mmol), CuI

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(2.5% mmol), **L**5 (5.0% mmol), K_3PO_4(2.00 mmol) and DMSO (1.0 mL) at 90 °C for 48 h in reaction tube under N_2 atmosphere; [b]Isolated yield.

In water, the scope of aryl halides was investigated by using CuI/**L5** system under the optimal conditions. As summarized in table 3, various functionalized aryl iodides, bromides and chlorides were subjected to this protocol at 70 °C, 100 °C and 120 °C, respectively. It was found that the reactions worked well in almost all cases. Aryl halides, including electron-rich, electron-neutral aryl iodides and bromides, afforded corresponding products in excellent isolated yields for 48 h (entries 1-3, 6-11) while less time was required to electron-deficient halides (entries 4, 12-16). The conditions of the N-arylation of imidazole promoted by Cu/L5 are comparable with that of several reported Cu/ligand systems which are comparatively efficient in water.[8b-d,12] 2-Bromoanisole afforded relatively lower yield (61%) than its *para*- and *meta*- isomers and the yield was increased to 82% when the temperature was raised to 110 °C (entry 17). This phenomenon about steric hindrance effect is coherent with previous studies.[7g,8d,10c] Furthermore, various functional groups, such as ketones, free amines and free hydroxyls, were well tolerated with excellent yields under optimal conditions (entries 9, 10, 12). In the case of ethyl 4-iodobenzoate, only a trace of desired product was determined due to the hydrolysis of the ester. However, the *N*-aryl imidazole was isolated with satisfactory yield when performed in DMSO (entry 5). Finally, 4-nitrochlorobenzene was successfully coupled with imidazole in moderate yield (67 %) at 120 °C (entry 18).

Table 4. CuI-Catalyzed *N*-Arylation of Imidazole with Aryl Halides in Water[a]

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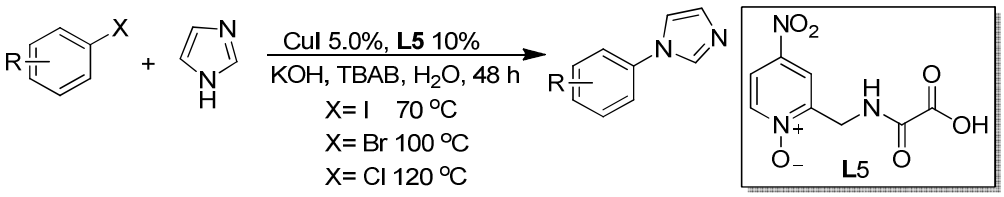
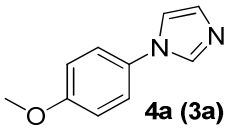
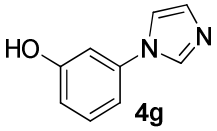
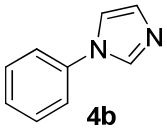
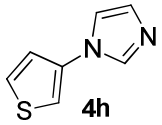
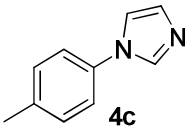
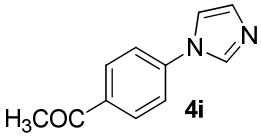
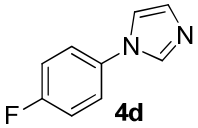
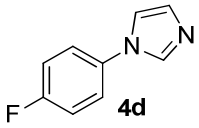
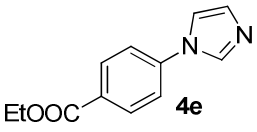
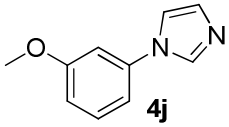
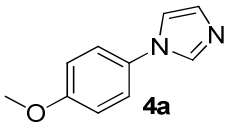
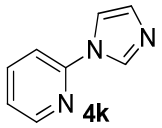
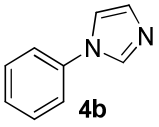
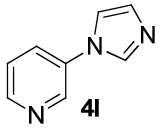
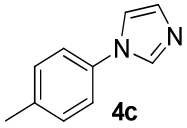
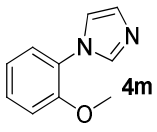
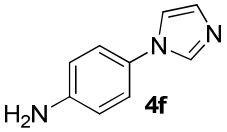
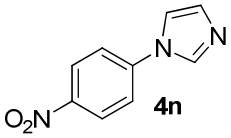


Entry	Product	Time (h)	Yield[b] [%]	Entry	Product	Time (h)	Yield[b] [%]
1 (ArI)	 **4a (3a)**	48	90 99[c] 90[d]	10 (ArBr)	 **4g**	48	98[f] 92[c,f] 97[d,f]
2 (ArI)	 **4b**	48	99	11 (ArBr)	 **4h**	48	99
3 (ArI)	 **4c**	48	97	12 (ArBr)	 **4i**	30	85
4 (ArI)	 **4d**	40	99	13 (ArBr)	 **4d**	36	92
5 (ArI)	 **4e**	48	76[e]	14 (ArBr)	 **4j**	36	99
6 (ArBr)	 **4a**	48	95	15 (ArBr)	 **4k**	6	99
7 (ArBr)	 **4b**	48	99	16 (ArBr)	 **4l**	40	99
8 (ArBr)	 **4c**	48	99	17 (ArBr)	 **4m**	48	61 82[g]
9 (ArBr)	 **4f**	48	99	18 (ArCl)	 **4n**	48	67

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[a]Unless otherwise noted, the reactions were carried out with aryl halides (1.00 mmol), imidazole (1.40 mmol), CuI (5.0 mol %), **L**5 (10 mol %), KOH (2.00 mmol), TBAB (0.10 mmol) and H_2O (1.0 mL) in schlenk tube under N_2 atmosphere; [b]Isolated yield; [c]The reaction was performed with **L**3 instead of **L**5; [d]The reaction was performed with **L**4 instead of **L**5; [e]The reaction was performed under the conditions given in Table 2; [f]KOH (3.00 mmol); [g]At 110 °C.

To further expand the substrate scope of this methodology, the CuI/**L5** system was explored with other *N*-containing heterocycles. As shown in table 4, a variety of azoles such as substituted imidazoles, pyrazoles, pyrroles indazoles and indoles were applied with varies aryl halides to give the corresponding *N*-arylazoles in moderate to excellent isolated yields under the optimized conditions but different temperature. 4-Methyl imidazole was found to be effective nucleophilic azole as well as imidazole when performed with 4-iodoanisole and 4-bromoanisole at 70 °C and 100 °C respectively. A mixture of N^1-and N^3-arylation isomers was obtained with good yields and moderate regioselectivity. The ratios of the isomers are shown in the parentheses while N^1-substituted product is the major product (entries 1, 11). 2-Methylimidazole and 2-acetylpyrrole as less nucleophilic partners with steric hindrance successfully coupled with iodobenzene in good yield at 110 and 100 °C (entries 2, 3). Notably, 2-bromopyridine could be conducted smoothly to provide 2-substituted pyridines with azoles examined here in excellent yields even the temperature was decreased to 90 °C (entries 10, 12, 13, 20). Indazole, indoles and pyrazole proceeded with aryl iodides to exclusively furnish the coupling products with good to excellent yield at 100 °C, 90 °C and 110 °C respectively while aryl bromides gave rise to moderate to excellent yield at 120 °C (entries 4-9, 14-20).

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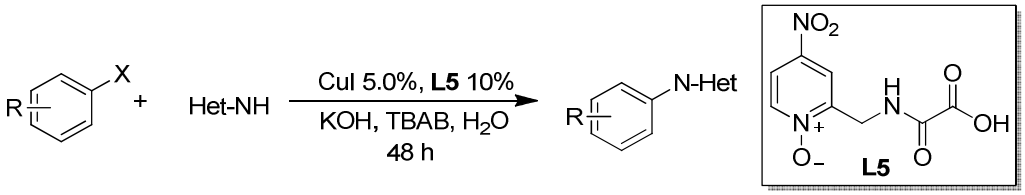
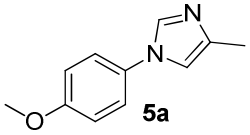
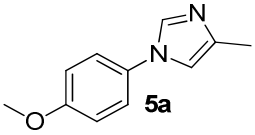
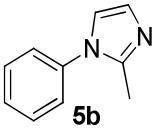
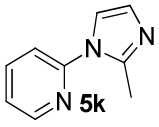
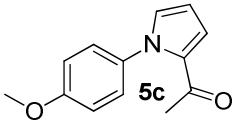
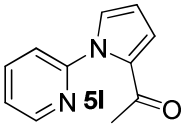
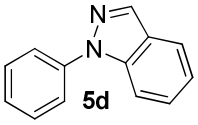
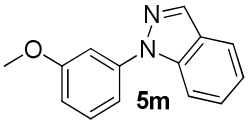
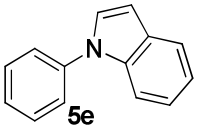
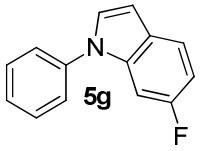
Several reactions with different azoles and aryl halides were carried out under the optimized conditions to examine the substrate scope of **L3** and **L4** (entries 1, 10 of Table 4 and entry 9 of Table 5). The outcomes pointed that the activity of these two ligands is comparable and sometimes even better than that of **L5**. **L3**, which can be synthesized easily due to its simple structure, is applicable in facilitating the *N*-arylation reactions in water.

Table 5. CuI-Catalyzed *N*-Arylation of Azoles with Aryl Halides[a]



Entry	Product	Temp (°C)	Yield [%]	Entry	Product	Temp (°C)	Yield [%]
1 (ArI)	 **5a**	70	88[c] (4:1)	11 (ArBr)	 **5a**	100	89[c] (3:1)
2 (ArI)	 **5b**	110	82	12 (ArBr)	 **5k**	90	98
3 (ArI)	 **5c**	100	80	13 (ArBr)	 **5l**	90	82
4 (ArI)	 **5d**	100	92	14 (ArBr)	 **5m**	120	69
5 (ArI)	 **5e**	90	87	15 (ArBr)	 **5g** F	120	61

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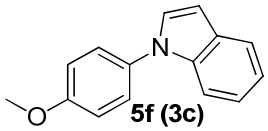
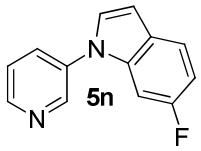
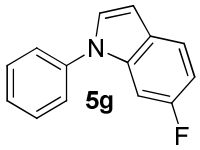
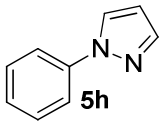
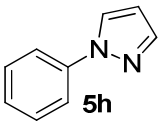
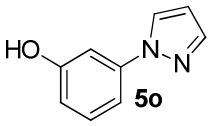
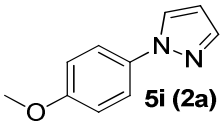
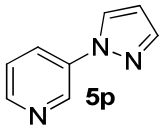
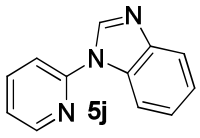
6 (ArI)	 5f (3c)	90	83	16 (ArBr)	 5n	120	73
7 (ArI)	 5g	90	90	17 (ArBr)	 5h	120	69
8 (ArI)	 5h	110	94	18 (ArBr)	 5o	120	70[f]
9 (ArI)	 5i (2a)	110	74 86[d] 80[e]	19 (ArBr)	 5p	120	89
10 (ArBr)	 5j	90	99	20 (ArBr)	 5q	90	99

[a]Unless otherwise noted, the reactions were carried out with aryl halides (1.00 mmol), imidazole (1.40 mmol), CuI (5.0% mmol), **L5** (10% mmol), KOH (2.00 mmol), TBAB(0.10 mmol) and H_2O (1.0 mL) in schlenk tube under N_2 atmosphere for 48 h; [b]Isolated yield; [c]4-Me:5-Me selectivity is reported in parentheses was determined by ^{1}H NMR spectra of the pure products; [d]The reaction was performed with **L**3 instead of **L**5; [e]The reaction was performed with **L**4 instead of **L**5. [f]KOH (3.0 mmol).

Mechanistic Study

The efficiencies of catalyst systems applied in copper-catalyzed C-N couplings are governed by several factors while ligands that coordinate to Cu play an important role in this process.[4b,10b] Most of the ligands used in Ullmann reactions are bidentate or multidentate chelators.[8d,9,13] **L3**, **L4** and **L5** as efficient ligands contain three functional groups which may coordinate to Cu, namely *N*-oxide[14a], amide[14b-h]and carbonyl groups[14h,i]. **L11** as bidentate ligand without carboxyl group

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could efficiently promote the coupling of imidazole and 4-bromoanisole in water to provide the desired product with slightly lower yield than **L3**. **L9** and **L10** showed poor activity in this reaction perhaps due to the absence of *N*-oxide or amide group in the ligands. These results indicated that the *N*-oxide and amide groups play important roles and the carboxyl group was not absolutely necessary in the catalytic process. Pyridine *N*-oxides and amides are efficient Cu-ligands which have been widely utilized in coordination and catalytic chemistry.[10b,c,14b-i] Therefore, the *N*-(1-oxy-2-picolyl)oxalamic acids may act as bidentate ligands and the two coordinated sites may be the *N*-oxide and amide groups. Meanwhile, the carboxyl groups should increase the efficiency of the ligands through changing the properties of the ligands. For example, they can elevate the solubility of the ligands in water which is favorable to aqueous phase reaction[8b,10c].

The amide group of oxalamic acid can efficiently coordinate to copper with nitrogen[14f,g,i] or oxygen atom[14e,h,i] of the amide. Structural feature analysis of previously reported Cu-oxalamic acid complexes reveals that the N-Cu coordinated form generally requires the deprotonation of the amide.[14f,g,i] The amide might directly coordinate to the Cu(I) with the oxygen atom without deprotonation since **L10** as similar ligand of **L3** without hydrogen on the amide was as effective as **L3** in promoting the coupling. In summary, we presumed that the effective ligands may act as *O*,*O*-ligand (the oxygen atoms of the N-oxide and amide) in the Cu-catalyzed process. As shown in Scheme 2, eight-member reactive species **A** formed by the chelating Cu(I) with the ligand participated the catalytic cycle with oxidative addition and reductive elimination to generate *N*-arylazoles and regenerate the complex **A**.[8d,9,10b,15]

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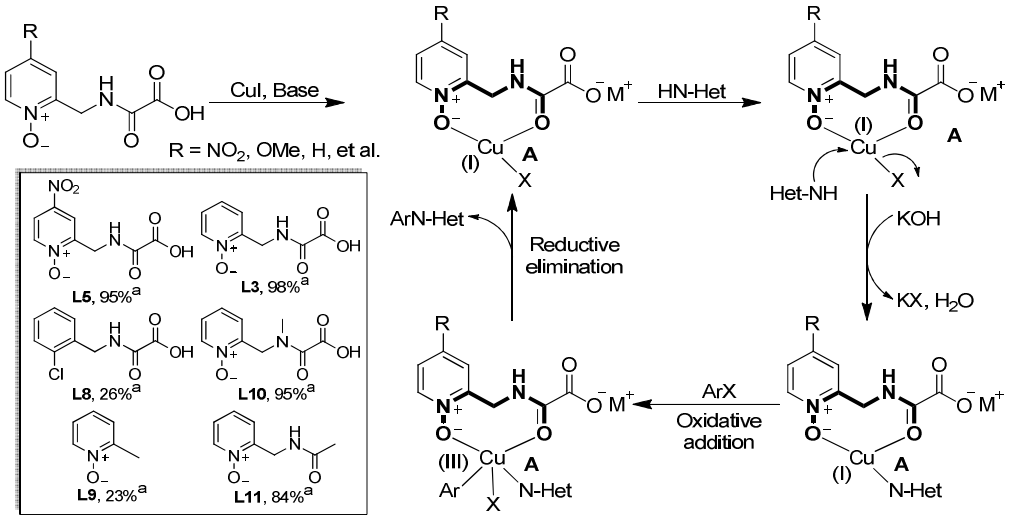
Figure 1. The Presumed Catalytic Mechanism of Cu/L in Promoting the *N*-Arylation of Azoles.



[a]Isolated yield when promoted the N-arylation of imidazole with 4-bromoanisole under the conditions of table 4.

Conclusion

In summary, we have developed an useful copper catalyzed system for the *N*-arylation of azoles with *N*-(1-oxy-pyridin-2-ylmethyl)oxalamic acids as ligands in water under relatively mild conditions. This process avoids the use of toxic organic solvents, expensive bases and harsh conditions. Moreover, the Cu/**L5** system, which is also efficient in organic solvent with low catalyst loading, can be used to promote the *N*-arylation reactions of azoles with water-sensitive materials. The presumed catalytic mechanism of CuI/**L** was verified by several experiments. The novel coordinate pattern and the applicability of **L5** to both aqueous-phase and organic solvent may lead to the development of new Cu/ligand systems. Applications of this type of ligands to other coupling reactions are being explored in our laboratory.

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Experimental Section

Synthesis of the Ligands. L1-L8 and **L10** was synthesized from amines (**L1a-L8a**) and **L9** was commercial available. The amines (**L1a-L8a**) were obtained through different methods. **L1a**, **L2a**, **L3a**, and 2-chlorobenzyamine (**L8a**) were purchased from commercial sources and used without further purification. **L6a** and **L7a** were synthesized according the literature but under normal atmosphere press[11a] while **L4a** and **L5a** were synthesized from 4-methoxy-2-pyridylmethol and 4-nitro-2-pyridylmethol respectively.

***tert*-Butyl *N*-(3-methyl-pyridin-2-yl)oxamate (L1b):** To a magnetically stirred solution of 2-amino-3-methylpyridine (320 mg, 3.0 mmol) and triethylamine (610 mg, 6 mmol) in CH_2Cl_2 (20 mL) was added, dropwise, a solution of *tert*-Butyl oxalyl chloride (600 mg, 3.64 mmol) in CH_2Cl_2 (6 mL). After it was stirred for 2 h, the mixture was diluted with CH_2Cl_2 (30 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified with silica gel chromatography to give the **L1b** (576 mg, 2.44 mmol, 81.3%). White solid; m.p. 123-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (br, 1H), 8.29 (d, J = 3.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.14 (dd, J_1 = 7.4 Hz, J_2 = 4.9 Hz, 1H), 2.29 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 155.3, 148.1, 146.0, 140.0, 128.6, 122.3, 85.0, 27.7, 18.1; HRMS calcd for $C_{12}H_{17}N_2O_3$ $(M + H)^+$, 237.1234, found 237.1233.

***tert*-Butyl *N*-(3-methyl-1-oxy-pyridin-2-yl)oxamate (L1c):** T To a magnetically stirred solution of **L1b** (500 g, 2.12 mmol) in CH_2Cl_2 (20 mL) was added 75% 3-Chloroperbenzoic acid (580 mg, 2.52 mmol) slowly. After 12 h, K_2CO_3 (600 mg, 4.34 mmol) was added into the mixture. It was stirred additional 6 h. The reaction mixture was filtered and eluted with CH_2Cl_2 (30 mL). The filtrate was concentrated, and the crude product was purified through recrystallization from

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PE/EA to give the **L1c** (460 mg, 1.82 mmol, 86.6%). Colorless-crystalline solid; m.p. 130-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (br, 1H), 8.19 (d, J = 6.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 6.5 Hz, 1H), 2.36 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 155.3, 142.0, 135.8, 131.4, 129.6, 121.6, 85.6, 27.7, 19.2; HRMS calcd for $C_{12}H_{17}N_2O_4$ $(M + H)^+$, 253.1183, found 253.1186.

***N*-(3-Methyl-1-oxy-pyridin-2-yl)oxalamic acid (L1):** To a magnetically stirred solution of **L1c** (400 mg, 1.58) in CH_2Cl_2 (20 mL), trifluoroacetic acid (6 ml) was added dropwise. After it was stirred for 24 h, the reaction solution was concentrated and the resulting residue was purified through recrystallization from PE/EA to give **L1** (238 mg, 1.21 mmol, 76.8%). White solid; m.p. 139-142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 16.50-11.30 (br, 1H), 10.58 (br, 1H), 8.22 (s, 1H), 7.28 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.9, 157.5, 141.6, 136.5, 132.9, 127.5, 123.2, 17.4; HRMS calcd for $C_8H_9N_2O_4$ $(M + H)^+$, 197.0557, found 197.0558.

***tert*-Butyl *N*-(7-methyl-quinolin-8-yl)oxamate (L2b):** The procedure was the same as described above for the synthesis of **L1b**. White solid; m.p. 125-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (br, 1H), 8.87 (dd, J_1 = 4.2 Hz, J_1 = 1.5 Hz, 1H), 8.12 (dd, J_1 = 8.2 Hz, J_1 = 1.4 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.2 Hz, J = 4.2 Hz, 1H), 2.50 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 155.1, 149.6, 142.6, 135.8, 133.9, 130.4, 130.3, 126.5, 125.2, 120.9, 84.8, 27.9, 20.6; HRMS calcd for $C_{16}H_{19}N_2O_3$ $(M + H)^+$, 287.1390, found 287.1393.

***tert*-Butyl *N*-(7-methyl-1-oxy-quinolin-8-yl)oxamate (L2c):** The procedure was the same as described above for the synthesis of **L1c**. Light brown solid; m.p. 141-143 °C; ^{1}H NMR (300 MHz, CDCl3) δ 13.9 (s, 1H), 8.44 (d, J = 6.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.4

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Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 6.1 Hz, J = 2.1 Hz, 1H), 2.42 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.0, 137.9, 136.1, 134.5, 132.6, 130.4, 128.5, 127.7 124.8, 120.2, 84.5, 27.9, 21.2; HRMS calcd for $C_{16}H_{19}N_2O_4$ $(M + H)^+$, 303.1339, found 303.1345.

***N*-(7-Methyl-1-oxy-quinolin-8-yl)oxalamic acid (L2):** The procedure was the same as described above for the synthesis of **L1**. Light brown-flaky solid; m.p. 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.33 (br, 1H), 13.62 (s, 1H), 8.58 (s, J = 5.9 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.4, 155.0, 138.2, 135.0, 133.5, 131.9, 130.2, 127.62, 127.59, 125.5, 121.4, 20.3; HRMS calcd for $C_{12}H_{11}N_2O_4$ $(M + H)^+$, 247.0713, found 247.0718.

***tert*-Butyl *N*-(pyridin-2-ylmethyl)oxamate (L3b):** To a magnetically stirred solution of 2-picolyamine (1.84 g, 17.0 mmol) and triethylamine (3.40 g, 33.7 mmol) in CH_2Cl_2 (60 mL) was added, dropwise, a solution of *tert*-Butyl oxalyl chloride (3.10 g, 18.8 mmol) in CH_2Cl_2 (10 mL). After it was stirred for 2 h, the mixture was diluted with CH_2Cl_2 (30 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified with silica gel chromatography to give the **L3b** (3.52 g, 14.2 mmol, 83.5%). Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 1H), 8.25 (br, 1H), 7.69 (td, J_1 =7.7 Hz, J_2 = 1.7 Hz, 1H), 7.29 (t, J = 3.5 Hz, 1H), 7.27-7.20 (m, 1H), 4.62 (d, J = 4.3 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 157.6, 155.2, 149.2, 136.9, 122.7, 122.2, 84.4, 44.7, 27.7; HRMS calcd for $C_{12}H_{17}N_2O_3$ $(M + H)^+$, 237.1234, found 237.1234.

***tert*-Butyl *N*-((1-oxy-pyridin-2-yl)methyl)oxamate (L3c):** To a magnetically stirred solution of **L3b** (2.30 g, 9.75 mmol) in CH_2Cl_2 (40 mL) was added 75% 3-Chloroperbenzoic acid (2.70 g, 11.7 mmol) slowly. After 12 h, K_2CO_3 (2.70 g, 19.6 mmol) was added into the mixture. It was

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stirred additional 6 h. The reaction mixture was filtered and eluted with CH_2Cl_2 (60 mL). The filtrate was concentrated, and the crude product was purified through recrystallization from PE/EA to give the **L3c** (2.13 g, 8.44 mmol, 86.6%). White-crystalline solid; m.p. 126-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (br, 1H), 8.26 (t, J = 4.2 Hz, 1H), 7.46 (t, J_2 = 5.2 Hz, 1H), 7.32-7.23 (m, 2H), 4.69 (d, J = 6.1 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.0, 146.5, 139.6, 126.5, 126.2, 125.4, 84.6, 39.7, 27.7; HRMS calcd for $C_{12}H_{17}N_2O_4$ $(M - H)^+$, 253.1183, found 253.1187.

***N*-((1-Oxy-pyridin-2-yl)methyl)oxalamic acid (L3):** To a magnetically stirred solution of **L3b** (1.00 g, 3.96 mmol) in CH_2Cl_2 (30 mL), trifluoroacetic acid (12 ml) was added dropwise. After it was stirred for 24 h, the reaction solution was concentrated and the resulting residue was purified through recrystallization from EA to give **L3** (0.730 g, 3.72 mmol, 94.0%). White solid; m.p. 185-187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 16.00-12.00 (br, 1H), 9.33 (t, J = 5.9 Hz, 1H), 8.32 (t, J_2 = 2.5 Hz, 1H), 7.44-7.30 (m, 3H), 4.43 (d, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.6, 158.8, 147.0, 139.0, 125.4, 124.8, 123.7, 38.5; HRMS calcd for $C_8H_9N_2O_4$ $(M + H)^+$, 197.0557, found 197.0559.

2-Bromomethyl-4-methoxypyridine (L4a-1): To a magnetically stirred solution of 4-methoxy- 2-(hydroxymethyl)pyridine (1.00 g, 7.19 mmol) in CH_2Cl_2 (40 mL) was added PBr_3 (2.54 g, 9.38 mmol) slowly in ice-water bath. After addition, the mixture was brought to reflux for 3 h. The reaction mixture was allowed to cool to room temperature and then added into water (30 ml) slowly. After the mixture was stirred for 5 min, 30 mL K_2CO_3 (1 M) was added to basify the mixture. The organic layer was separated and the aqueous layer was extracted by 2*30 ml CH_2Cl_2. The organic layer was combined, washed with brine, dried over Na_2SO_4 and then evaporated. The

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resulting residue as extremely unstable oil was directly used in next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 5.8 Hz, 1H), 6.96 (d, J = 2.3 Hz, 1H), 6.73 (dd, J_1 = 5.7 Hz, J_1 = 2.3 Hz, 1H), 4.50 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.3, 150.8, 109.5, 109.1, 55.3, 33.9.

2-((4-Methoxy-pyridin-2-yl)methyl)isoindoline-1,3-dione (L4a-2): To a magnetically stirred solution of the above product in DMF (20 ml) was added Phthalimide K (1.86 g, 10.0 mmol). After it was stirred for 24 h, the reaction mixture was diluted with water (60 mL) and the aqueous layer was extracted with 3*20 ml ethyl acetate. The organic layer was combined and then washed with water and brine, dried over Na_2SO_4 and evaporated. The crude product was purified through recrystallization from PE/EA to give **L4a-2** (1.47g, 5.48 mmol, combined yield of two steps was 76.2%). White solid; m.p. 116-118 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.33 (d, J = 5.7 Hz, 1H), 7.91-7.83 (m, 2H), 7.76-7.66 (m, 2H), 6.79 (d, J = 2.1 Hz, 1H), 6.69 (dd, J_1 = 5.7 Hz, J_2 = 2.3 Hz, 1H), 4.96 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 166.3, 157.0, 150.9, 134.0, 132.2, 123.5, 108.5, 107.7, 55.2, 42.9; HRMS calcd for $C_{15}H_{13}N_2O_3$ $(M + H)^+$, 269.0921, found 269.0918.

(4-Methoxy-pyridin-2-yl)methylamine (L4a):[16] To a magnetically stirred solution of **L4a-2** (1.07 g, 3.99 mmol) in MeOH (40 ml) was added H_2NNH_2•H_2O (1.25 g, 80%, 20.0 mmol). The reaction mixture was heated to reflux for 4 h after the addition. The reaction solution was allowed to cool to room temperature, filtered and then eluted with MeOH (10 mL). The filtrate was concentrated, added 40 ml H_2O and basified by adding 10 mL KOH (1 M). The aqueous layer was extracted by 4*20 ml DCM. The organic layer was combined, dried over Na_2SO_4 and evaporated to give **L4a** (460 mg, 3.33 mmol) as yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 4.4

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Hz, 1H), 6.73 (s, 1H), 6.59 (d, J = 3.2 Hz, 1H), 3.82 (s, 2H), 3.74 (s, 3H), 1.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 163.6, 150.3, 108.1, 106.8, 55.0, 47.7; HRMS calcd for $C_7H_{11}N_2O$ (M + H)$^+$, 139.0866, found 139.0868.

***tert*-Butyl *N*-((4-methoxy-pyridin-2-yl)methyl)oxamate (L4b):** The procedure was the same as described above for the synthesis of **L3b**. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (br, 1H), 8.25 (d, J = 5.8 Hz, 1H), 6.70 (s, 1H), 6.65 (dd, J_1 = 5.7 Hz, J_1 = 2.2 Hz, 1H), 4.45 (d, J = 5.4 Hz, 2H), 3.74 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 159.3, 157.5, 157.1, 150.3, 109.0, 107.8, 84.2, 55.1, 44.7, 27.6; HRMS calcd for $C_{13}H_{19}N_2O_4$ (M + H)$^+$, 267.1339, found 267.1340.

***tert*-Butyl *N*-((4-methoxy-1-oxy-pyridin-2-yl)methyl)oxamate (L4c):** The procedure was the same as described above for the synthesis of **L3c**. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 5.7 Hz, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.83 (d, J_1 = 7.2 Hz, J_2 = 3.4 Hz, 1H), 4.67 (d, J = 6.3 Hz, 2H), 3.87 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.3, 158.1, 147.3, 140.2, 111.6, 111.4, 84.4, 56.2, 39.8, 27.6; HRMS calcd for $C_{13}H_{19}N_2O_5$ (M + H)$^+$, 283.1288, found 283.1296.

***N*-((4-Methoxy-1-oxy-pyridin-2-yl)methyl)oxalamic acid (L4):** The procedure was the same as described above for the synthesis of **L3**. White solid; m.p. 188-189 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.0 (br, 1H), 9.27 (t, J = 5.9 Hz, 1H), 8.22 (d, J = 7.2 Hz, 1H), 7.02 (dd, J_1 = 7.2 Hz, J_2 = 3.5 Hz, 1H), 6.91 (d, J = 3.4 Hz, 1H), 4.42 (d, J = 6.1 Hz, 2H), 3.82 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.6, 158.9, 157.3, 148.0, 114.0, 110.6, 109.8, 56.3, 38.7; HRMS calcd for $C_9H_{11}N_2O_5$ (M + H)$^+$, 227.0662, found 227.0666.

2-Bromomethyl-4-nitropyridine (L5a-1):[17] The procedure was the same as described above

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for the synthesis of **L4a-1**. Unstable colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J = 5.4 Hz, 1H), 8.20 (d, J = 1.7 Hz, 1H), 7.97 (dd, J_1 = 5.3 Hz, J_1 = 2.0 Hz, 1H), 4.67 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 154.6, 151.8, 116.2, 115.6, 32.2.

2-((4-Nitro-pyridin-2-yl)methyl)isoindoline-1,3-dione(L5a-2): The procedure was the same as described above for the synthesis of **L4a-2**. White solid; m.p. 194-195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (d, J = 5.4 Hz, 1H), 8.26 (s, 1H), 8.03 (d, J = 3.7 Hz, 1H), 7.98-7.84 (m, 4H), 5.12 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 159.1, 154.7, 152.2, 135.1, 132.2, 123.8, 115.8, 114.9, 42.5; HRMS calcd for $C_{14}H_{10}N_3O_4$ $(M + H)^+$, 284.0666, found 284.0670.

(4-Nitro-pyridin-2-yl)methylamine (L5a): The procedure was the same as described above for the synthesis of **L4a**. Extremely unstable erythrine oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J = 5. Hz, 1H), 8.10 (s, 1H), 7.89 (d, J_1 = 3.6 Hz, 1H), 4.16 (s, 2H), 1.71 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 114.3, 113.7, 47.6.

***tert*-Butyl *N*-((4-nitro-pyridin-2-yl)methyl)oxamate (L5b):** The procedure was the same as described above for the synthesis of **L3b**. White solid; m.p. 91-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 5.3 Hz, 1H), 8.09 (br, 1H), 8.02 (s, J = 1.5 Hz, 1H), 7.96 (dd, J_1 = 5.3 Hz, J_2 = 1.8 Hz, 1H), 4.77 (d, J = 5.7 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.2, 157.9, 154.4, 151.6, 115.2, 114.6, 84.8, 44.8, 27.6; HRMS calcd for $C_{12}H_{16}N_3O_5$ $(M + H)^+$, 282.1084, found 282.1086.

***tert*-Butyl *N*-((4-nitro-1-oxy-pyridin-2-yl)methyl)oxamate (L5c):** The procedure was the same as described above for the synthesis of **L3c**. Yellowish solid; m.p. 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 7.1 Hz, 1H), 8.34-8.26 (m, 2H), 8.11 (dd, J_1 = 6.9 Hz, J_2 = 2. 9 Hz, 1H), 4.71 (d, J = 6.2 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.3, 1148.3,

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142.2, 140.4, 120.6, 119.6, 85.0, 39.5, 27.6; HRMS calcd for $C_{12}H_{15}N_3NaO_6$ $(M + H)^+$, 320.0853, found 320.0859.

***N*-((4-Nitro-1-oxy-pyridin-2-yl)methyl)oxalamic acid (L5):** The procedure was the same as described above for the synthesis of **L3**. White solid; m.p. 193-195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.2 (br, 1H), 9.45 (t, J = 5.7 Hz, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.19 (dd, J_1 = 7.2 Hz, J_2 = 3.1 Hz, 1H), 8.11 (d, J = 2.9 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5, 159.0, 148.9, 141.8, 140.5, 119.3, 118.3, 38.4; HRMS calcd for $C_8H_7N_3NaO_6$ $(M + H)^+$, 264.0227, found 264.0231.

***tert*-Butyl *N*-((5-fluoro-pyridin-2-yl)methyl)oxamate (L6b):** The procedure was the same as described above for the synthesis of **L3b**. Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 2.5 Hz, 1H), 8.17 (br, 1H), 7.41 (td, J_1 = 8.5 Hz, J_2 = 2.8 Hz, 1H), 7.37-7.29 (m, 1H), 4.60 (d, J = 5.6 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 158.8 (d, $^1J_{CF}$ = 254.1 Hz), 157.6, 151.6 (d, $^4J_{CF}$ = 3.6 Hz), 137.3 (d, $^2J_{CF}$ = 23.9 Hz), 123.7 (d, $^2J_{CF}$ = 18.5 Hz), 123.1 (d, $^3J_{CF}$ = 4.3 Hz), 84.5, 44.2, 27.7; HRMS calcd for $C_{12}H_{16}FN_2O_3$ $(M + H)^+$, 255.1139, found 255.1144.

***tert*-Butyl *N*-((5-fluoro-1-oxy-pyridin-2-yl)methyl)oxamate (L6c):** The procedure was the same as described above for the synthesis of **L3c**. Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (br, 1H), 8.24 (dd, J_1 = 6.3 Hz, J_2 = 2.3 Hz, 1H), 7.49 (t, J = 8.6 Hz, 1H), 7.10 (td, J_1 = 7.0 Hz, J_2 = 2.2 Hz, 1H), 4.65 (d, J = 6.4 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 158.9, 158.1, 143.6 (d, $^4J_{CF}$ = 4.0 Hz), 129.6 (d, $^2J_{CF}$ = 35.5 Hz), 126.3 (d, $^3J_{CF}$ = 9.2 Hz), 113.9 (d, $^2J_{CF}$ = 19.6 Hz), 84.5, 38.9, 27.6; HRMS calcd for $C_{12}H_{14}FN_2O_4$ $(M - H)^-$, 269.0943, found 269.0946.

***N*-((5-Fluoro-1-oxy-pyridin-2-yl)methyl)oxalamic acid (L6):** The procedure was the same

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as described above for the synthesis of **L3**. White solid; m.p. 184-186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.99 (br, 1H), 9.30 (t, J = 5.8 Hz, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.39 (d, J = 7.4 Hz, 2H), 4.39 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5, 159.0 (d, $^{1}J_{CF}$ = 246.5 Hz), 158.8, 144.3 (d, $^{4}J_{CF}$ = 3.9 Hz), 129.0 (d, $^{2}J_{CF}$ = 35.7 Hz), 124.1 (d, $^{3}J_{CF}$ = 9.7 Hz), 113.3 (d, $^{2}J_{CF}$ = 19.9 Hz), 38.1; HRMS calcd for $C_8H_8FN_2O_4$ $(M + H)^+$, 215.0463, found 215.0464.

***tert*-Butyl *N*-((3, 5-difluoro-pyridin-2-yl)methyl)oxamate (L7b):** The procedure was the same as described above for the synthesis of **L3b**. Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 2.1 Hz, 1H), 8.22 (br, 1H), 7.27 (td, J_1 = 9.1 Hz, J_2 = 2.3 Hz, 1H), 4.66 (d, J = 5.1 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 158.7 (dd, $^{1}J_{CF}$ = 259.5 Hz, $^{3}J_{CF}$ = 5.1 Hz), 157.5, 156.2 (dd, $^{1}J_{CF}$ = 262.4 Hz, $^{3}J_{CF}$ = 6.1 Hz), 139.6 (dd, $^{2}J_{CF}$ = 15.8 Hz, $^{4}J_{CF}$ = 3.7 Hz), 133.1 (dd, $^{2}J_{CF}$ = 23.2 Hz, $^{4}J_{CF}$ = 4.8 Hz), 111.6 (t, $^{2}J_{CF}$ = 21.2 Hz), 84.5, 38.9, 27.7; HRMS calcd for $C_{12}H_{14}F_2N_2NaO_3$ $(M + Na)^+$, 295.0865, found 295.0871.

***tert*-butyl *N*-((3, 5-difluoro-1-oxy-pyridin-2-yl)methyl)oxamate (L7c):** The procedure was the same as described above for the synthesis of **L3c**. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br, 1H), 8.11 (t, J = 1.8 Hz, 1H), 7.00 (td, J_1 = 7.8 Hz, J_2 = 1.9 Hz, 1H), 4.71 (d, J = 5.7 Hz, 2H), 1.52 (d, J = 1.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (dd, $^{1}J_{CF}$ = 251. 9 Hz, $^{3}J_{CF}$ = 15.5 Hz), 158.8, 158.1 (dd, $^{1}J_{CF}$ = 253.4 Hz, $^{3}J_{CF}$ = 15.0 Hz), 157.7, 134.8 (dd, $^{2}J_{CF}$ = 36.5 Hz, $^{4}J_{CF}$ = 9.4 Hz), 126.7 (dd, $^{2}J_{CF}$ = 36.0 Hz, $^{4}J_{CF}$ = 5.0 Hz), 103.9 (t, $^{2}J_{CF}$ = 24.2 Hz), 84.5, 32.7, 27.6; HRMS calcd for $C_{12}H_{15}F_2N_2O_4$ $(M + H)^+$, 289.0994, found 289.1002.

***N*-((3, 5-Difluoro-1-oxy-pyridin-2-yl)methyl)oxalamic acid (L7):** The procedure was the same as described above for the synthesis of **L3**. White solid; m.p. 183-184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.99 (br, 1H), 8.98 (s, 1H), 8.62 (s, 1H), 7.69 (t, J = 8.8 Hz, 1H), 4.48 (d, J =

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2.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5, 158.8 (dd, $^1J_{CF}$ = 246.5 Hz, $^3J_{CF}$ = 17.7 Hz), 158.4 (dd, $^1J_{CF}$ = 248.9 Hz, $^3J_{CF}$ = 15.6 Hz), 158.3, 134.7 (dd, $^2J_{CF}$ = 26.8 Hz, $^4J_{CF}$ = 5.1 Hz), 126.6 (dd, $^2J_{CF}$ = 36.8 Hz, $^4J_{CF}$ = 5.0 Hz), 103.5 (t, $^2J_{CF}$ = 25.2 Hz), 32.5; HRMS calcd for $C_8H_7F_2N_2O_4$ $(M + H)^+$, 233.0368, found 233.0378.

Ethyl *N*-(2-chlorobenzyl)oxamate (L8b): To a magnetically stirred solution of the 2-chlorobenzylamine (2.40 g, 17.0 mmol) and triethylamine (2.63 g, 26.0 mmol) in CH_2Cl_2 (60 mL) was added, dropwise, a solution of ethyl oxalyl monochloride (2.32 g, 17.0 mmol) in CH_2Cl_2 (10 mL). After it was stirred for 2 h, the mixture was diluted with 30 ml CH_2Cl_2 and then washed with water and brine。The organic phase was dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel chromatography and then recrystallized from PE/EA to give the amide as white solid (3.36 g, 13.9 mmol, 81.8%). White solid; m.p. 55-57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (br, 1H), 7.43-7.34 (m, 2H), 7.30-7.21 (m, 2H), δ 4.62 (d, J = 6.3 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), δ 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 156.5, 134.2, 133.8, 130.4, 129.7, 129.4, 127.2, 63.3, 41.8, 14.0; HRMS calcd for $C_{11}H_{11}ClNO_3$ $(M - H)^-$, 240.0433, found 240.0439.

***N*-(2-Chlorobenzyl)oxalamic acid (L8):** To a magnetically stirred solution of the above product (2.80 g, 11.6 mmol) in a mixture of THF (15 ml) and water (15 ml) was added NaOH (974 mg 17.4 mmol) slowly. After it was stirred for 2 h at room temperature, the mixture was diluted with water (40 ml) and then washed with ethyl acetate (20 ml). The aqueous layer was extracted with ethyl acetate after acidified by adding *conc.* HCl (4 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. The crude product was recrystallized from PE/EA to give **L8** as white solid (2.20 g, 10.3 mmol, 88.8%). White solid; m.p. 136-138 °C; ^{1}H

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NMR (300 MHz, DMSO-d_6) δ 16.00-12.00 (br, 1H), 9.37 (d, J = 5.9 Hz, 1H), 7.50-7.40 (m, 1H), 7.38-7.24 (m, 3H), δ 4.42 (d, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.9, 158.7, 135.2, 131.8, 129.1, 128.7, 128.5, 127.1, 40.3; HRMS calcd for $C_9H_9ClNO_3$ $(M + H)^+$, 214.0265, found 214.0272.

***tert*-Butyl *N*-methyl-*N*-(pyridin-2-ylmethyl)oxamate (L10b):** An oven dried two-necked flask was charged with **L11** (944 mg, 4.0 mmol) and a magnetic stir bar, and the flask was fitted with a rubber septum. The vessel was evacuated and back filled with nitrogen, and this sequence was repeated additional two times. Anhydrous THF (30 mL) and MeI (1.14 g, 8.0 mmol) were then added successively. NaH (65%, 220 mg, 6.0 mmol) was added slowly in ice-water bath and the reaction mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ solution was added very slowly to quench the reaction and 20 mL DCM and 20 mL H_2O was then added to the mixture. Organic layer was separated, washed with brine, dried over Na_2SO_4 and then concentrated. The crude product was purified with silica gel chromatography to give **L10b** (690 mg, 2.74 mmol, 68.4%). Yellowish solid; m.p. 75-78 °C; the product was analyzed as a about 1:1 mixture of rotamers (25°C); ^{1}H NMR (300 MHz, $CDCl_3$) for the major rotamer: δ 8.56 (t, J = 6.2 Hz, 1H), 7.69 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 4.70 (s, 2H), 3.04 (s, 3H), 1.58 (s, 9H); ^{1}H NMR (300 MHz, $CDCl_3$) for the major rotamer: δ 8.56 (t, J = 6.2 Hz, 1H), 7.73 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 4.61 (s, 2H), 2.96 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 162.42, 162.37, 162.32, 155.9, 155.8, 149.5, 149.2, 137.1, 137.0, 122.8, 122.7, 122.3, 121.3, 84.52, 84.45, 55.4, 51.7, 35.3, 32.3, 27.9, 27.8; HRMS calcd for $C_{13}H_{19}N_2O_3$ $(M - H)^-$, 251.1390, found 251.1395.

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***tert*-Butyl *N*-methyl-*N*-((1-oxy-pyridin-2-yl)methyl)oxamate (L10c):** The procedure was the same as described above for the synthesis of **L3c**. White solid; m.p. 117-119 °C; the product was analyzed as a 5:4 mixture of rotamers (25°C). ^{1}H NMR (300 MHz, $CDCl_3$) for the major rotamer: δ 8.29 (t, J = 5.9 Hz, 1H), 7.40-7.21 (m, 3H), 4.81 (s, 2H), 3.21 (s, 3H), 1.59 (s, 9H); ^{1}H NMR (300 MHz, $CDCl_3$) for the minor rotamer: δ 8.29 (t, J = 5.9 Hz, 1H), 7.40-7.21 (m, 3H), 4.77 (s, 2H), 3.04 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 162.9, 162.0, 161.6, 146.7, 146.3, 139.6, 126.0, 125.8, 125.4, 124.8, 124.7, 123.7, 84.9, 84.8, 49.1, 45.9, 36.8, 33.2, 27.9, 27.8; HRMS calcd for $C_{13}H_{19}N_2O_4$ $(M + H)^+$, 267.1339, found 267.1341.

***N*-methyl-*N*-((1-Oxy-pyridin-2-yl)methyl)oxalamic acid (L10):** The procedure was the same as described above for the synthesis of **L3**. White solid; m.p. 156-158 °C; the product was analyzed as a 7:5 mixture of rotamers (25°C). ^{1}H NMR (300 MHz, DMSO-d_6) for the major rotamer: δ 14.4 (br, 1H), 8.34 (d, J = 2.8 Hz, 1H), 7.60-7.36 (m, 2H), 7.18 (t, J = 4.6 Hz, 1H), 4.60 (s, 2H), 3.10 (s, 3H); ^{1}H NMR (300 MHz, DMSO-d_6) for the minor rotamer: 14.4 (br, 1H), 8.34 (d, J = 2.8 Hz, 1H), 7.60-7.36 (m, 2H), 7.33 (t, J = 5.0 Hz, 1H), 4.68 (s, 2H), 2.91 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.5, 164.1, 163.5, 163.4, 145.9, 145.5, 139.3, 139.2, 125.6, 125.4, 125.3, 125.0, 124.3, 123.6, 48.5, 45.3, 36.0, 32.3; HRMS calcd for $C_9H_{10}N_2NaO_4$ $(M + Na)^+$, 233.0533, found 233.0538.

N-(pyridin-2-ylmethyl)acetmide (L11a): The procedure was the same as described above for the synthesis of **L3b**. ^{1}H NMR (300 MHz, $CDCl_3$) 8.52 (d, J = 4.5 Hz, 1H), 7.67 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.20 (dd, J_1 = 7.0 Hz, J_2 = 5.5 Hz, 1H), 7.11 (br, 1H), 4.55 (d, J = 5.0 Hz, 2H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 156.5, 148.9, 136.9, 122.4, 122.2, 44.5, 23.1; ESI-MS m/z 173.1 $(M + Na)^+$.

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N-((1-oxy-pyridin-2-yl)methyl)acetmide (L11): The procedure was the same as described above for the synthesis of **L3c**. ^{1}H NMR (300 MHz, $CDCl_3$) 8.25 (dd, J_1 = 5.4 Hz, J_1 = 1.7 Hz, 1H), 7.51-7.36 (m, 2H), 7.34-7.22 (m, 2H), 4.61 (d, J = 6.2 Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 147.2, 138.9, 125.9, 124.5, 38.9, 22.6; HRMS calcd for $C_8H_{11}N_2O_3$ $(M + H)^+$, 167.0815, found 167.0816.

General Procedure for the reactions in DMSO. A reaction tube was charged with CuI (2-2.5 mol %), **L**igand (4-5 mol %), azole (solid, 1.4 equiv), aryl iodide (solid, 1 mmol), K_3PO_4 (2 mmol) and a magnetic stir bar, and the reaction tube was fitted with a rubber septum. The vessel was evacuated and back filled with nitrogen, and this sequence was repeated additional two times. Azole (liquid, 1.4 equiv), aryl iodide (liquid, 1 mmol) and DMSO (1 mL) were then added successively. The reaction tube was sealed and stirred in an oil bath at 90 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with 20 ml water, and extracted with 2*20 ml EA. The organic layer was combined, washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatograph using a mixture of PE and EA to give the desired product. Representative examples are as follows.

1-(4-Methoxyphenyl)-1*H*-imidazole (1a, 3a, 4a):[18] Yellowish solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.28 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 7.17 (s, 1H), 6.96 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 135.8, 130.6, 130.0, 123.1, 118.7, 114.8, 55.5; ESI-MS m/z 175.1 $(M + H)^+$.

1-(4-Methoxyphenyl)-1*H*-pyrazole (2a, **5i):**[10b,18a,b] Light brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 2.2 Hz, 1H), 7.69 (d, J = 1.1 Hz, 1H), 7.57 (d, J = 9.0 Hz, 2H), 6.95 (d, J =

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9.0 Hz, 2H), 6.41 (t, J = 2.1 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 140.6, 134.0, 126.8, 120.8, 114.5, 107.2, 55.5; ESI-MS m/z 175.1 $(M + H)^+$.

1-(4-Methoxyphenyl)-1*H*-pyrrole (3b):[19] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.9 Hz, 2H), 6.98 (t, J = 1.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.31 (t, J = 1.9 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 134.5, 122.2, 119.7, 114.7, 109.9, 55.6; ESI-MS m/z 174.1 $(M + H)^+$.

1-(4-Methoxyphenyl)-1*H*-indole (3c):[12a] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J_1 = 7.0 Hz, J_2 = 1.1 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.9 Hz, 2H), 7.24 (d, J = 3.2 Hz , 1H), 7.22-7.10 (m, 2H), 6.98 (d, J = 8.9 Hz , 2H), 6.45 (d, J = 2.9 Hz , 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 136.4, 132.9, 129.0, 128.4, 126.0, 122.2, 121.1, 120.2, 114.8, 110.4, 103.0, 55.6; ESI-MS m/z 224.1 $(M + H)^+$.

1-Phenyl-1*H*-benzimidazole (3d):[18b] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.92-7.84 (m, 1H), 7.60-7.40 (m, 6H), 7.37-7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 142.3, 136.3, 133.7, 130.1, 128.0, 124.0, 123.7, 122.8, 120.6, 110.5; ESI-MS m/z 217.1 $(M + Na)^+$.

2-Amino-1-phenyl-1*H*-benzimidazole (3e):[8c] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.48 (m, 2H), 7.48-7.34 (m, 4H), 7.15-7.05 (m, 1H), 7.01-6.92 (m, 2H), 5.84 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 142.3, 135.0, 134.9, 130.3, 128.7, 126.7, 122.0, 119.9, 116.1, 108.3; ESI-MS m/z 210.1 $(M + H)^+$.

General Procedure for the reactions in water. A schlenk tube was charged with CuI (5 mol %), **L**igand (10 mol %), azole (solid, 1.4 equiv), aryl halide (solid, 1 mmol), base (2 mol), additive

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(0.1-0.2 equvi) and a magnetic stir bar, and the reaction tube was fitted with a rubber septum. The vessel was evacuated and back filled with nitrogen, and this sequence was repeated additional two times. Aryl halide (liquid, 1 mol), azole (liquid, 1.4 equiv) and solvent (1 mL) were then added successively. The reaction tube was sealed and stirred in an oil bath for 6-48 hours. The reaction mixture was then cooled to room temperature, diluted with 20 ml water, and extracted with 2*20 ml. The organic layer was combined, washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatograph using a mixture of PE and EA to give the desired product. Representative examples are as follows.

1-Phenyl-1*H*-imidazole (4b):[3f,12a,18,19] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.42-7.32 (m, 3H), 7.28 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 135.5, 130.3, 129.9, 127.5, 121.4, 118.2; ESI-MS m/z 145.0 $(M + H)^+$.

1-(4-Methylphenyl)-1*H*-imidazole (4c):[18a,b,20] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.19-7.12 (m, 5H), 7.09 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.6, 134.9, 130.3, 130.1, 121.4, 118.3, 20.9; ESI-MS m/z 159.1 $(M + H)^+$.

1-(4-Fluorophenyl)-1*H*-imidazole (4d):[21] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.42-7.31 (m, 2H), 7.23 (s, 1H), 7.21-7.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (d, $^1J_{CF}$ = 245.8 Hz), 135.6, 133.5, 130.3, 123.3 (d, $^3J_{CF}$ = 8.5 Hz), 118.5, 116.6 (d, $^2J_{CF}$ = 22.8 Hz); ESI-MS m/z 163.1 $(M + H)^+$.

Ethyl 4-(imidazol-1-yl)benzoate (4e):[3f,18a,20c] White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 2H), 7.97 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.37 (s, 1H), 7.25 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 140.6, 135.4, 131.4,

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131.0, 129.3, 120.5, 117.8, 61.3, 14.3; ESI-MS m/z 217.1 $(M + H)^+$.

4-(1*H*-Imidazol-1-yl)aniline (4f):[18a] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.19-7.09 (m, 4H), 6.73 (d, J = 8.5 Hz, 2H), 3.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 135.9, 129.7, 128.7, 123.3, 118.9, 115.5; ESI-MS m/z 160.1 $(M + H)^+$.

3-(1*H*-Imidazol-1-yl)phenol (4g):[22] Pale pink solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.20 (s, 1H), 7.68 (s, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.10 (s, 1H), 7.05 (dd, J_1 = 8.0 Hz, J_1 = 1.3 Hz, 1H), 7.01 (t, J = 2.1 Hz, 1H), 6.79 (dd, J_1 = 8.1 Hz, J_1 = 1.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.0, 138.5, 135.9, 131.1, 130.2, 118.5, 114.4, 111.4, 108.0; ESI-MS m/z 161.1 $(M + H)^+$.

1-(Thiophen-3-yl)-1*H*-imidazole (4h):[20b] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.42 (dd, J_1 = 5.1 Hz, J_2 = 3.2 Hz, 1H), 7.23 (s, 1H), 7.22-7.13 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 135.8, 130.0, 127.2, 121.4, 118.5, 113.2; ESI-MS m/z 151.1 $(M + H)^+$.

1-(4-(1*H*-Imidazol-1-yl)phenyl)enthanone (4i):[3f,18b,c] Yellowish soild; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.5 Hz, 2H), 7.97 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.38 (s, 1H), 7.24 (s, 1H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 140.7, 135.7, 135.3, 131.1, 130.3, 120.6, 117.7, 26.6; ESI-MS m/z 187.1 $(M + H)^+$.

1-(3-Methoxyphenyl)-1*H*-imidazole (4j):[22,23] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.35 (t, J = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 6.95 (d, J_1 = 8.6 Hz, 1H), 6.92-6.84 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 138.4, 135.5, 130.6, 130.2, 118.2, 113.5, 112.6, 107.6, 55.7; ESI-MS m/z 175.1 $(M + H)^+$.

1-(pyridin-2-yl)-1*H*-imidazole (4k):[8b,18b,c] Yellowish oil; ^{1}H NMR (300 MHz, CDCl3) δ 8.44 (d, J = 3.9 Hz, 1H), 8.37 (s, 1H), 7.79 (td, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 7.65 (s, 1H), 7.35 (d,

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J = 8.2 Hz, 1H), 7.27-7.15 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 148.9, 138.9, 134.8, 130.4, 121.9, 116.1, 112.2; ESI-MS m/z 146.1 $(M + H)^+$.

1-(pyridin-3-yl)-1*H*-imidazole (4l):[24] Yellowish oil; ^{1}H NMR (300 MHz, CDCl3) δ 8.76 (d, J_1 = 2.5 Hz, 1H), 8.64 (dd, J_1 = .7 z, J_2 = 1.1 Hz, 1H), 7.92 (s, 1H), 7.81-7.73 (m, 1H), 7.47 (dd, J_1 = 8.2 Hz, J_2 = 4.8 Hz 1H), 7.34 (s, 1H), 7.26 (s, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 148.7, 142.7, 135.4, 133.8, 130.9, 128.9, 124.3, 118.1; ESI-MS m/z 146.1 $(M + H)^+$.

1-(2-Methoxyphenyl)-1*H*-imidazole (4m):[18a,22] Yellowish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.33 (td, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.23 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 7.08-6.96 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 137.7, 128.9, 128.6, 126.3, 125.4, 121.0, 120.2, 112.3, 55.7; ESI-MS m/z 175.1 $(M + H)^+$.

1-(4-Nitrophenyl)-1*H*-imidazole (4n):[18c,25] Yellowish solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.36 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 9.1 Hz, 2H), 7.96 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.7, 142.1, 136.5, 131.2, 125.9, 120.8, 118.3; ESI-MS m/z 190.1 $(M + H)^+$.

4-methyl-1-(4-Methoxyphenyl)-1*H*-imidazole (5a):[18a] A mixture of regioisomers of N^1-and N^3-substituted products as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) for the N^3-substituted products δ 7.66 (s, 1H), 7.31-7.23 (m, 2H), 7.02-6.90 (m, 3H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 139.1, 134.8, 127.0, 122.8, 114.8, 114.6, 55.6, 13.6; ESI-MS m/z 189.1 $(M + H)^+$.

2-Methyl-1-phenyl-1*H*-imidazole (5b):[26] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.36 (m, 3H), 7.26 (d, *J* = 7.1 Hz, 2H), 7.01 (s, 1H), 6.98 (s, 1H), 2.35(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 137.9, 129.4, 128.1, 127.5, 125.4, 120.5, 13.6; ESI-MS m/z 159.1 (M +

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H)$^+$.

2-Acetyl-1-(pyridin-2-yl)-1*H*-pyrrole (5c): Light brown solid; m.p. 67-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.14 (m, 2H), 7.07 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 6.96-6.87 (m, 3H), 6.27 (dd, J_1 = 3.9 Hz, J_2 = 2.6 Hz, 1H), 3.84 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 158.9, 133.9, 131.7, 131.3, 127.2, 120.2, 113.8, 108.9, 55.5, 27.3; HRMS calcd for $C_{13}H_{14}NO_2$ (M + H)$^+$, 216.1019, found 216.1022.

1-Phenyl-1*H*-indazole (5d):[27] White solid; m.p. 75-77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.84-7.66 (m, 4H), 7.51 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 138.8, 135.5, 129.5, 127.2, 126.7, 125.4, 122.8, 121.6, 121.4, 110.5; HRMS calcd for $C_{13}H_{11}N_2$ (M + H)$^+$, 195.0917, found 195.0919.

1-Phenyl-1*H*-indole (5e):[8b,12a] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.50-7.43 (m, 4H), 7.36-7.26 (m, 2H), 7.25-7.11 (m, 2H), 6.66 (d, J = 3.2 Hz , 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 136.0, 129.7, 129.4, 128.0, 126.5, 124.4, 122.4, 121.2, 120.4, 110.6, 103.6; ESI-MS m/z 194.1 (M + H)$^+$.

6-Fluoro-1-phenyl-1*H*-indole (5g):[28] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, J_1 = 8.6 Hz, J_2 = 5.4 Hz, 1H), 7.47-7.33 (m, 4H), 7.33-7.16 (m, 3H), 6.91 (td, J_1 = 9.3 Hz, J_2 = 2.3 Hz, 1H), 6.62 (d, J = 3.2 Hz , 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (d, $^1J_{CF}$ = 236.5 Hz), 139.6, 136.0 (d, $^3J_{CF}$ = 11.8 Hz), 129.8, 128.5 (d, $^4J_{CF}$ = 3.7 Hz), 126.8, 125.9, 124.3, 122.0 (d, $^3J_{CF}$ = 10.1 Hz), 109.2 (d, $^2J_{CF}$ = 24.5 Hz), 103.8, 97.2 (d, $^2J_{CF}$ = 26.8 Hz); HRMS calcd for $C_{14}H_{11}FN$ (M + H)$^+$, 212.0870, found 212.0865.

1-Phenyl-1*H*-pyrazole (5h):[12a,18b] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J =

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2.3 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.66 (s, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 6.43 (t, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 140.2, 129.4, 126.8, 126.5, 119.2, 107.6; ESI-MS m/z 145.1 $(M + H)^+$.

1-(Pyridin-2-yl)-1*H*-benzimidazole (5j):[8b,18b,c,20b] Pink solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 2H), 8.03 (dd, J_1 =5.4 Hz, J_2 = 2.4 Hz, 1H), 7.89-7.77 (m, 2H), 7.50 (d, J = 8.2 Hz, 1H), 7.40-7.28 (m, 2H), 7.23 (dd, J_1 =7.3 Hz, J_2 = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 149.4, 144.6, 141.3, 138.9, 132.1, 124.2, 123.3, 121.8, 120.6, 114.3, 112.7; ESI-MS m/z 196.1 $(M + H)^+$.

2-Methyl-1-(pyridin-2-yl)-1*H*-imidazole (5k):[8b,10c] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 3.7 Hz, 1H), 7.86 (t, J = 7.4 Hz, 2H), 7.38-7.24 (m, 3H), 7.03 (s, 1H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 149.1, 144.9, 138.7, 127.9, 122.3, 118.9, 117.2, 15.3; ESI-MS m/z 160.1 $(M + H)^+$.

2-Acetyl-1-(pyridin-2-yl)-1*H*-pyrrole (5l): Yellowish solid; m.p. 55-57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 3.6 Hz,, 1H), 7.75 (td, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1H), 7.34-7.20 (m, 3H), 7.11 (dd, J_1 = 3.8 Hz, J_2 = 1.4 Hz, 1H), 6.32 (t, J = 3.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 152.5, 148.4, 137.6, 131.5 130.4, 122.7, 121.5, 120.7, 109.8, 27.1; HRMS calcd for $C_{11}H_{11}N_2O$ $(M + H)^+$, 187.0866, found 187.0868.

1-(3-Methoxy-phenyl)-1*H*-indazole (5m):[20a] White solid. m.p. 87-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 0.5 Hz, 1H), 7.76 (dd, J_1 = 9.2 Hz, J_2 = 1.2 Hz, 2H), 7.45-7.35 (m, 1H), 7.35-7.26 (m, 2H), 7.19 (t, J = 8.0 Hz, 1H), 6.92-6.83 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 141.3, 138.8, 135.4, 130.2, 127.2, 125.4, 121.6, 121.4, 114.7, 112.6, 110.6, 108.4, 55.5; HRMS calcd for $C_{14}H_{13}N_2O$ $(M + H)^+$, 225.1022, found 225.1022.

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6-Fluoro-1-(pyridin-3-yl)-1*H*-indole (5n): Light brown solid; m.p. 81-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 2.0 Hz, 1H), δ 8.60 (d, J = 3.8 Hz, 1H), δ 7.76 (d, J = 8.0 Hz, 1H), 7.57 (dd, J_1 = 8.6 Hz, J_2 = 5.4 Hz, 1H), 7.43 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H), δ 7.27 (d, J = 3.2 Hz, 1H), 7.17 (dd, J_1 = 9.8 Hz, J_2 = 1.2 Hz, 1H), 6.94 (td, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1H), δ 6.68 (d, J = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (d, $^1J_{CF}$ = 237.8 Hz), 147.9, 145.5, 136.1, 135.8 (d, $^3J_{CF}$ = 12.2 Hz), 131.2, 127.9 (d, $^4J_{CF}$ = 3.7 Hz), 125.9, 124.2, 122.2 (d, $^3J_{CF}$ = 9.9 Hz), 109.7 (d, $^2J_{CF}$ = 24.3 Hz), 104.8, 96.7 (d, $^2J_{CF}$ = 27.0 Hz); HRMS calcd for $C_{13}H_{10}FN_2$ $(M + H)^+$, 213.0823, found 213.0824.

3-(1*H*-pyrazol-1-yl)phenol (5o): White solid; m.p. 120-122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.43 (d, J = 2.3 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.32-7.22 (m, 3H), 6.76-6.69 (m, 1H), 6.52 (t, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 141.3, 141.2, 130.7, 128.1, 113.7, 109.3, 108.1, 106.1; HRMS calcd for $C_9H_9N_2O$ $(M + H)^+$, 161.0709, found 161.0708.

1-(Pyridin-3-yl)-1*H*-pyrazole (5p):[24] Yellowish solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 4.3 Hz, 1H), 8.11-8.03 (m, 1H), 7.97 (d, J = 2.4 Hz, 2H), 7.77 (d, J = 1.0 Hz, 2H), 7.41 (dd, J_1 = 8.3 Hz, J_2 = 4.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 141.9, 140.5, 136.5, 126.8, 126.5, 123.9, 108.4; ESI-MS m/z 146.1 $(M + H)^+$.

1-(Pyridin-2-yl)-1*H*-pyrazole (5q):[18c,24] Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 2.4 Hz, 1H), 8.38 (d, J = 4.0 Hz, 1H), 7.97 (d, J = 8.3 Hz 1H), 7.83-7.69 (m, 2H), 7.14 (dd, J_1 = 7.2 Hz, J_1 = 5.6 Hz 1H), 6.45 (t, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 148.0, 142.0, 138.6, 127.0, 121.3, 112.4, 107.8; ESI-MS m/z 168.0 $(M + Na)^+$.

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Supplementary Information: ^{1}H NMR and ^{13}C NMR spectra of all compounds.

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