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Transition-Metal-Free *O*-, *S*-, and *N*-Arylation of Alcohols, Thiols, Amides, Amines, and Related Heterocycles†

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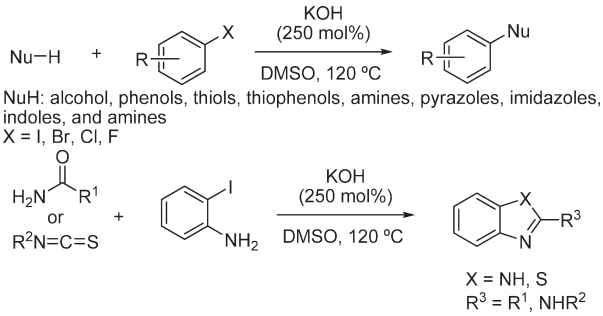

A new protocol for the Ullmann-type arylation process of different aromatic heterocycles without any transition-metal catalyst, implying the use of a combination of an excess of potassium hydroxide and dimethyl sulfoxide, is described. The reaction can be performed between a broad range of starting nucleophiles including phenol, alcohols, amines, nitrogen-containing five-membered systems such as pyrazoles, imidazoles, and indoles, and amides with haloarenes, iodide and bromide derivatives giving the best results, the possible pathway involving the in situ generation of the corresponding benzyne intermediate. When the reaction was performed with 2-iodoaniline and either carboxamides or isothiocyanato derivatives, the corresponding benzoazole derivatives were obtained.

1. Introduction

The cross-coupling reaction between either amines or *N*-heterocycles and aryl halides, also known as the Ullmann-type reaction,[1] as well as the related one using alcohols and thiols as nucleophiles, is a well-documented process and very important for the preparation of many compounds of interest in biological, pharmaceutical, and material sciences.[2] Historically, the common methods used for their preparation required very polar solvents, such as nitrobenzene, *N*-methylpyrrolidone, or DMF, at high temperature, usually higher than 200 °C. Furthermore, the need of stoichiometric amounts of copper salts to carry out the process decreased the atom efficiency,[3] and led to some waste problems.

However, these limitations have been partially overcome, in the case of nitrogen-containing nucleophiles with the use of catalytic systems derived from iron,[4,5] cobalt,[6] nickel,[7] copper,[8] and palladium.[9] In many of the above protocols the solvent of choice was a polar system, such as DMSO, in the presence of stoichiometric amounts of bases at temperatures

† Dedicated to Professor Carmen Nájera on occasion of her 60th birthday and after becoming Correspondent Member of the Real Academia de Ciencias Exactas, Físicas y Naturales of Spain.

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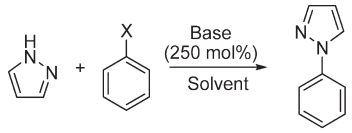
higher than 100 °C. The above copper-catalyzed protocol with DMSO as solvent has been extended to other nucleophiles, such as phenols[10] and sulfur-containing compounds.[11] In the last case, the use of polyfunctionalized sulfur compounds allowed the synthesis of different interesting heterocyclic compounds, such as phenothiazines[12] and benzothiazoles.[13]

Alternatively, a similar arylation transformation can be performed by nucleophilic addition of the corresponding nucleophilic compounds to an in situ generated aryne intermediate under strong basic conditions.[14,15]

TABLE 1. Reaction-Condition Optimization



1a **2a**: X = I, **2b**: X = Br, **2c**: X = Cl, **2d**: X = F **3a**

entry	X	solvent	base	T (°C)	t (h)	yield (%)[a]
1	I	DMSO	KOH[b]	120	24	0
2	I	DMSO	KOH	120	24	92
3	I	DMSO	KOH[c]	120	24	83
4	I		KOH	120	24	< 5
5	I	PhMe	KOH	120	24	0
6	I	Dioxane	KOH	120	24	< 5
7	I	MeCN	KOH	120	24	20
8	I	DMF	KOH	120	24	0
9	Br	DMSO	KOH	120	144	81
10	Cl	DMSO	KOH	120	144	57
11	F	DMSO	KOH	120	144	52
12	I	DMSO	KOH	120[d]	2	55
13	I	DMSO	NaOH	120	24	67
14	I	DMSO	KO*t*Bu	120	24	79
15	I	DMSO	K_2CO_3	120	72	0
16	I	DMSO	KOH	90	96	65

[a]Isolated yield. [b]The reaction was carried out with only 40 mol % of base. [c]The reaction was carried out with 200 mol % of base. [d]The reaction was carried out with microwaves (80 W).

2. Results and Discussion

In our ongoing project on the use of copper-impregnated magnetite,[16] we realized that the transition-metal catalyst could be eliminated in the *N*-Ullmann type reaction by the correct choice of reaction conditions. Here, we report a simple, mild, and uncatalyzed protocol to perform the arylation of different oxygen-, nitrogen-, and sulfur-containing nucleophiles.[17]

2.1. Optimization of the Reaction Conditions. To optimize the reaction conditions we studied the reaction between pyrazol (**1a**) and different phenyl halides **2** to give the corresponding compound **3a**, as depicted in Table 1. The reaction with stoichiometric amounts of all reagents failed after 1 day of reaction at 120 °C, recovering the starting materials unchanged (entry 1 in Table 1). However, increasing the amount of base to 250 mol % allowed us to obtain the expected product **3a** in an excellent yield. A further increase in the base amount to 500 mol % did not provoke any improvement on the reaction time or on the yield (compare entries 2 and 3). Once the optimal amount of base was established, we studied the influence of the nature of solvent (or their absence) and in all cases the reaction either failed or gave a very low yield (compare entries 2 and 4−8 in Table 1). Then, the influence of the halide at the phenyl ring in compound **2** was evaluated (Table 1, entries 9−11), and in all cases the reaction required longer reaction times and only in the case of bromobenzene was the yield comparable with

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that of the related iodobenzene. Also, the influence of microwaves was tested.[18] We found that the reaction time could be shortened to 2 h, albeit the yield was lower with a broad range of different byproducts (compare entries 2 and 12 in Table 1). The nature of the base also has a great importance on the obtained yields (entries 13−15 in Table 1). Thus, the yield was surprisingly lower in the case of using sodium hydroxide, meanwhile potassium *tert*-butoxide[19] gave similar results to potassium hydroxide, and the reaction failed with a weaker base such as potassium carbonate. Finally, decreasing the temperature decreased the chemical yield and increased the reaction time (compare entries 2 and 16 in Table 1).

It should be pointed out that copper (0.001%) and nickel (0.001%) are impurities present in the KOH. This minor amount (0.0025 mol % of copper) might be the true catalyst, as it was previously demonstrated for the iron cases.[5] However, in the case of the potassium *tert*-butoxide, copper impurities are not present, with the reaction results being similar. Despite that, we performed ICP-MS studies of the obtained solution after running the reaction as in entry 14 in Table 1, finding that the amount of copper was 5×10^{-10} mol %, and palladium was not detected. Therefore, we are confident that the possible impurities are not responsible for the reaction depicted in this process.

2.2. *N*-Arylation Process. Once the best conditions were found for this Ullmann process (entry 2 in Table 1), the same protocol was applied to other substrates in order to study the scope of the reaction (Table 2). Similar results were obtained when different 4-substituted haloarenes were used as arylating agent, obtaining in all cases a 1:1 mixture of 3- and 4-substituted arenes **3**, independently of the electronic nature of the substituent (entries 2−4 in Table 2), and indicating that the reaction probably proceeded by hydrogen iodide elimination to form the corresponding substituted aryne, followed by statistic nucleophilic addition of pyrazole **1a** at both possible positions. When the reaction was carried out with 2-bromopyridine (**2h**), only the isomeric 2-pyridyl compound **3e** was obtained (Table 2, entry 5). However, when the same protocol was employed with 3-iodopiridine a 1:1 mixture of 3-:4-isomers was obtained with good yield (Table 2, entry 6). Instead of pyrazole derivatives, other heterocyclic compounds such as imidazole **1b** and the benzo derivatives **1c** and **1d** could be used in the arylation process with use of either iodobenzene (**2a**) or 2-bromopyridine (**2h**) without any substantial changes in the results obtained (entries 7−11 in Table 2).

A similar protocol could be employed with aliphatic secondary amines **4a**,**b** only increasing the reaction time (Scheme 1), obtaining the corresponding *N*,*N*-disubstituted aniline derivatives **5a** and **5b** with excellent results. In the case of using benzamide (**4c**) the above protocol rendered the expected *N*-phenylbenzamide (**5c**) albeit in a lower yield (68%).

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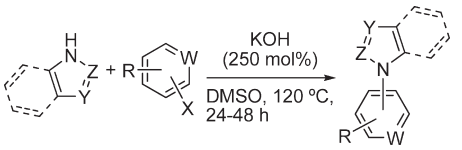
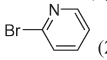
TABLE 2. *N*-Arylation of Aromatic Nitrogenated Heterocycles

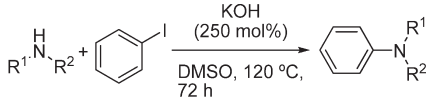


1 2 3

Entry	Heterocycle (**1**)	Haloarene (**2**)	Product **3**	Yield (%)[a]
1	 (**1a**)	PhI (**2a**)	**3a**	92
2	(**1a**)	4-MeOC$_6$H$_4$I (**2e**)	**3b**	92[b,c]
3	(**1a**)	4-MeC$_6$H$_4$I (**2f**)	**3c**	94[b,c]
4	(**1a**)	4-ClC$_6$H$_4$I (**2g**)	**3d**	85[b,c]
5	(**1a**)	 (**2h**)	**3e**	94
6	(**1a**)	 (**2i**)	**3f**	91[c]
7	 (**1b**)	(**2a**)	**3g**	96[b]
8	 (**1c**)	(**2a**)	**3h**	74[b]
9	(**1c**)	(**2h**)	**3i**	90[b]
10	 (**1d**)	(**2a**)	**3j**	80
11	(**1d**)	(**2h**)	**3k**	99

[a]Isolated yield after 24 h of reaction time. [b]Reaction performed during 48 h. [c]A 1:1 mixture of isomers at 3- and 4-position was detected.

SCHEME 1. Phenylation of Amines and Amides



4a: R^1-R^2 = $(CH_2)_4$
4b: R^1-R^2 = $(CH_2)_2O(CH_2)_2$
4c: R^1 = PhCO, R^2 = H

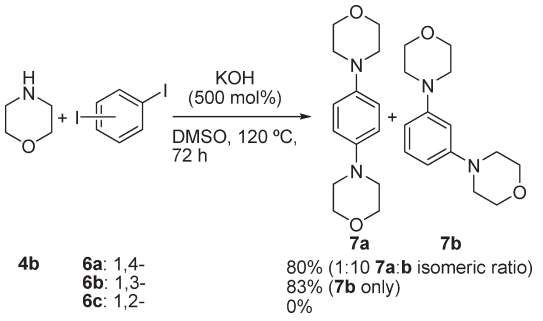
2a

5a (99%)
5b (90%)
5c (68%)

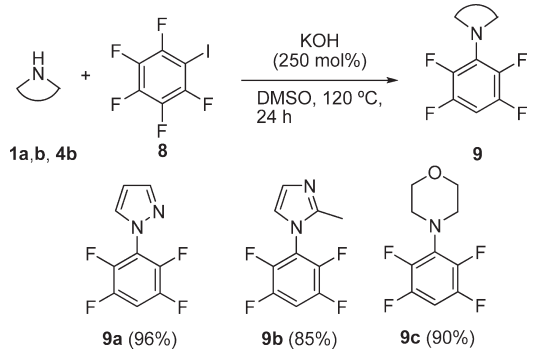
Owing to the excellent result obtained in the phenylation of morpholine (**4b**), we focused on the problem of double substitution in diiodobenzene derivatives **6** (Scheme 2). The reaction, using in these cases a double amount of base as well as amine, gave a mixture of the isomeric products **7**. When the reaction was performed with 1,4-diiodobenzene (**6a**), the diamine products **7** were obtained in good yields (80%) as a 1:10 mixture of para- and meta-disubstituted compounds **7a** and **7b**, respectively. Surprisingly, when the same reaction was performed with the related 1,3-diiodobenze (**6b**) the only amine detected from the reaction crude was compound **7b**, which was isolated in a 83% yield. Finally, the reaction with 1,2-diiodobenzene did not afford any of the possible amines, giving a mixture of decomposition products.

Although our hypothesis of reaction pathway involved the formation of benzyne intermediate by dehydrohalogenation on the reaction media, we did not have any empirical proof of it, and to discard another possible mechanism, as for instance a direct nucleophilic aromatic substitution, we performed the reaction with a very electronic poor arene such as pentafluoroiodobenzene (**8** in Scheme 3). The reaction with

SCHEME 2. Double Coupling Process with 1,*n*-Diiodobenzenes



SCHEME 3. Arylation Process with Pentafluoroiodobenzene



pyrazol (**1a**), under standard conditions, gave compound **9a**, with an excellent result, in which the hydrogen is located at the para-position, as it was probed by ^{19}F NMR experiments. The reaction with either 2-methylimidazole (**1b**) or morpholine gave the same type of product **9b** and **9c** in excellent yields.

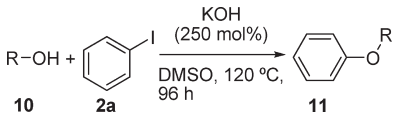
2.3. *O*-Arylation Process. Once we demonstrated that this new transition-metal-free protocol could be used for standard *N*-arylation processes, we faced the problem of the arylation of alcohols and phenols (Table 3). The reaction with these oxygenated nucleophiles **10** gave the expected phenyl ethers **11** with, in general, good yields, although the reaction times should be increased. The results were practically the same, for the case of phenol derivatives independently of the presence of substituents at the para-position, as well as the electronic nature of this substituent, with the protocol allowing the use of chlorinated phenols. The reaction with aliphatic alcohols also produced the desired product, although in lower yield (entry 4).

2.4. *S*-Arylation Process. Not only oxygenated nucleophiles but also sulfur-containing nucleophiles could be used with this protocol also with good results (Table 4). As in the previous cases, the yields were not affected by the presence of substitution at the aromatic ring. Moreover, in the case of high nucleophilic thiols, the yield obtained for the aliphatic derivatives was as high as the one obtained for aromatic ones.

2.5. Synthesis of Benzoazole Derivatives. Finally, the protocol was tested in the tandem process of arylation and cyclization to prepare benzoimidazole derivatives, starting from 2-iodoaniline (**14**). The reaction of equimolecular amounts of primary amides (**4c**−**e**) with compound **14** gave the expected 2-substituted-1*H*-benzo[*d*]imidazole **15** in moderate to good yields (Table 5). The reaction times were somehow longer, due to the weaker nucleophilicity of carboxamides (see Scheme 1 and the corresponding comment). The following cyclization process could be difficult due to a nonselective reaction with the benzyne intermediate. However, in fact the yields were higher than 50% showing that the addition of amide was quite selective, with the possible *N*-(3-aminophenyl) amide derivative not being detected in the reaction crude by ^{1}H NMR and GC-MS. Moreover, no formation of the corresponding 2-substituted benzo[*d*]oxazole seems to indicate that the benzyne formation takes places prior to the aniline derivatization by reaction with the carboxamide.

A similar reaction with equimolecular amounts of compound **14** and different isothiocyanato derivatives **16** gave the expected *N*-substituted benzo[*d*]thiazol-2-amine derivatives **17** in good yields (Table 6). As in all previous cases, the yields were not affected by the nature of the nucleophile

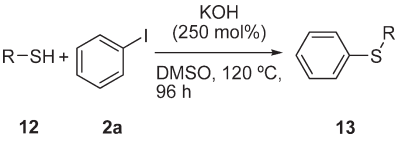
TABLE 3. *O*-Phenylation of Phenols and Alcohols



entry	R	product **11**	yield (%)[a]
1	Ph	**11a**	80[b]
2	4-MeOC$_6$H$_4$	**11b**	88
3	4-ClC$_6$H$_4$	**11c**	83
4	Me(CH$_2$)$_6$	**11d**	53

[a]Isolated yield after flash chromatography. [b]Reaction performed during 5 days.

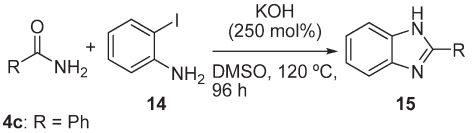
TABLE 4. *S*-Phenylation of Thiophenols and Thioalcohols



entry	R	product **13**	yield (%)[a]
1	Ph	**13a**	92
2	4-MeC$_6$H$_4$	**13b**	97
3	Me(CH$_2$)$_7$	**13c**	99

[a]Isolated yield after flash chromatography.

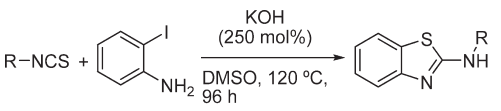
TABLE 5. Synthesis of 2-Substituted Benzoimidazole Derivatives



entry	R	product **15**	yield (%)[a]
1	Ph	**15a**	70
2	4-ClC$_6$H$_4$	**15b**	60[b]
3	*t*Bu	**15c**	51[b]

[a]Isolated yield after flash chromatography. [b]Reaction performed during 5 days.

TABLE 6. Synthesis of *N*-Substituted-2-Benzothiazoleamine Derivatives



16 14 17

entry	R	product **17**	yield (%)[a]
1	Ph	**17a**	80[b]
2	3,5-$(CF_3)_2C_6H_3$	**17b**	77
3	*t*Bu	**17c**	74

[a]Isolated yield after flash chromatography. [b]Reaction performed during 5 days.

(aromatic or aliphatic) or by the presence of substituents in the case of aromatic substituents. Contrary to the previous case, two possible mechanism pathways could be active, since isothiocyanato derivatives have a higher electrophilic character compared to carboxamides **4c**−**e**.

3. Conclusions

In conclusion, we have demonstrated that the arylation process of different nucleophiles, including oxygen, sulfur, and nitrogen derivatives, even with the related heterocyclic compounds, could be successfully performed under basic conditions in DMSO without the presence of a transition-metal catalyst. These conditions are quite similar (in terms of reaction times, amount of base, and temperature) to others in which the use of metallic catalysts was required, highlighting the superfluous effect of some catalyst in these transformations. The reaction could be performed with a broad range of substrates, keeping the high level of the results, and permits the easy entry to the synthesis of interesting benzo-condensed heterocycles. Finally, it should be pointed out that the reaction seems to follow a pathway in which a benzyne is involved.

4. Experimental Section

4.1. General Procedure for the Arylation Processes. A pressure tube was charged with the corresponding nitrogenated heterocycle (**1**), amine (**4**), amide (**4**), alcohol (**10**), thiol (**12**), or isothiocyanato derivatives (**16**, 1 mmol), KOH (2.5 mmol, 140 mg), haloarene (**2** or **14**, 1 mmol), and dry DMSO (1.5 mL) under argon atmosphere. The resulting mixture was stirred in an oil bath at 120 °C until the end of the reaction. The mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate (2 × 10 mL). The organic phase was dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The product was purified by column chromatography on silica gel (decreasing hexane/ethyl acetate ratio). Analytical, physical, and spectroscopic data, as well as literature for known compounds, follow:

1-Phenyl-1*H*-pyrazole (3a):[4d] R_f 0.82 (hexane/ethyl acetate 4:1); IR (melted) ν 1716, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (t, J = 2 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.35−7.37, 7.68−7.72 (2 m, 2 and 3H), 7.92 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.6, 119.2, 126.4, 126.7, 129.4, 140.2, 141; EI-MS m/z 145 ($M^+ + 1$, 11%), 144 (M^+, 100), 143 (12), 117 (15), 116 (19), 90 (20), 77 (33), 50 (21).

1-(4-Methoxyphenyl)-1*H*-pyrazole and 1-(3-methoxyphenyl)-1*H*-pyrazole (3b):[20] R_f 0.27 (hexane/ethyl acetate 4:1); IR (film) ν 1592, 1520, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74, 3.76 (2s, 3 and 3H, respectively), 6.39−6.45 (m, 2H), 6.76−6.88 (m, 1H), 6.96−7 (m with d at 6.97, J = 9.6 Hz, 3H), 7.13−7.16 (m, 1H), 7.24−7.26 (m, 1H), 7.56−7.6 (d, J = 9 Hz, 2H), 7.69−7.7 (m, 2H), 7.81−7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 55.6, 106.2, 107.2, 107.8, 114.5, 114.9, 116, 117.9, 121, 127, 130.3, 133.9, 138.3, 140.5, 140.6, 150.7, 158.3; EI-MS m/z 175 ($M^+ + 1$, 12%), 146 (M^+, 100), 159 (68), 131 (22), 77 (12).

1-(*p*-Tolyl)-1*H*-pyrazole and 1-(*m*-tolyl)-1*H*-pyrazole (3c):[20] R_f 0.43 (hexane/ethyl acetate 4:1); IR (film) ν 1615, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36, 2.40 (2s, 3 and 3H, respectively), 6.42−6.44 (m, 2H), 7.71 (m, 1H), 7.23 (d, J = 9 Hz, 2H), 7.28−7.33, 7.43−7.46, 7.54−7.57 (3 m, 1, 1 and 3H, respectively), 7.7−7.71 (m, 2H), 7.85−7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.4, 107.2, 107.4, 116.1, 119.1, 119.9, 126.6, 126.7, 127.1, 129.1, 129.8, 136.1, 137.9, 139.4, 140, 140.7, 140.8; EI-MS m/z 159 ($M^+ + 1$, 12%), 158 (M^+, 100), 157 (27), 130 (30), 91 (13), 65 (10).

1-(4-Chlorophenyl)-1*H*-pyrazole and 1-(3-chlorophenyl)-1*H*-pyrazole (3d):[20] R_f 0.47 (hexane/ethyl acetate 4:1); IR (film) ν 1597, 1514, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (m, 2H), 7.13−7.43 (m, 5H), 7.57−7.65 (m, 3H), 7.74−7.76 (m, 2H), 7.88−7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.9, 108, 115.9, 116.9, 119.4, 120.2, 126.3, 126.7, 129.4, 129.7, 130.4, 135.1, 138.2, 141.3, 141.4, 154.5; EI-MS m/z 180 ($M^+ + 1$, 33%), 179 (M^+, 13), 178 (100), 151 (15), 116 (13), 111 (19), 89 (11), 75 (15).

2-(1*H*-Pyrazol-1-yl)pyridine (3e):[4c] R_f 0.57 (hexane/ethyl acetate 4:1); IR (film) ν 1615, 1603, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (m, 1H), 7.13 (t, J = 5.9 Hz, 1H), 7.73−7.79 (m, 2H), 7.96−7.99 (m, 1H), 8.38 (d, J = 4.7 Hz, 1H), 8.57 (d, J = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.6, 112.2, 121.2, 126.8, 138.5, 141.9, 147.9, 151.4; EI-MS m/z: 146 ($M^+ + 1$, 10%), 145 (M^+, 100), 118 (32), 78 (74).

3-(1*H*-Pyrazol-1-yl)pyridine (3f):[4c] R_f 0.47 (ethyl acetate); IR (film) ν 1589, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (t, J = 1.9 Hz, 1H), 7.38−7.42 (m, 1H), 7.62 (d, J = 2 Hz, 1H), 7.97 (d, J = 2.5 Hz, 1H), 8.05−8.07 (m, 1H), 8.53−8.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4, 123.9, 126.6, 126.8, 136.5, 140.3, 141.9, 147.3; EI-MS m/z 146 ($M^+ + 1$, 10%), 145 (M^+, 100), 118 (23), 91 (12), 78 (14).

4-(1*H*-Pyrazol-1-yl)pyridine (3f′):[21] mp 63−67 °C (ethyl acetate/hexane); R_f 0.33 (ethyl acetate); IR (KBr) ν 1600, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53−6.55 (m, 1H), 7.64−7.66 (m, 2H), 7.78−7.79 (m, 1H), 8.04−8.05 (m, 1H), 8.65−8.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109, 112.4, 126.5, 142.5, 145.9, 151.2; EI-MS m/z 146 ($M^+ + 1$, 10%), 145 (M^+, 100), 144 (13), 118 (17), 78 (13).

2-Methyl-1-phenyl-1*H*-imidazole (3g):[8c] R_f 0.7 (hexane/ethyl acetate 3:2); IR (film) ν 1596, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34−2.35 (m, 3H), 6.99−7.01, 7.26−7.28, 7.4−7.49 (3 m, 2, 2, and 3H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 120.3, 125.2, 127.2, 127.9, 129.2, 137.6, 144.3; EI-MS m/z 159 ($M^+ + 1$, 12%), 158 (M^+, 100), 157 (29), 131 (10), 130 (39), 117 (15), 90 (22), 77 (28).

1-Phenyl-1*H*-benzo[*d*]imidazole (3h):[17c] R_f 0.13 (hexane/ethyl acetate 4:1); IR (film) ν 1712, 1589, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.37, 7.43−7.6, 7.87−7.9 (3 m, 2, 6 and 1H, respectively), 8.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.4, 120.5, 122.8, 123.7, 124, 128, 130, 133, 136.3, 142.2, 143.9; EI-MS m/z 195 ($M^+ + 1$, 14%), 194 (M^+, 100), 193 (23).

1-(Pyridin-2-yl)-1*H*-benzo[*d*]imidazole (3i):[8b] R_f 0.5 (ethyl acetate); IR (film) ν 1669, 1588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14−7.17 (m, 1H), 7.29−7.35 (m, 2H), 7.42 (d, J =

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8.2 Hz, 1H), 7.72−7.76, 7.83−7.86, 8−8.03, 8.49−8.51 (4 m, 1, 1, 1 and 1H, respectively), 8.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.4, 113.7, 120.1, 121.3, 122.8, 123.7, 131.6, 138.5, 140.9, 144.2, 148.9, 149.3; EI-MS m/z 196 ($M^+ + 1$, 14%), 195 (M^+, 100), 194 (53), 169 (43), 78 (10).

1-Phenyl-1*H*-indole (3j):[4b] R_f 0.67 (hexane/ethyl acetate 4:1); IR (film) ν 1591 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, J = 2.6 Hz, 1H), 7.14−7.22, 7.31−7.33, 7.47−7.48 (3 m, 2, 2 and 4H, respectively), 7.55 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 110.5, 120.3, 121.1, 122.3, 124.3, 126.4, 127.9, 129.3, 129.6, 135.8, 139.8; EI-MS m/z 194 ($M^+ + 1$, 15%), 193 (M^+, 100), 192 (16); 165 (21).

1-(Pyridin-2-yl)-1*H*-indole (3k):[9e] R_f 0.6 (hexane/ethyl acetate 4:1); IR (film) ν 1688, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71−6.72, 7.14−7.22, 7.27−7.31, 7.48−7.51, 7.65−7.67, 7.72−7.73, 7.79−7.83, 8.19−8.22, 8.56−8.58 (9 m, 1, 2, 1, 1, 1, 1, 1, 1 and 1H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.4, 112.9, 114.3, 119.9, 120.9, 121.1, 123, 125.8, 130.3, 134.9, 138.2, 148.7, 152.3; EI-MS m/z 195 ($M^+ + 1$, 15%), 194 (M^+, 100), 193 (57), 167 (12).

1-Phenylpyrrolidine (5a):[4b] R_f 0.8 (hexane/EtOAc 4:1); IR (film) ν 1609, 1509, 1362 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87−2.06 (m, 4H), 3.15−3.33 (m, 4H), 6.53−6.55, 6.62−6.66, 7.18−7.22 (3 m, 2, 1 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 47.4, 111.5, 115.2, 129, 147.8; EI-MS m/z 147 (M^+, 72%), 146 (100), 104 (15), 91 (41), 77 (23).

4-Phenylmorpholine (5b):[4d] R_f 0.23 (hexane/ethyl acetate 4:1); IR (film) ν 1591, 1502, 1253, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13−3.15 (m, 4H), 3.84−3.86 (m, 4H), 6.86−6.92, 7.23−7.29 (2 m, 3 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.2, 66.8, 115.6, 119.9, 129.1, 151.2; EI-MS m/z 163 (M^+, 75%), 106 (10), 105 (100), 104 (41), 77 (24).

***N*-Phenylbenzamide (5c):**[4d] mp 138−143 °C (ethyl acetate/hexane); R_f 0.53 (hexane/ethyl acetate 3:2); IR (KBr) ν 3339, 1656, 1596, 1522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11−7.29, 7.32−7.38, 7.41−7.53, 7.57−7.65, 7.83−7.86, 8.09−8.11 (6 m, 1, 2, 4, 2, 1 and 1H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.3, 124.6, 127, 128.7, 129, 131.8, 134.8, 137.8, 166; EI-MS m/z 197 (M^+, 52%), 105 (100), 77 (45), 51 (10).

1,4-Dimorpholinobenzene (7a):[7a] R_f 0.13 (hexane/ethyl acetate 3:2); IR (film) ν 1585, 1514, 1294, 1111, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06−3.09, 3.85−3.88 (2 m, 8 and 8H, respectively), 6.90 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 67, 117.3, 145; EI-MS m/z 249 ($M^+ + 1$, 17%), 248 (M^+, 100), 190 (36), 132 (34), 131 (11).

1,3-Dimorpholinobenzene (7b):[19] R_f 0.2 (hexane/ethyl acetate 3:2); IR (film) ν 1585, 1264, 1116, 867 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13−3.16, 3.83−3.86, 6.46−6.49, 7.15−7.25 (2 m, 8, 8, 3 and 1H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.6, 66.9, 103.8, 108.1, 129.7, 152.3; EI-MS m/z 249 ($M^+ + 1$, 16%), 248 (M^+, 100), 247 (11), 233 (24), 191 (15), 190 (41), 132 (48), 104 (10).

1-(2,3,5,6-Tetrafluorophenyl)-1*H*-pyrazole (9a): R_f 0.73 (hexane/ethyl acetate 4:1); IR (KBr) ν 1650, 1618, 1194, 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53−6.55 (m, 1H), 7.17 (tt, $^2J_{HF}$ = 9.7 Hz, $^3J_{HF}$ = 7.1 Hz), 7.72−7.73 (m, 1H), 7.83−7.84 ppm (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 105 (t, $^2J_{CF}$ = 22.7 Hz), 107.7, 120.9 (t, $^2J_{CF}$ = 15 Hz), 132, 141.8 (ddd, $^1J_{CF}$ = 254 Hz, $^2J_{CF}$ = 16 Hz, $^3J_{CF}$ = 3.8 Hz), 142.3, 146.2 ppm (dtd, $^1J_{CF}$ = 249.1 Hz, $^2J_{CF}$ = $^3J_{CF}$ = 11 Hz, $^4J_{CF}$ = 4.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −138.1 (m, 2F), −148.6 (m, 2F); EI-MS m/z 217 (M^++1, 10%), 216 (M^+, 100), 189 (13), 162 (24), 149 (23), 99 (22); HRMS calcd for $C_9H_4F_4N_2$ 216.0311, found 216.0310. Anal. Calcd for $C_9H_4F_4N_2$: C, 50.01; H, 1.87; N, 12.96. Found C, 50.09; H, 1.79; N, 12.89.

2-Methyl-1-(2,3,5,6-tetrafluorophenyl)-1*H*-imidazole (9b): mp 131−135 °C (ethyl acetate/hexane); R_f 0.13 (hexane/ethyl acetate 4:1); IR (KBr) ν 1513, 1072, 942 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.96−6.97 (m, 1H), 7.12−7.13 (m, 1H), 7.26 ppm (tt, $^2J_{HF}$ = 9.6 Hz, $^3J_{HF}$ = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.8, 106.7 (t, $^2J_{CF}$ = 23 Hz), 118 (t, $^2J_{CF}$ = 15 Hz), 120.7, 129, 142.5 (ddd, $^1J_{CF}$ = 254 Hz, $^2J_{CF}$ = 14 Hz, $^3J_{CF}$ = 6 Hz), 145.8, 146.1 ppm (dtd, $^1J_{CF}$ = 252 Hz, $^2J_{CF}$ = $^3J_{CF}$ = 11 Hz, $^4J_{CF}$ = 6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.3 (m, 2F), −146.5 (m, 2F); EI-MS m/z 231 ($M^+ + 1$, 11%), 230 (M^+, 12), 229 (11), 211 (28), 203 (10), 189 (15), 162 (18), 149 (21), 99 (23). HRMS calcd for $C_{10}H_6F_4N_2$ 230.0467, found 230.0479. Anal. Calcd for $C_{10}H_6F_4N_2$: C, 52.18; H, 2.63; N, 12.17. Found: C, 52.22; H, 2.64; N, 12.21.

4-(2,3,5,6-Tetrafluorophenyl)morpholine (9c):[22] mp 81−85 °C (ethyl acetate/hexane); R_f 0.6 (hexane/ethyl acetate 4:1); IR (KBr) ν 1643, 1607, 1270, 1108, 1031, 947, 871 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27−3.29 (m, 4H), 3.82 (m, 4H), 6.71 (tt, $^2J_{HF}$ = 9.8 Hz, $^3J_{HF}$ = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.2, 67.3, 99 (t, $^2J_{CF}$ = 23 Hz), 130.5 (t, $^2J_{CF}$ = 11 Hz), 142.2 (ddt, $^1J_{CF}$ = 245 Hz, $^2J_{CF}$ = 13 Hz, $^3J_{CF}$ = 5.2 Hz), 146.5 (dtd, $^1J_{CF}$ = 245 Hz, $^2J_{CF}$ = $^3J_{CF}$ = 14 Hz, $^4J_{CF}$ = 4.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −140.7 (m, 2F), −151.6 (m, 2F); EI-MS m/z 235 (M^+, 61%), 178 (12), 177 (100), 176 (69), 149 (14), 99 (10).

Diphenyl ether (11a):[8f] R_f 0.9 (hexane/ethyl acetate 4:1); IR (film) ν 1580, 1485, 1235, 867 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95−7.02, 7.06−7.1, 7.25−7.38 (3 m, 4, 2 and 4H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.8, 123.2, 129.7, 157.2; EI-MS m/z 171 ($M^+ + 1$, 13%), 170 (M^+, 100), 169 (24), 142 (28), 141 (51), 115 (12), 77 (17).

1-Methoxy-4-Phenoxybenzene (11b):[8f] R_f 0.63 (hexane/ethyl acetate 4:1); IR (film) ν 1585, 1230, 1183, 1154, 831 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.83−6.85, 6.91−6.97, 6.98−7.02, 7.24−7.27 (4 m, 2, 4, 1 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 114.8, 117.5, 120.7, 122.3, 129.6, 150, 155.8, 158.4; EI-MS m/z 201 ($M^+ + 1$, 15%), 200 (M^+, 100), 185 (50), 129 (24), 77 (40), 51 (12).

1-Chloro-4-phenoxybenzene (11c):[8f] R_f 0.77 (hexane/ethyl acetate 4:1); IR (film) ν 1578, 1234, 1161, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82−6.93, 6.97−7, 7.07−7.12, 7.23−7.27, 7.3−7.34 (5 m, 2, 2, 1, 2 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.9, 120, 123.6, 128.1, 129.7, 129.8, 155.9, 156.8; EI-MS m/z 206 (33%), 205 ($M^+ + 1$, 15%), 204 (M^+, 100), 169 (10), 141 (46), 77 (25).

Heptyloxybenzene (11d):[23] R_f 0.8 (hexane/ethyl acetate 4:1); IR (film) ν 1603, 1509, 1241, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.28−1.39, 1.41−1.48, 1.74−1.81 (3 m, 6, 2 and 2H, respectively), 3.94 (t, J = 6.6, 2H), 6.88−7.02, 7.23−7.29 (2 m, 3 and 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26, 29, 29.3, 31.8, 67.9, 114.5, 120.4, 129.4, 159.1; EI-MS m/z 192 (M^+, 19%), 94 (100).

Phenylsulfanylbenzene (13a):[11c] R_f 0.77 (hexane/ethyl acetate 4:1); IR (film) ν 1568, 1479, 1437, 677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84−7.11, 7.18−7.35 (2 m, 6 and 4H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.9, 129, 130.9, 135.7; EI-MS m/z 187 ($M^+ + 1$, 16%), 186 (M^+, 100), 185 (78), 184 (33).

4-Phenylsulfanyltoluene (13b):[11f] R_f 0.77 (hexane/ethyl acetate 4:1); IR (film) ν 1585, 1495, 1469, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 7.05−7.1, 7.11−7.15, 7.18−7.24, 7.25−7.29 (4 m, 2, 1, 4 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21, 126.3, 128.9, 129.7, 130, 131.2, 132.2, 137, 137.4; EI-MS m/z 201 ($M^+ + 1$, 16%), 200 (M^+, 100), 199 (26), 185 (33), 184 (32), 167 (11), 91 (16).

Octylsulfanylbenzene (13c):[11b] R_f 0.87 (hexane/ethyl acetate 4:1); IR (film) ν 1582, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.18−1.32, 1.36−1.43, 1.58−1.66

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(3 m, 8, 2 and 2H, respectively), 2.88 (t, J = 7.3, 2H), 7.09−7.13, 7.2−7.24, 7.28−7.3 (3 m, 1, 2 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14, 22.6, 28.8, 29, 29.1, 31.7, 33.4, 125.4, 128.6, 128.7, 137; EI-MS m/z 222 (M^+, 50%), 123 (20), 110 (100), 109 (11).

2-Phenyl-1*H*-benzo[*d*]imidazole (15a):[8g] mp 225−227 °C (ethyl acetate/hexane); R_f 0.13 (hexane/ethyl acetate 3:2); IR (KBr) ν 3416, 1585, 1538 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18−7.22, 7.46−7.5, 7.52−7.56, 7.66−7.68, 8.17−8.2 (5 m, 2, 1, 3, 1 and 2H, respectively), 13 (s, br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.4, 118.9, 121.7, 122.6, 126.5, 129, 129.8, 130.2, 135, 143.8, 151.3; EI-MS m/z 195 ($M^+ + 1$, 15%), 194 (M^+, 100), 193 (26).

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (15b):[24] mp 282−285 °C (ethyl acetate/hexane); R_f 0.4 (hexane/ethyl acetate 3:2); IR (KBr) ν 3423, 1602, 1598, 1534, 1082 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.2−7.26, 7.53−7.55, 7.62−7.65, 7.67−7.68, 8.18−8.21 (5 m, 2, 1, 2, 1 and 2H, respectively), 13 (s, br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.9, 119.4, 122.3, 123.2, 128.6, 129.5, 135, 135.5, 144.2, 150.6, 170.8; EI-MS m/z 230 (34%), 229 ($M^+ + 1$, 18), 228 (M^+, 100), 227 (10), 193 (13).

2-*tert*-Butyl-1*H*-benzo[*d*]imidazole (15c):[25] mp 287−290 °C (ethyl acetate/hexane); R_f 0.43 (hexane/ethyl acetate 3:2); IR (KBr) ν 1592, 1535, 1400, 1365 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.4 (s, 9H), 7.1 (d, J = 3.9 Hz, 2H), 7.41 (d, J = 6.5 Hz, 1H), 7.53 (d, J = 6.5 Hz, 1H), 12.1 (s, br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.7, 33.6, 111.2, 118.7, 121.1, 121.8, 135, 143.2, 162.6; EI-MS m/z 174 (M^+, 34%), 173 (24), 160 (12), 159 (100), 119 (13).

***N*-Phenylbenzo[*d*]thiazol-2-amine (17a):**[15a] mp 161−163 °C (ethyl acetate/hexane); R_f 0.13 (hexane/ethyl acetate 4:1); IR (KBr) ν 3230, 1621, 1597, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11−7.19 (m, 2H), 7.26 (s, 1H), 7.27−7.29, 7.31−7.35, 7.39−7.43, 7.49−7.52, 7.57−7.59, 7.62−7.64 (5 m, 1, 2, 2, 1, and 1H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.3, 120.2, 120.8, 122.4, 124.3, 126.1, 129.6, 129.8, 139.8, 151.3, 164.7; EI-MS m/z 227 ($M^+ + 1$, 15%), 226 (M^+, 74), 225 (100).

***N*-(3,5-Bis(Trifluoromethyl)phenyl)benzo[*d*]thiazol-2-amine (17b):**[13b] mp 150−155 °C (ethyl acetate/hexane); R_f 0.43 (hexane/ethyl acetate 3:2); IR (KBr) ν 3188, 1615, 1579, 754, 715 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.1−7.14 (m, 1H), 7.26−7.30 (m, 1H), 7.5 (s, 1H), 7.59−7.61 (m, 1H), 7.67−7.7 (m, 1H), 8.42 (s, 2H), 9.97 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.2, 118.2, 121, 121.7, 124, 124.3 (q, $^1J_{CF}$ = 271.4 Hz), 126.8, 131.1, 132.2 ($^2J_{CF}$ = 32.2 Hz), 143.1, 152.6, 161.2; EI-MS m/z 363 ($M^+ + 1$, 20%), 362 (M^+, 100), 361 (85), 343 (11).

***N*-*tert*-butylbenzo[*d*]thiazol-2-amine (17c):**[26] mp 91−95 °C (ethyl acetate/hexane); R_f 0.6 (hexane/ethyl acetate 3:2); IR (KBr) ν 3241, 1597, 1538, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 5.25 (s, br, 1H), 7.03−7.09, 7.24−7.3, 7.52−7.55 (3 m, 1, 1 and 2H, respectively); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29, 53.3, 119, 120.4, 121.4, 125.7, 130.7, 152.4, 164.6; EI-MS m/z 206 (M^+, 23%), 151 (11), 150 (100).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR for all compounds **3**, **5**, **7**, **9**, **11**, **13**, **15**, and **17**, as well as copies of ^{19}F NMR for compounds **9**, and General Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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