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An efficient D-glucosamine-based copper catalyst for C-X couplings and its application in the synthesis of Nilotinib intermediate

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D-glucosamine has been studied for C-N and C-S bond formations *via* cross-coupling reactions of nitrogen and sulfur nucleophiles with both aryl iodides and bromides. Imidazoles, benzimidazole, indole, pyrrole and diphenyl disulfide undergo reactions with aryl halides in the presence of 10 mol% D-glucosamine, 10 mol% CuI, 2 equive of Cs_2CO_3 in DMSO-H_2O at moderate temperature to give the corresponding products in good to excellent yields. Substrates bearing halides, free amino, trifuoromethyl and heterocycles were well tolerate. The high water solubility of the ligand enables easy catalyst removal. In addition, the application of this catalytic system to the synthesis of Nilotinib intermediate was also successfully demonstrated using commercially available substrates.

Introduction

The method of building the carbon-heteroatom structure has long been a hot topic in the field of organic synthesis because of its widely existing in the natural products which has biological activities, drug and polymer materials.[1-4] During the past few decades, many efforts from different groups have led to the discovery of a wide variety of Pd-catalyzed methods for the formation of carbon-heteroatom bonds.[5-6] Although such coupling reaction has high efficiency, the high price of Pd and the bigger toxicity of Pd hindered the application of cross-coupling reaction on many occasions. In the context of advocacy of green chemistry in the 21st century, copper catalysts showed attractive advantages to us which were cheap and low toxicity.[7-8] They make the applicability of the reaction higher and avoid the phenomenon of the shift of double bonds which was caused by the eliminating of β-H when catalytic coupling by the Pd catalyst. At present, the C-N coupling catalyzed by copper has achieved fruitful results,[9-14] but some reactions often suffer from several drawbacks such as the use of stoichiometric copper catalysts, the high polarity and toxicity solvents, harsh reaction conditions, and special ligands including phenanthrolines,[15] amino acids,[16] diketones,[17] diamines,[18] oximes,[19] carbohydrates[20] and others,[21] some conditions above not only cause great waste, but also pollute the environment we live by.

D-glucosamine has been selected as a cheap and readily available chiral scaffold for the synthesis of a series of novel ligands and organocatalysts because of its excellent advantages that green and environmental protection, economic and efficient.[22-23] The design and fine-tuning of carbohydrate-based ligands are facilitated by the multiple functional groups within this class of compounds.[24-27] In preliminary communication,[28] we reported the catalysis of chitosan(CS) for the cross-coupling reactions of aryl halides and sodium sulfinates, which provides a simple and extremely efficient new route to unsymmetrical diaryl sulfones. These features led us to further study the scope of the D-glucosamine for the catalysis of the carbon-heteroatom cross-coupling reactions.[29]

In this paper, we describe an efficient D-glucosamine-based catalytic system for C-N and C-S bond formations *via* cross-coupling reactions of nitrogen and sulfur nucleophiles with both aryl iodides and bromides. Imidazoles, benzimidazole, indole, pyrrole and diphenyl disulfide undergo reactions with aryl halides in the presence of 10 mol% CuI, 2 equive of Cs_2CO_3 in DMSO-H_2O at moderate temperature using 10 mol% D-Glucosamine as a green ligand. In addition, the application of this catalytic system to the synthesis of Nilotinib intermediate is also successfully demonstrated using commercially available substrates.

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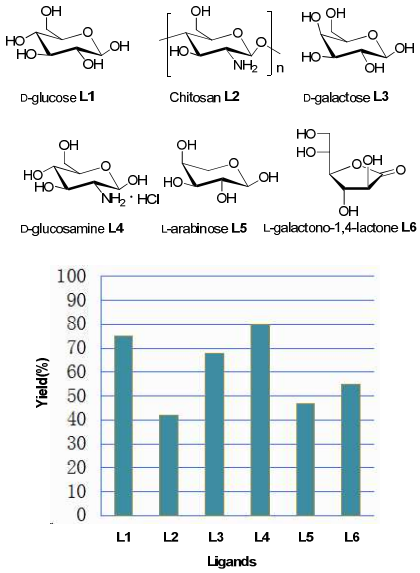
† Electronic Supplementary Information (ESI) available: ^{1}H NMR spectra, ^{13}C NMR spectrum, GC/MS profile, HRMS profile. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Results and discussion

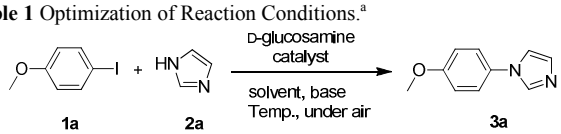
At first, 4-iodoanisole (**1a**) and imidazole (**2a**) were selected as the model substrates and screened a series of natural ligands under the conditions of 10 mol% CuI, 10 mol% ligand, 2 equive of K_2CO_3 as the base and DMSO-H_2O (3 mL, 1:1) mixture as the solvent at 100 ℃ for 10 h. D-glucose **L1** was used as ligand firstly, the desired product **3a** was obtained in 75% yield. Chitosan **L2** only gave the product in 42% yield due to poor solubility. Then, other monosaccharide molecules such as D-galactose **L3**, D-glucos- amine **L4**, L-arabinose **L5** and L-galactono-1,4-lactone **L6** were investigated (Scheme 1). According to the results in Scheme 1, it was obvious that D-glucosamine was the most efficient ligand examined and gave the coupling product in 80% yield under air.



Scheme 1. Ligand comparison in Cu-catalyzed *N*-arylation of imidazole with 4-iodoanisole. (Reaction conditions: 4-iodoanisole **1a** (1.0 mmol), imidazole **2a** (1.2 mmol), CuI (0.1 mmol), ligand (0.1 mmol), K_2CO_3 (2.0 mmol), DMSO-H_2O (3 mL, 1:1), under air, 10 h.)

Next, several catalysts, organic solvent/H_2O (1:1) mixtures, bases and temperatures were screened for this reaction. With D-glucosamine as ligand, different kinds of copper sources were screened under other identical conditions. Only 16% yield was obtained without ligand (Table 1, entry 1). Compared with the catalytic effect of CuI, the other copper sources, such as CuBr, $CuBr_2$ and CuF_2 and $Cu(OAc)_2{\cdot}H_2O$ showed slightly lower catalytic activities (Table 1, entries 1-5). No C-N coupling product was obtained when the reaction was carried out with $Pd(OAc)_2$ as catalyst (Table 1, entry 6). The reactions were free from the formation of homocoupled biaryl compound, and the controlled experiments without D-glucosamine showed no reaction (Table 1, entry 7). Besides DMSO, DMF, THF and CH_3CN were further surveyed, nevertheless, the solvents were not good choices here and the yields were comparatively lower(Table 1, entries 8-10). Next, several bases such as Cs_2CO_3, KOH, NaOH, Na_2CO_3 and LiOH were screened for this coupling reaction. Fortunately, we found the desired product **3a** was obtained in 90% yield with the Cs_2CO_3 as the base (Table 1, entry 11). While checking the minimum requirement of catalyst loading for the best performance of the reaction, it has been found that decreasing the catalyst loading will affect the yield of the product. For example, when 5 mol% of **L5** was used, only 71% yield was achieved. Finally, the reaction temperature were screened for this reaction. When the reaction was performed at 60 or 80 °C, the reaction was found to be inefficient (Table 1, entries 16 and 17).When the reaction temperature was increase the temperature to 120 ℃ under other identical conditions, the yield was very similar to the former that 100 ℃ was the optimum condition of reaction temperature(Table 1, entry 18).

Table 1 Optimization of Reaction Conditions.[a]



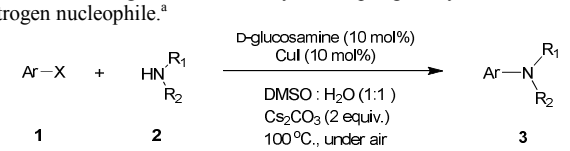
Entry	Catalyst (10 mol)	Solvent :H_2O(1:1)	Base (2equiv)	Temp [°C]	Yield (%)[b]
1	CuI	DMSO	K_2CO_3	100	80(16)[c]
2	CuBr	DMSO	K_2CO_3	100	55
3	$CuBr_2$	DMSO	K_2CO_3	100	64
4	CuF_2	DMSO	K_2CO_3	100	54
5	Cu(OAc)	DMSO	K_2CO_3	100	7
6	$Pd(OAc)_2$	DMSO	K_2CO_3	100	trace
7	-	DMSO	K_2CO_3	100	0
8	CuI	DMF	K_2CO_3	100	13
9	CuI	THF	K_2CO_3	100	14
10	CuI	CH_3CN	K_2CO_3	100	trace
11	**CuI**	**DMSO**	**Cs_2CO_3**	**100**	**90(71)**[d]
12	CuI	DMSO	KOH	100	67
13	CuI	DMSO	NaOH	100	84
14	CuI	DMSO	Na_2CO_3	100	39
15	CuI	DMSO	LiOH	100	55
16	CuI	DMSO	Cs_2CO_3	60	67
17	CuI	DMSO	Cs_2CO_3	80	72
18	CuI	DMSO	Cs_2CO_3	120	88

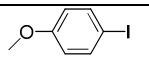
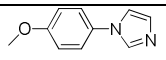
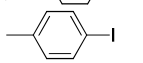
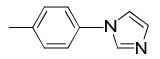
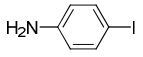
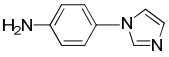
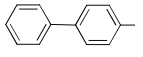
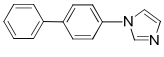
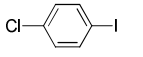
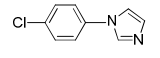
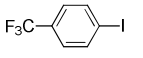
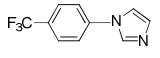
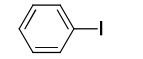
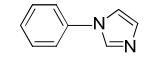
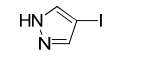
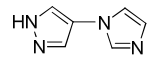
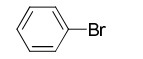
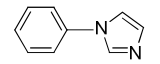
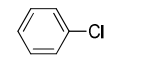
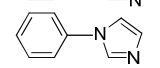
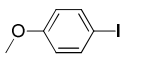
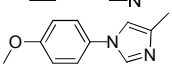
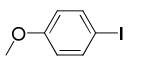
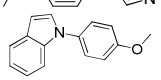
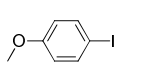
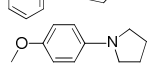
[a] Reaction conditions: 4-iodoanisole **1a** (1.0 mmol), imidazole **2a** (1.2 mmol), CuI (0.1 mmol), D-glucosamine (0.1 mmol), base (2.0 mmol), solvent : H_2O (3.0 mL 1:1), under air, 10 h. [b] GC-MS yield. [c] Without ligand. [d] 5 mol% of D-glucosamine was used.

With the optimized reaction conditions in hand (DMSO:H_2O(1:1) as solvent, 10 mol% of D-glucosamine as ligand, 10 mol% of CuI as catalyst, 2 equiv of Cs_2CO_3 as base, and completing the reaction at 100 ℃ under air, 10 h.), we initiated our investigation into the scope of the D-glucosamine catalyzed coupling of aryl halides and nitrogen nucleophile and the results were summarized in Table 2. The results showed that good yields were obtained for the coupling of aryl iodides with imidazole (Table 2, entries 1-7). In general, aryl iodides bearing electron-withdrawing groups, such as -CF_3 and -Cl were more reactive than aryl iodides bearing electron-donating groups, such as -OMe, -Me and -NH_2, which afforded the corresponding *N*-arylated imidazoles in lower yields. For example, the reaction of 1-trifluoromethyl-4-iodoben zene and imidazole proceeded with 87% isolated yield (Table 2, entry 6), where as the inactive 4-iodoaniline required more than 24 h reaction time to give the

corresponding product in 70% isolated yield (Table 2, entry 3). Next the coupling of imidazole with

Table 2 CuI/D-glucosamine-catalyzed coupling of aryl halides and nitrogen nucleophile.[a]



Entry	Aryl halides	Nitrogen nucleophile	Product	Yield (%)[b]
1				84**(3a)**
2				81**(3b)**
3				70**(3c)**[c]
4				71**(3d)**
5				86**(3e)**
6				87**(3f)**
7				82**(3g)**
8				70**(3h)**
9				82**(3g)**[c]
10				n.r.[d]
11				70**(3i)**
12				72**(3j)**
13				55**(3k)**
14				72**(3l)**

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), CuI (0.1 mmol), D-glucosamine (0.1 mmol), Cs_2CO_3 (2.0 mmol), DMSO: H_2O (3.0 mL 1:1), under air.[b] Isolated yield.[c] 24 h.[d] No reaction.

4-iodo-pyrazole was examined using the same optimized conditions. 4-iodo-pyrazole gave the product in 70% isolated yield (Table 2, entry 8). Fortunately, it was found that bromobenzene worked well, affording the corresponding product in satisfactory yield (Table 2, entry 9). However, the *N*-arylation of imidazole with chlorobenzene was unsuccessful under the same conditions (Table 1, entry 10). We also employed 4-methylimidzaole as a nucleophilic reagent, it only gave a moderate yield (Table 2, entry 11). Further experiments with different nitrogen nucleophile such as indole and pyrrole were carried out under these optimized conditions. It was clear that amination proceeded very effectively and afforded the corresponding products **3j** and **3k** in good yields (Table 2, entries 12 and 13). Considering the development of catalytic methods that selectively produce the *N*-arylated product from the substrate which have two nucleophilic nitrogens (NH and NH_2 group) is still challenging.[30] Nextly we explored the chemoselective C-N coupling using 2-aminobenzimidazole as reaction model under

Table 3. CuI/D-glucosamine-catalyzed coupling of aryl halides and diphenyl disulfide.[a]

Entry	Aryl halides	Product	Yield (%)[b]
1			95(92)[c] **(5a)**
2			82**(5b)**
3			85**(5c)**
4			80**(5d)**
5			77**(5e)**
6			81**(5f)**
7			92**(5g)**
8			83**(5g)**[d]

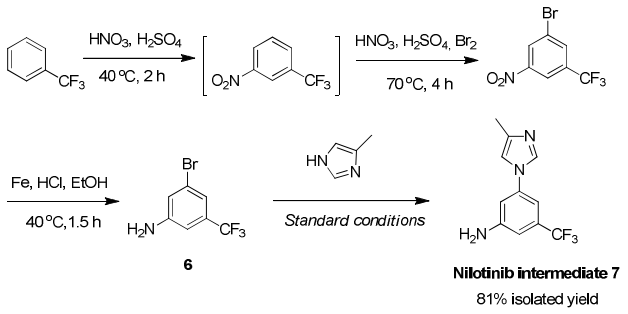
[a] Reaction conditions: CuI (0.1 mmol), D-glucosamine (0.1 mmol), **1** (1.0 mmol), **4a** (0.6 mmol), Cs_2CO_3 (2.0 mmol), DMSO: H_2O (3.0 ml 1:1), 100 ℃ under air, 12 h.[b] Isolated yield.[c] 2.0 mmol K_2CO_3 were used as base. [d] 24 h.

our optimal conditions and the corresponding product **3l was obtained in 72% yield** (Table 2, entry 14).

To further expand the scope of this methodology, the C-S cross-coupling reactions which is a powerful tool in organic synthesis[32] were studied uder optimal system (Table 3). The diphenyl disulfide were investigated as representative example with aryl iodides having 4-NO_2, 4-Cl, 2-Me, and 4-Ph substituents. The reactions occurred efficiently to afford the C-S cross-coupled products with up to 95% yield. In general, good yields were obtained for the cross-coupling of sterically unhindered aryl iodides. *ortho*-Substituted aryl iodides also gave satisfying yields even with steric effects (Table 3, entry 5). No significant electronic effects were observed for both *ortho*- and *para*-substituted aryl iodides (entries 1-5). Under these conditions, aryl iodides with 4-iodo-1*H*-pyrazole showed moderate reactivity, leading to the cross-coupled product in 81% yield (Table 3, entry 6). Satisfactory yields were obtained in the coupling of the bromobenzene withdiphenyl disulfide (Table 3, entry 8). Interesting, in all examples, only the unsymmetrical diaryl sulfide pruducts were obtained in good yields under air. For the reaction mechanism, based on the results of experiments which showed the amino-containing D-glucosamine has better catalytic activity than other sugar-based ligands, so we think the 1-OH and 2-NH_2 of the D-glucosamine may play important role for the coordination to the CuI. The plausible mechanism for C-N and C-S couplings here is similar to previously our reported results.[22b]

With this methodology in hand, we turned our attention to the synthesis of clinically important anticancer drug Nilotinib,[31] a

second-generation BCR-ABL tyrosine kinase inhibitor that shows greater efficacy than imatinib (Gleevec) in the treatment of chronic myelogenous leukemia (CML). Herein, we apply our newly developed copper-catalyzed cross-coupling strategy to synthesize the key intermediate for the preparation of Nilotinib. Key Nilotinib intermediate **7** was prepared from aryl bromide **6** which was prepared from trifluoromethylbenzene by 3 steps in 62% yield (Scheme 2). When aryl bromide **6** (1.0 mmol) was treated with 4-methylimidazole (1.2 mmol) in the presence of 10 mol% of CuI and 10 mol% of D-glucosamine in DMSO-H_2O at 100 °C for 10 h, Nilotinib intermediate **7** was isolated in 81% yield as a single regioisomer.



Scheme 2. Application in synthesis of Nilotinib intermediate **7**.

The incorporation of the cross-coupling strategy to the synthetic route provides a convenient and rapid method for chemical modifications to access a large range of structurally related analogues.

Conclusion

In summary, we have develped a simple, general, and efficient procedure for C-N and C-S bond formations *via* cross-coupling reactions of nitrogen and sulfur nucleophiles with both aryl iodides and bromide using D-glucosamine as green ligand. Amides, amines, imidazoles, indole, pyrrole and phenyl disulfide undergo reactions with aryl halides in the presence of 10 mol% D-glucosamine, 10 mol% CuI, 2 equive of Cs_2CO_3 in DMSO-H_2O. The cross coupling was successful with electron-rich and electron-poor aromatic iodides. Substrates bearing halides, free amino, trifuoromethyl and heterocycles were well tolerate. In all, this protocol not only provide new catalytic system for Buchwald-Hartwig amination reaction but also allow the synthesis of sulfur-containing compounds from more effective synthetic routes in high yields.The high water solubility of the ligand enables easy catalyst removal. In addition, the application of this catalytic system to the synthesis of Nilotinib intermediate was also successfully demonstrated using commercially available substrates. Further investigation to broaden the scope of this catalytic system to other coupling reactions is currently ongoing in this laboratory.

Experimental section

General information

The starting materials were commercially available and were used without further purification except solvents. The products were isolated by column chromatography on silica gel (200-300 mesh) using petroleum ether (60-90°C) and ethyl acetate. Melting points were determined on an X-5 Data microscopic melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature with $CDCl_3$ or DMSO-d_6 as solvent unless otherwise noted and tetramethylsilane (TMS) as the internal standard. ^{1}H NMR data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet and br = broad), coupling constant (*J* values, Hz). ^{13}C NMR data were reported in terms of chemical shift (δ ppm). Mass spectra (EI-MS) were acquired on an Agilent 5975 spectrometer. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates.

General procedure for C-N cross-coupling reactions

A mixture of aryl halide (1 mmol), nitrogen nucleophile (1.2 mmol), CuI (0.1 mmol), D-glucosamine(0.1 mmol), and 3 mL of DMSO-H_2O (1:1) in a tube was heated to 100 °C under air. The progress of the reaction was monitored by TLC using EtOAc and hexane as eluent. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After drying with anhydrous $MgSO_4$ overnight, the liquid was analyzed by GC-MS and then the residue was purified on short pad of silica gel using EtOAc and hexane as eluent. All compounds were characterized by ^{1}H NMR and GC-MS spectroscopy, which were consistent with those reported in the literature.

Selected spectral data of the products

1-(4-Methoxy-phenyl)-1*H*-imidazole 3a[19]. Rufous solid; m.p.: 60–62 ℃. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.13 (s, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.09 (t, *J* = 9.6 Hz, 3H), 3.80 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for $C_{10}H_{10}N_2O$: 174.1, found: 174.

1-(*p*-Tolyl)-1*H*-imidazole 3b[7, 19]. White solid; m.p.: 45–47 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.69 (s, 1H), 7.53 (d, *J* = 6.8 Hz, 2H), 7.31 (d, *J* = 6.4 Hz, 2H), 7.11 (s, 1H), 2.34 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for $C_{10}H_{10}N_2$: 158.1, found: 158.

4-(1*H*-Imidazol-1-yl)aniline 3c[7, 19]. White needles; m.p.: 141-143 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.38 (d, *J* = 7.2 Hz, 2H), 8.01 (t, *J* = 7.2 Hz, 3H), 7.24 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_9H_9N_3$: 159.1, found: 159.

1-Biphenyl-4-yl-1*H*-imidazole 3d[19]. Yellow solid; m.p.: 150–152 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.81 (t, *J* = 4.4 Hz, 3H), 7.75 (d, *J* = 6.8 Hz, 2H), 7.72 (d, *J* = 5.6 Hz, 2H), 7.50 (t, *J* = 6 Hz, 2H), 7.40 (t, *J* = 5.6 Hz, 1H), 7.16 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_{15}H_{12}N_2$: 220.1, found: 220.

1-(4-Chlorophenyl)-1*H*-imidazole 3e[7]. Brown oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.76 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 6.8 Hz, 2H), 7.13 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_9H_7ClN_2$: 178.0, found: 178.

1-(4-(Trifluoromethylphenyl)-1*H*-imidazole 3f[7]. Brown solid; m.p.: 69–71 ℃. ^{1}H NMR (400MHz, DMSO): δ 7.93 (s, 1H), 7.76 (d, J = 8 .0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.34 (s, 1H), 7.27 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_{10}H_7F_3N_2$: 212.1, found: 212.

1-Phenyl-1*H*-imidazole 3g[19]. Slightly yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.75 (s, 1H), 7.66 (d, J = 6 Hz, 2H), 7.53 (t, J = 6 Hz, 2H), 7.38 (t, J = 5.6 Hz, 1H), 7.13 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_9H_8N_2$: 144.1, found: 144.

1-(1*H*-Pyrazol-4-yl)-1*H*-imidazole 3h[7]. Brown oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 7.93 (t, J = 7.2 Hz, 4H), 7.17 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for $C_6H_6N_4$: 134.1, found: 134.

1-(4-Methoxyphenyl)-4-methyl-1*H*-imidazole 3i[9c]. White needles; m.p.: 78–80 ℃. ^{1} H NMR (400 MHz, DMSO-d_6): δ 7.64 (s, 1H), 7.27 (d, J = 9.5, 2H), 6.97 (d, J = 9.2 H), 6.82 (s, 1H) 3.84 (s, 3H) 2.29 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for $C_{11}H_{12}N_2O$: 188.1, found: 188.

1-(4-Methoxyphenyl)-1*H*-indole 3j[9d]. White crystalline solid; mp 59−61 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61(d, J = 7.32 Hz, 1 H), 7.39-7.36 (m, 3 H), 7.23-7.20 (m, 1 H), 7.15-7.06 (m, 2 H), 6.99-6.96 (m, 2 H), 6.58-6.57 (d, J = 2.93 Hz, 1 H), 3.85 (s, 3 H); GC-MS (EI) [M]+: m/z calcd. for $C_{15}H_{13}NO$: 223.1, found: 223.

1-(4-Methoxyphenyl)pyrrolidine 3k[9d]. Yellow solid; m.p.: 46–48 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.97-2.01 (m, 4H), 2.22-3.26 (m, 4H), 3.74 (s, 3H), 6.58-6.61 (d, 2H), 6.81-6.85 (m, 2H); GC-MS (EI) [M]+: m/z calcd. for $C_{11}H_{15}NO$: 177.1, found: 177.

1-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazol-2-amine 3l[30]. Yellow solid; m.p.: 195–197 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (d, J = 6.8 Hz, 2H), 7.23 (d, J = 6 Hz, 1H), 7.16 (d, J = 4 Hz, 2H), 7.02 (t, J = 6.8 Hz, 1H), 6.88 (t, J = 8 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 6.21 (s, 2H); GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{13}N_3O$: 239.1, found: 239.

General procedure for C-S cross-coupling reactions

A mixture of aryl halide (1 mmol), phenyl disulfide (0.6 mmol), CuI (0.1 mmol), D-glucosamine (0.1 mmol), and 3 mL of DMSO-H_2O (1:1) in a tube was heated to at 80-110 °C under air. Monitoring of the reaction, workup procedure, and purification of the C-S cross-coupled products were performed as described for the C-N cross-coupling reactions. All compounds were characterized by ^{1}H NMR and GC-MS spectroscopy, which were consistent with those reported in the literature.

4-Methoxyphenyl phenyl sulfide 5a[32]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.8 Hz, 2H), 7.27-7.08 (m, 5H), 6.88 (J = 8.8 Hz, 2H), 3.80 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}OS$: 216.1, found: 216.

(4-Nitrophenyl)(phenyl)sulfane 5b[32]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.8, 2.4 Hz, 2H), 7.55-7.53 (m, 2H), 7.47-7.45 (m, 3H), 7.16 (dd, J = 8.8, 2.8 Hz, 2H); GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9NO_2S$: 231.0, found: 231.

4-Chlorophenyl phenyl sulfide 5c[32]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 9H). GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9ClS$: 220.0, found: 220.

(Naphthalen-2-yl)(phenyl)sulfane 5d[32]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.76 (m, 2H), 7.74-7.70 (m, 2H), 7.48-7.44 (m, 2H), 7.41-7.36 (m, 2H), 7.32-7.23 (m, 4H); GC-MS (EI) [M]+: m/z calcd. for $C_{18}H_{14}S$: 262.1, found: 262.

Phenyl(*o*-tolyl)sulfane 5e[36]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.16- 7.37 (m, 9H). GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}S$: 200.1, found: 200.

4-(Phenylthio)-1*H*-pyrazole 5f[36]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95-7.07 (m, 3H), 7.09-7.19 (m, 2H), 7.68 (s, 2H); GC-MS (EI) [M]+: m/z calcd. for $C_9H_8N_2S$: 176.0, found: 176.

Diphenyl sulfide 5g[36]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.16 (m, 10H). GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}S$: 186.1, found: 186.

Nilotinib intermediate 7[31]. Colorless oil ;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, H), 7.01 (s, H), (m, 2H), 6.94 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 4.18 (b, 2H), 2.30 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for $C_{11}H_8F_3N_3O_2$: 241.0, found: 241.

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