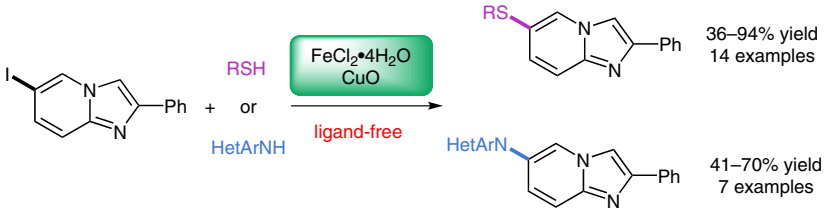
Synthesis Z. Tber et al. Paper

Use of Ligand-Free Iron/Copper Cocatalyst for Nitrogen and Sulfur Cross-Coupling Reaction with 6-Iodoimidazo[1,2-*a*]pyridine

Zahira Tber[a,b]
Marie-Aude Hiebel[a]
Mohamed Akssira[b]
Gérald Guillaumet[a]
Sabine Berteina-Raboin[*a]

[a] Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans UMR-CNRS 7311, BP 6759, rue de Chartres, 45067 Orléans cedex 2, France
[b] Laboratoire de Chimie Physique et Chimie Bioorganique URAC 22, Université Hassan II-Mohammedia-Casablanca, FST, BP 146, 28800 Mohammedia, Morocco
sabine.berteina-raboin@univ-orleans.fr



Received: 11.12.2014
Accepted after revision: 18.02.2015
Published online: 21.04.2015
DOI: 10.1055/s-0034-1380383; Art ID: ss-2014-z0746-op

Abstract A ligand-free cooperative bimetallic iron/copper catalysis system was found to introduce various azoles and thiols onto 6-iodoimidazo[1,2-*a*] pyridine. After optimization, the inexpensive, nontoxic, air-stable, and commercially available CuO and $FeCl_2 \cdot 4H_2O$ enabled a regioselective N- and S-arylation of common nitrogen heterocycles and of a broad range of mercaptans including aliphatic, aromatic, and heterocyclic thiols.

Key words iron, copper, bimetallic catalysis, imidazo[1,2-*a*]pyridine, N and S cross-coupling

Imidazo[1,2-*a*]pyridines demonstrate a high pharmaceutical and biological potential.[1] Several synthetic drugs exhibiting an imidazo[1,2-*a*]pyridine motif have already been commercialized, such as the sedative zolpidem, the anxiolytic alpidem or saridipem, or the heart failure drug olprinone (Figure 1).

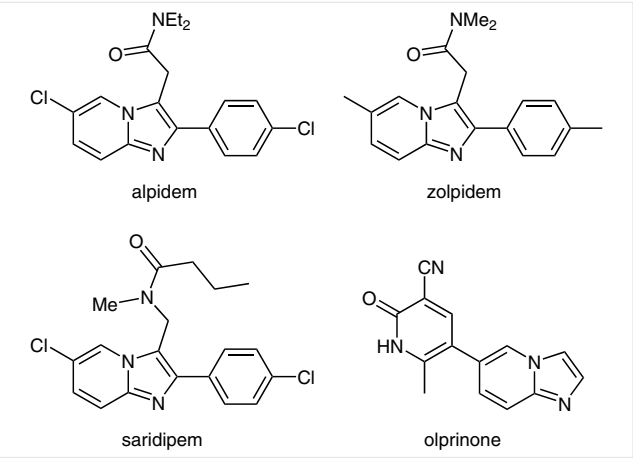


Figure 1 Commercialized drugs with an imidazo[1,2-*a*]pyridine motif

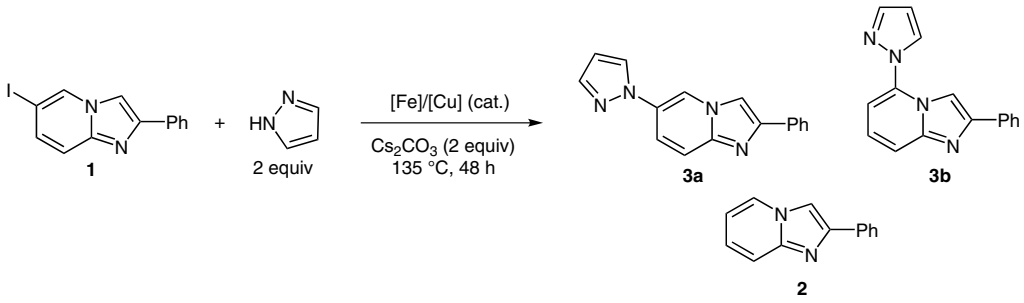
The synthesis and functionalization of these drugs has received considerable attention.[2] Lately, the possible use of a low-cost and environmentally sound catalytic system was made possible by the significant breakthrough reported independently by Buchwald[3] and Taillefer[4] groups in copper-catalyzed cross coupling of N–H heterocycles by using chelating agents. Since then several copper catalyst systems were reported recently to introduce various azoles, amides, and thiophenols at the 5 and 6 positions of the imidazo[1,2-*a*]pyridine.[5] However, these modified Ullmann and Goldberg coupling reactions still often required the addition of an external ligand to promote the reaction[6] even though examples of efficient systems in ligand-free conditions are known.[6e] Because of its potential low cost and its high terrestrial abundance, interest in iron catalysts has been renewed. Kochi et al. were the first to use an iron catalyst in a cross-coupling reaction;[7] it is now being gradually reintroduced as copper cocatalyst without ligands or other additives for arylation, alkylnylation, C–H functionalization, and conjugate addition reactions.[8] Moreover, Taillefer et al. reported the first example of iron/copper co-catalyzed C-, O-, or N-arylation.[4d] To the best of our knowledge, no procedure has been reported using a combination of iron salts with copper as a catalytic system for cross-coupling reactions on imidazo[1,2-*a*]pyridines. Based on our interest in developing environmentally sound methods[9] and our background in the synthesis and functionalization of imidazo[1,2-*a*]pyridines,[10] we therefore disclose herein a ligand-free iron/copper cocatalyst to perform N and S cross-coupling reactions. In view of our diversity-targeting purpose, we focused on introducing miscellaneous challenging

azoles, and aliphatic, aromatic, and heterocyclic thiols since it would give an access to numerous biologically active appealing compounds.

First, the conditions described by Taillefer et al.[4c] at 90 °C were attempted at a higher temperature on our substrate (Table 1, entry 1), but a mixture of 2-phenyl-6-(1*H*-pyrazol-1-yl)imidazo[1,2-*a*]pyridine (**3a**), 2-phenyl-5-(1*H*-pyrazol-1-yl)imidazo[1,2-*a*]pyridine (**3b**), and a dehalogenated product **2** was obtained.

The formation of 5-substituted derivatives had already been observed by Gueiffier et al.[5b] and seemed to be favored by the absence of copper. In our case, the use of an iron catalyst appeared to emphasize this effect since **3b** was obtained in a better yield with $FeCl_2{\cdot}4H_2O$ compared with cesium carbonate alone (Table 1, entries 7 and 9, 58% and 45%, respectively). In order to increase the formation of our desired product **3a**, a survey of the iron/copper catalytic system was undertaken. While $FeCl_3$/CuO also gave a mixture of products, a significant improvement was obtained with the $FeCl_2{\cdot}4H_2O$/CuO system, where **3a** was isolated in 61% yield along with 21% of dehalogenated product **2** easily removed by column chromatography (entry 3). Copper ferrite induced interesting results, but the formation of **3a** came along with a small amount of **3b**, which is significantly tough to remove (entry 4). Therefore, because of the difficulty of isolating the desired product, this experimental condition was disfavored. Other copper sources with different oxidation states (0, I) were then used but without improvement (entries 5 and 6). The combination of $FeCl_2{\cdot}4H_2O$ and CuO gave the best results. The crucial presence of iron was underlined as CuO alone was not able to efficiently promote the reaction (entry 8). Even if brominated products undergo reduction slower, brominated imidazo[1,2-*a*]pyridines induced no yield improvement even after a longer reaction time (entry 10). The reduction of the reactivity was underlined in the case of 6-chloroimidazo[1,2-*a*]pyri-

Table 1 Optimization of the Iron/Copper Catalytic System for the N-Arylation of Pyrazole with 6-Iodoimidazo[1,2-*a*]pyridine



Entry	[Fe] cat. (0.3 equiv)	[Cu] cat. (0.1 equiv)	Solvent	Yield (%)[a] of **2**/**3a**/**3b**
1	$Fe(acac)_3$	CuO	DMF	30:20:30
2	$FeCl_3$	CuO	DMF	40:20:35
3	$FeCl_2{\cdot}4H_2O$	CuO	DMF	21:61:0
4	$CuFe_2O_4$ (0.1 equiv)		DMF	2:60:16[b]
5	$FeCl_2{\cdot}4H_2O$	CuI	DMF	18:45:25
6	$FeCl_2{\cdot}4H_2O$	Cu	DMF	20:45:30
7	$FeCl_2{\cdot}4H_2O$	–	DMF	24:10:58
8	–	CuO	DMF	16:27:26
9	–	–	DMF	2:0:45[b]
10	$FeCl_2{\cdot}4H_2O$	CuO	DMF	28:40:10[b,c]
11	$FeCl_2{\cdot}4H_2O$	CuO	H_2O–MeCN	20:0:0[b]
12	$FeCl_2{\cdot}4H_2O$	CuO	toluene	0:0:0[b,d]
13	$FeCl_2{\cdot}4H_2O$	CuO	*i*-PrOH	0:0:0[b,e]
14	$FeCl_2{\cdot}4H_2O$	CuO	DMF	18:55:0[f]

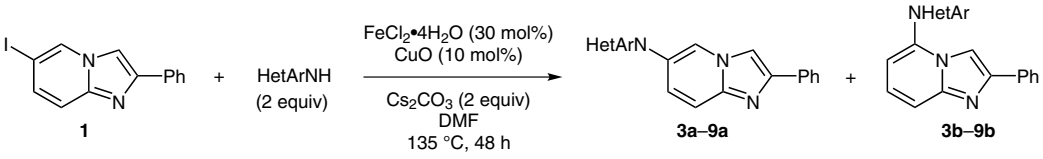
[a] Isolated yields.
[b] After 86 h.
[c] 6-Bromoimidazo[1,2-*a*]pyridine was used instead of the 6-iodo substrate.
[d] Degradation.
[e] Starting material recovered.
[f] Reaction temperature at 90 °C, isolated yield after 72 h.

dine, which gave no cross-coupling adduct. Different solvents and temperature were then examined, without inducing any progress. It was found that the optimal coupling conditions were $FeCl_2{\cdot}4H_2O$ (30 mol%), CuO (10 mol%), Cs_2CO_3 (2 equiv) with pyrazole (2 equiv) in DMF for 48 hours at 135 °C (entry 3).

In an endeavor to expand the scope of the methodology, the reactivity of various azoles was examined (Table 2).

We were pleased to observe that the imidazo[1,2-*a*]pyridines substituted at 6 position **3a**–**9a** were obtained in moderate to good yields as the major product. However, for indole and imidazole, a small amount of product substituted at C5 was isolated (Table 2, entries 5 and 6). Arylation with indazole proceeded exclusively at N-1, meaning that the possible previous equilibrium between the copper N-1 and N-2 indazole did not occur.[3b] It was found that the less acidic pyrrole NH was successfully introduced with a longer reaction time without changing the base (entry 4). Then, the challenging 7-azaindole as well as 1,2,4-triazole gave regioselectively the expected products **5a** and **9a** in 45 and 58% yield, respectively. Furthermore, except in the case of pyrazole, 2-phenylimidazo[1,2-*a*]pyridine **2** was not observed or only in trace amounts.

Table 2 N-Arylation of 6-Iodoimidazo[1,2-*a*]pyridine with Various Nitrogen-Containing Heterocycles



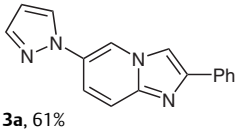
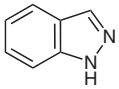
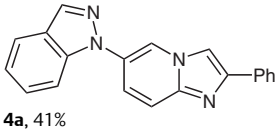
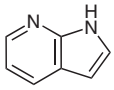
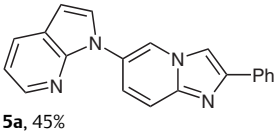
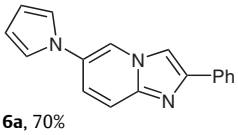
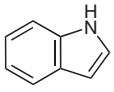
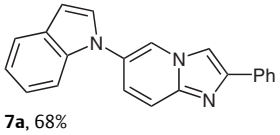
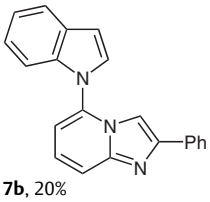
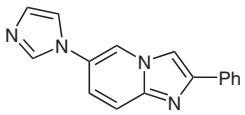
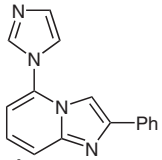
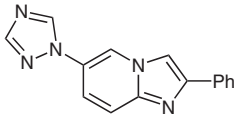
Entry	HetArNH	Product **a**[a]	Product **b**[a]
1		 **3a**, 61%	–
2		 **4a**, 41%	–
3		 **5a**, 45%	–
4[b]		 **6a**, 70%	–
5		 **7a**, 68%	 **7b**, 20%

Table 2 (continued)

Entry	HetArNH	Product **a**[a]	Product **b**[a]
6		 **8a**, 50%	 **8b**, 20%
7		 **9a**, 58%	–

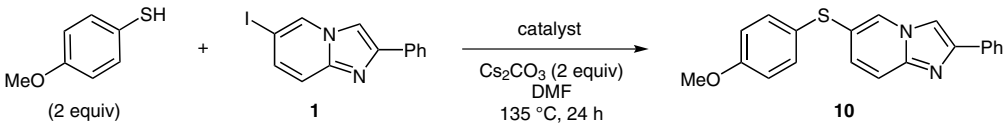
[a] Isolated yields.
[b] Yield after 72 h of reaction.

In order to demonstrate the generality of our method, extension to the C–S coupling reaction was next examined with the same catalytic system. Thiols tend to deactivate metal-based catalysts by a strong coordination and they can also easily form disulfide moieties.[11] In our case, in the presence of 4-methoxybenzenethiol, **10** was obtained in 75% yield. The combined effect of iron and copper catalyst was next investigated (Table 3).

Each catalyst alone gave mainly the dehalogenated product **2**; furthermore only traces of the expected product were obtained with cesium carbonate in the absence of any catalyst, indicating an efficient cooperative bimetallic catalysis with iron and copper. Next, these conditions were employed in a wide range of substrates including aromatic, aliphatic, and heterocyclic thiols on 6-iodoimidazo[1,2-*a*]pyridine (Table 4).

In general, the reactions were very clean and the expected products were synthesized in moderate to excellent yields. First, different aromatic thiols were introduced (products **10**–**13**). It was found that substrates with electron-withdrawing and -donating groups gave the expected product with excellent yield. Then, alkyl thiols, which are known to be more difficult to react than thiols at sp^2-carbon centers, gave the expected product in moderate to good yields.[12] Cyclic, linear, and branched-chain aliphatic saturated mercaptans were well tolerated. Unlike phenyl groups, benzylic substituents exhibited a different reactivity toward the presence of electron-donating and -withdrawing groups on the aromatic ring products **14** and **15**, respectively. With 4-fluorobenzenethiol, a longer reaction time was required to obtain completion of the reaction, and along with **15**, the by-product **2** was also isolated in 20% yield, demonstrating the difficulty of the arylation. Aliphatic thiols, such as the challenging cyclopentyl, and *tert*-butylmercaptans reacted with 6-iodoimidazo[1,2-*a*]pyridine to give **19** and **20** in 69 and 36% yield, respectively. Lastly, we also extended the scope of thiol substrates to thiols bearing benzo[*d*]thiazole. Our iron/copper system was able to efficiently promote the coupling reaction, allowing access to interesting heterocyclic sulfide derivatives.[13] Be-

Table 3 Extension to C–S Coupling reactions



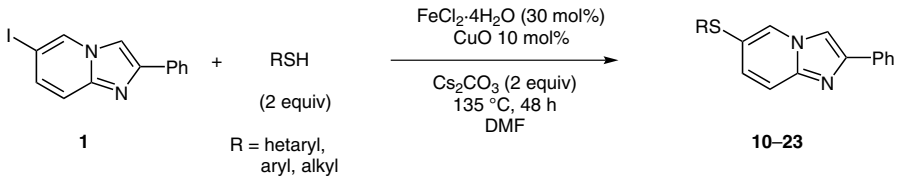
Entry	[Fe] cat. (0.3 equiv)	[Cu] cat. (0.1 equiv)	Yield (%)[a] of **10**/**2**
1	$FeCl_2·4H_2O$	CuO	75:0
2	$FeCl_2·4H_2O$	–	25:50
3	–	CuO	35:46
4	–	–	8:20[b]

[a] Isolated yields.
[b] Recovered 6-iodoimidazo[1,2-*a*]pyridine: 60%.

sides, it is worth noting that except in the case of 4-fluorobenzenethiol, neither dehalogenated product **2** nor diaryl disulfides were formed during the reaction.

In summary, we have developed an efficient cooperative bimetallic iron/copper catalyst system to introduce various azoles and thiols on 6-iodoimidazo[1,2-*a*]pyridine. After optimization, it was found that CuO (10 mol%) and $FeCl_2{\cdot}4H_2O$ (30 mol%) in the presence of Cs_2CO_3 (2 equiv) promoted a regioselective N-arylation of common nitrogen heterocycles in moderate to good yields. Next, the scope of the reaction was widened to a broad range of mercaptans including aliphatic, aromatic, and heterocyclic thiols, without changing the experimental conditions. It is the first general method, which is able to successfully introduce this wide variety of substituents. The salient features of our method are the use of the inexpensive, nontoxic, air-stable, and commercially available iron and copper salts. The cooperative effect of Cu and Fe was demonstrated and avoided the additional use of ligands.

Table 4 S-Arylation and S-Alkylation of 6-Iodoimidazo[1,2-*a*]pyridine with Various Mercaptans



1 **10–23**

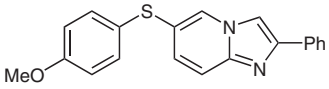
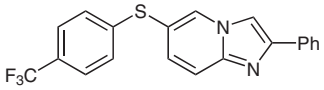
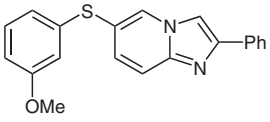
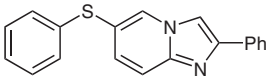
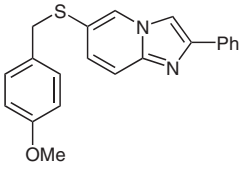
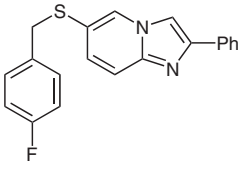
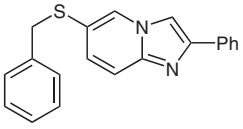
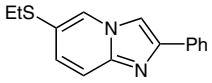
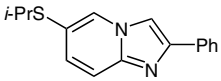
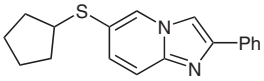
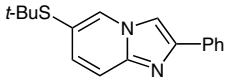
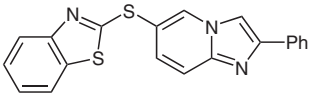
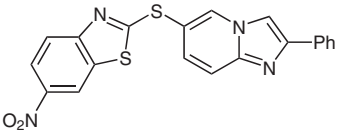
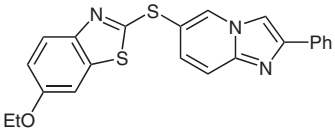
Entry	Product	Entry	Product
1	**10**		75%
2	**11**		80%
3	**12**		74%
4	**13**		70%
5	**14**		70%
6	**15**		45%[a]
7	**16**		60%

Table 4 (continued)

Entry	Product	Entry	Product
8	**17**		73%
9	**18**		51%
10	**19**		69%
11	**20**		36%
12	**21**		94%
13	**22**		60%[b]
14	**23**		92%

[a] Yield after 72 h of reaction, 20% of **2**.
[b] Yield after 28 h of reaction.

All reactions were run under an inert atmosphere (argon) with oven-dried (120 °C) glassware using standard techniques for manipulating air-sensitive compounds. The reactions were monitored by TLC analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040 0.063 mm). Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 40–60 °C. Melting points were taken on samples in open capillary tubes and are uncorrected. The IR spectra of compounds were recorded on a Thermo Scientific Nicolet iS10 (ATR, neat). ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer at 250.13 MHz (^{13}C, 62.9 MHz) or 400.13 MHz (^{13}C, 100.62 MHz). Chemical shifts are given in parts per million from TMS as internal standard. Standard abbreviations are used to denote the proton spectra multiplicities. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G by the 'Federation de Recherche' ICOA/CBM (FR2708) platform.

6-Iodo-2-phenylimidazo[1,2-*a*]pyridine (1)[14]

Under an argon atmosphere, 2-amino-5-iodopyridine (2 g, 9.09 mmol) and $NaHCO_3$ (916 mg, 10.90 mmol) were added to a solution of 2-bromoacetophenone (1.99 g, 9.99 mmol) in EtOH (20 mL). The resulting solution was heated to reflux for 12 h and then cooled down to r.t. After concentration under reduced pressure, the residue was diluted with CH_2Cl_2 (20 mL), the CH_2Cl_2 layer was washed with H_2O (2 × 10 mL), and dried ($MgSO_4$). After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (EtOAc–PE, 1:2) to afford **1** as a white solid; yield: 2.037 g (70%); mp 196–197 °C.

IR (neat): 695, 768, 1516, 2995 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.33 (t, *J* = 7.4 Hz, 1 H), 7.41–7.46 (m, 4 H), 7,95 (d, *J* = 7.6 Hz, 2 H), 8.31 (s, 1 H), 8.90 (s, 1 H).

^{13}C NMR (100.62 MHz DMSO-d_6): δ = 76.0, 108.9, 117.9, 125.6 (2 × CH), 127.9, 128.7 (2 × CH), 131.4, 132.4, 133.4, 143.4, 144.6.

MS (IS): *m*/*z* = 321 [M + 1].

N-Arylation Reaction; General Procedure

Under an argon atmosphere, Cs_2CO_3 (203 mg, 0.624 mmol), CuO (2 mg, 0.031 mmol) and $FeCl_2{\cdot}4H_2O$ (19 mg, 0.093 mmol) were placed as a suspension in DMF (3 mL) in a sealed tube. After stirring for 5 min under argon, **1** (100 mg, 0.312 mmol) and the respective azole (0.624 mmol) were added to the mixture and then heated to 135 °C. After 48 h at this temperature, the mixture was cooled to r.t. and diluted with CH_2Cl_2 (10 mL). Next, the mixture was filtered on Celite. The resulting filtrate was washed with H_2O (3 × 5 mL) and dried ($MgSO_4$). After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel.

2-Phenylimidazo[1,2-*a*]pyridine (2)[14]

Obtained as a by-product in the reactions of **1** with pyrazole (Table 2, entry 1) and **1** with 4-fluorobenzyl mercaptan (Table 4, entry 6); yellow solid; mp 132–133 °C.

IR (neat): 916, 1080, 1142, 1243, 1369, 1474, 3035 cm^{-1}.

^1H NMR (250.13 MHz, $CDCl_3$): δ = 6.73 (t, *J* = 6.7 Hz, 1 H), 7.14 (dd, *J* = 6.9, 8.9 Hz, 1 H), 7.32 (ddd, *J* = 7.3, 3.7, 1.2 Hz, 1 H), 7.38–7.47 (m, 2 H), 7.62 (d, *J* = 9.1 Hz, 1 H), 7.82 (s, 1 H), 7.95 (d, *J* = 7.3 Hz, 2 H), 8.07 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 108.2, 112.5, 117.6, 124.7, 125.7, 126.1 (2 × CH), 128.0, 128.8 (2 × CH), 133.8, 145.9, 145.7.

MS (IS): *m*/*z* = 195 [M + H].

2-Phenyl-6-(1*H*-pyrazol-1-yl)imidazo[1,2-*a*]pyridine (3a) and 2-Phenyl-5-(1*H*-pyrazol-1-yl)imidazo[1,2-*a*]pyridine (3b)

Prepared from pyrazole (42 mg, 0.624 mmol) and separated by column chromatography using EtOAc–PE (2:8) as eluent.

3a

Yield: 50 mg (61%); rusty red solid; mp 179–180 °C.

IR (neat): 702, 801, 920, 1051, 1229, 1394, 1543 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 6.51 (t, *J* = 2.1 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.48 (dd, *J* = 9.7, 2.0 Hz, 1 H), 7.69 (d, *J* = 9.6 Hz, 1 H), 7.75 (d, *J* = 1.6 Hz, 1 H), 7.87 (d, *J* = 2.4 Hz, 1 H), 7.90 (s, 1 H), 7.96 (d, *J* = 7.4 Hz, 2 H), 8.61 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 108.3, 109.5, 117.2, 118.0, 118.8, 126.3 (2 × CH), 127.5, 128.5, 129.0 (2 × CH), 129.1, 133.6, 141.7, 144.4, 147.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4$: 261.1135; found: 261.1137.

3b

Brown solid; mp 165–166 °C.

IR (neat): 724, 775, 1083, 1390, 1525, 1526, 1643 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 6.59 (t, *J* = 2.2 Hz, 1 H), 6.81 (d, *J* = 7.1 Hz, 1 H), 7.22–7.29 (t, *J* = 7.1 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.70 (d, *J* = 9.0 Hz, 1 H), 7.88 (d, *J* = 2.5 Hz, 1 H), 7.93–8.00 (m, 3 H), 8.21 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 106.8, 107.1, 108.2, 117.1, 124.3, 126.5 (2 × CH), 128.4, 128.9 (2 × CH), 131.3, 133.3, 133.7, 142.9, 146.5, 147.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4$: 261.1135; found: 261.1137.

1-(2-Phenylimidazo[1,2-*a*]pyridin-6-yl)-1*H*-indazole (4a)

Prepared from indazole (73 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (2:8) as eluent; yield: 80 mg (41%); beige solid; mp 199–200 °C.

IR (neat): 624, 737, 815, 1201, 1336, 1466, 1539 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.4 Hz, 1 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.39–7.51 (m, 3 H), 7.58 (d, *J* = 9.3 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 9.1 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.91 (s, 1 H), 7.96 (d, *J* = 7.5 Hz, 2 H), 8.22 (s, 1 H), 8.48 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 109.3, 109.9, 117.9, 120.3, 121.7, 122.0, 122.0, 125.4, 126.2 (2 × CH), 127.8, 128.4 (2 × CH), 128.4, 128.9, 133.4, 136.1, 139.3, 144.4, 147.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_4$: 311.1291; found: 311.1293.

2-Phenyl-6-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)imidazo[1,2-*a*]pyridine (5a)

Prepared from 7-azaindazole (73 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (3:7); yield: 43 mg (45%); brown solid; mp 138–141 °C.

IR (neat): 692, 722, 777, 894, 1221, 1275, 1426, 1514, 1592 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 3.5 Hz, 1 H), 7.18 (dd, *J* = 7.8, 4.7 Hz, 1 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 7.42–7.44 (t, *J* = 7.6 Hz, 2 H), 7.50 (d, *J* = 3.6 Hz, 2 H), 7.75 (d, *J* = 9.5 Hz, 1 H), 8.00 (m, 4 H), 8.39 (d, *J* = 4.0 Hz, 1 H), 8.84 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 102.6, 109.4, 117.3, 117.8, 121.2, 121.7, 122.7, 126.2, 126.2 (2 × CH), 127.5, 128.3, 128.9 (2 × CH), 129.6, 133.7, 143.9, 144.2, 147.0, 147.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_4$: 311.1291; found: 311.1293.

2-Phenyl-6-(1*H*-pyrrol-1-yl)imidazo[1,2-*a*]pyridine (6a)

Prepared from pyrrole (86 mL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (5:95); yield: 56 mg (70%); brown solid; mp 146–148 °C.

IR (neat): 613, 802, 1122, 1299, 1482, 1648 cm^{-1}.

^1H NMR (400.13 MHz, $CDCl_3$): δ = 6.28 (s, 2 H), 6.88 (s, 2 H), 7.15 (d, *J* = 9.3 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.53 (d, *J* = 9.5 Hz, 1 H), 7.70 (s, 1 H), 7.83 (d, *J* = 7.5 Hz, 2 H), 7.99 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 109.2, 111.1 (2 × CH), 117.7, 118.0, 120.1 (2 × CH), 121.3, 126.2 (2 × CH), 128.3, 128.9 (2 × CH), 129.4, 133.6, 144.2, 147.0;

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3$: 260.1182; found: 260.1186.

6-(1*H*-Indol-1-yl)-2-phenylimidazo[1,2-*a*]pyridine (7a) and 5-(1*H*-Indol-1-yl)-2-phenylimidazo[1,2-*a*]pyridine (7b)

Prepared from indole (73 mg, 0.624 mmol) and separated by column chromatography eluting with EtOAc–PE (1:9).

7a

Yield: 66 mg (68%); red ochre solid; mp 203–204 °C.

IR (neat): 695, 715, 737, 761, 775, 809, 1218, 1537 cm^{-1}.

^1H NMR (400.13 MHz, DMSO-d_6): δ = 6.74 (d, *J* = 3.3 Hz, 1 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.51 (dd, *J* = 9.5, 2.1 Hz, 1 H), 7.57 (d, *J* = 8.2 Hz, 1 H), 7.64–7.71 (m, 2 H), 7.77 (d, *J* = 9.5 Hz, 1 H), 8.01 (d, *J* = 7.5 Hz, 2 H), 8.47 (s, 1 H), 8.92 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 103.6, 110.2, 110.3, 117.1, 120.4, 120.9, 122.4, 122.6, 123.6, 125.6 (2 × CH), 126.3, 127.9, 128.8 (2 × CH), 128.8, 129.0, 133.7, 135.8, 143.5, 145.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_3$: 310.1339; found: 310.1342.

7b

Yield: 19 mg (20%); yellow solid; mp 139–140 °C.

IR (neat): 691, 716, 734, 762, 1455, 1519 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 3.3 Hz, 1 H), 6.91 (d, *J* = 7.1 Hz, 1 H), 7.10 (d, *J* = 7.7 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.29–7.34 (m, 2 H), 7.35–7.41 (m, 3 H), 7.49 (s, 1 H), 7.73–7.79 (m, 2 H), 7.87 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 106.0, 106.1, 110.2, 110.9, 117.0, 121.7 (2 × CH), 123.6, 124.7, 126.3 (2 × CH), 127.4, 128.4, 128.8 (2 × CH), 129.1, 132.4, 133.5, 136.2, 146.4, 147.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N_3$: 310.1339; found: 310.1342.

6-(1*H*-Imidazol-1-yl)-2-phenylimidazo[1,2-*a*]pyridine (8a) and 5-(1*H*-Imidazol-1-yl)-2-phenylimidazo[1,2-*a*]pyridine (8b)

Prepared from imidazole (42 mg, 0.624 mmol) and separated by column chromatography eluting with EtOAc–PE (2:8).

8a

Yield: 40 mg (50%); brown solid; mp 154–156 °C.

IR (neat): 653, 692, 779, 804, 1050, 1226 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.21–7.30 (m, 3 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 2 H), 7.72 (d, *J* = 9.5 Hz, 1 H), 7.82 (s, 1 H), 7.93 (s, 1 H), 7.96 (d, *J* = 7.8 Hz, 2 H), 8.26 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 109.3, 118.5, 119.2, 119.3, 121.2, 125.8, 126.2 (2 × CH), 128.6, 129.0 (2 × CH), 131.0, 133.2, 136.4, 144.4, 147.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4$: 261.1135; found: 261.1137.

8b

Yield: 16 mg (20%); orange solid; mp 162–163 °C.

IR (neat): 656, 717, 1243, 1478, 1518, 1642, 3109 cm^{-1}.

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 6.84 (dd, *J* = 7.1, 1.0 Hz, 1 H), 7.28–7.48 (m, 6 H), 7.62 (s, 1 H), 7.75 (d, *J* = 9.1 Hz, 1 H), 7.91 (dd, *J* = 8.6, 1.7 Hz, 3 H).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 105.0, 109.3, 118.0, 119.4, 124.5, 126.3 (2 × CH), 128.7, 128.9 (2 × CH), 130.0, 131.3, 133.0, 137.4, 146.8, 147.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4$: 261.1135; found: 261.1134.

2-Phenyl-6-(1*H*-1,2,4-triazol-1-yl)imidazo[1,2-*a*]pyridine (9a)

Prepared from 1,2,4-triazole (43 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (9:1); yield: 94 mg (58%); beige solid; mp 223–225 °C.

IR (neat): 778, 814, 993, 1042, 1273, 1344, 1500 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.34 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.78 (s, 2 H), 7.99 (d, *J* = 7.5 Hz, 2 H), 8.31 (s, 1 H), 8.51 (s, 1 H), 9.15 (s, 1 H), 9.28 (s, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 110.6, 117.3, 118.8, 118.9, 125.1 (2 × CH), 125.7, 128.0, 128.8 (2 × CH), 133.4, 143.0, 143.7, 145.8, 152.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_5$: 262.1087; found: 262.1090.

S-Arylation/Alkylation Reaction General Procedure

Under an argon atmosphere, Cs_2CO_3 (203 mg, 0.624 mmol), CuO (2mg, 0.031mmol), and $FeCl_2{\cdot}4H_2O$ (19 mg, 0.093 mmol) were placed as a suspension in DMF (3 mL) in a sealed tube. After stirring for 5 min under argon, **1** (100 mg, 0.312 mmol) and the respective thiol (0.624 mmol) were added to the mixture and then heated to 135 °C. After 24 h at this temperature, the mixture was cooled to r.t. and diluted with EtOAc (10 mL) and filtered on Celite. The filtrate was washed with aq 5 N NaOH (2 × 5 mL) and H_2O (2 × 5 mL) and dried ($MgSO_4$). After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel.

6-(4-Methoxyphenylsulfanyl)-2-phenylimidazo[1,2-*a*]pyridine (10)

Prepared from 4-methoxythiophenol (76 mL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (2:8); yield: 77 mg (75%); beige solid; mp 135–136 °C.

IR (neat): 719, 814, 1025, 1338, 1492, 1589 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.10 (dd, *J* = 9.6, 1.8 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.37 (dd, *J* = 8.4, 6.6 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.55 (d, *J* = 9.4 Hz, 1 H), 7.79 (s, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 8.10 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 55.5, 108.4, 115.2 (2 × CH), 117.6, 122.2, 125.0, 126.1 (2 × CH), 126.2, 128.2, 128.5, 128.9 (2 × CH), 133.5, 133.7 (2 × CH), 144.6, 146.4, 159.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2OS$: 333.1056; found: 333.1059.

2-Phenyl-6-{[4-(trifluoromethyl)phenyl]thio}imidazo[1,2-*a*]pyridine (11)

Prepared from 4-(trifluoromethyl)thiophenol (85 µL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (3:7); yield: 92 mg (80%); beige solid; mp 150–151 °C.

IR (neat): 726, 1063, 1165, 1240, 1420, 1604, 3008 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.19 (dd, *J* = 9.3, 1.6 Hz, 1 H), 7.27 (d, *J* = 9.0 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 8.3 Hz, 2 H), 7.66 (d, *J* = 9.3 Hz, 1 H), 7.88 (s, 1 H), 7.96 (d, *J* = 7.3 Hz, 2 H), 8.40 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 108.6, 116.60, 118.5, 124.0 [q, *J*(CF_3) = 272 Hz], 126.1 [q, *J*(CF_3) = 4 Hz, 2 × CH], 126.3 (2 × CH), 127.5 (2 × CH), 128.5 [q, *J*(CF_3) = 33 Hz], 128.6, 129.0 (2 × CH), 130.25, 130.45, 133.3, 142.2, 144.9, 147.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.53 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{13}F_3N_2S$: 371.0824; found: 3710829.

6-[(3-Methoxyphenyl)thio]-2-phenylimidazo[1,2-*a*]pyridine (12)

Prepared from 3-methoxythiophenol (77 µL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (3:7); yield: 74 mg (72%); beige solid; mp 139–140 °C.

IR (neat): 679, 719, 764, 857, 1035, 1243, 1480, 1576, 1588 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 3.72 (s, 3 H), 6.83 (d, *J* = 6.8 Hz, 3 H), 7.21–7.29 (m, 2 H), 7.35 (t, *J* = 7.0 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.64 (d, *J* = 9.3 Hz, 1 H), 7.98 (d, *J* = 7.4 Hz, 2 H), 8.42 (s, 1 H), 8.85 (s, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 55.2, 109.7, 112.3, 113.6, 116.5, 117.3, 120.3, 125.6 (2 × CH), 127.9, 128.8 (2 × CH), 129.8, 130.4, 130.8, 133.4, 137.4, 143.9, 145.1, 159.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2OS$: 333.1056; found: 333.1059.

2-Phenyl-6-(phenylthio)imidazo[1,2-*a*]pyridine (13)[15]

Prepared from thiophenol (63 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (3:7); yield: 66 mg (70%); creamy white solid; mp 163–164 °C.

IR (neat): 683, 721, 735, 813, 1024, 1245, 1476, 1581 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 9.6, 1.8 Hz, 1 H), 7.18 – 7.32 (m, 5 H), 7.33 (t, *J* = 7.7 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.57 (d, *J* = 9.4 Hz, 1 H), 7.80 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 2 H), 8.25 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 108.6, 118.0, 119.2, 126.3 (2 × CH), 127.0, 128.4, 128.9, 129.0 (2 × CH), 129.4 (2 × CH), 129.5 (2 × CH), 130.0, 133.6, 136.3, 144.93, 146.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_2S$: 303.0950; found: 303.0952.

6-[(4-Methoxybenzyl)thio]-2-phenylimidazo[1,2-*a*]pyridine (14)

Prepared from 4-methoxy-α-toluenethiol (86 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (2:8); yield: 76 mg (70%); beige solid; mp 124–126 °C.

IR (neat): 722, 801, 1029, 1244, 1508, 1607 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 3.70 (s, 3 H), 4.14 (s, 2 H), 6.84 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.26 (dd, *J* = 9.5, 1.8 Hz, 1 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.54 (d, *J* = 9.3 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 2 H), 8.49 (s, 1 H), 8.31 (s, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 38.2, 55.0, 109.2, 113.8 (2 × CH), 116.5, 119.0, 125.6 (2 × CH), 127.9, 128.0, 128.8 (2 × CH), 128.9, 129.2, 130.0 (2 × CH), 133.6, 143.7, 144.7, 158.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}N_2OS$: 347.1213; found: 347.1215.

6-[(4-Fluorobenzyl)thio]-2-phenylimidazo[1,2-*a*]pyridine (15)

Prepared from 4-fluorobenzyl mercaptan (73 μL, 0.624 mmol) and separated from the by-product **2** (20%) by column chromatography eluting with EtOAc–PE (2:8); yield: 47 mg (45%); beige solid; mp 113–114 °C.

IR (neat): 777, 1015, 1156, 1200, 1330, 1414, 1598, 2920 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.99 (s, 2 H), 6.94 (t, *J* = 8.5 Hz, 2 H), 7.11 (t, *J* = 7.2 Hz, 3 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.54 (d, *J* = 9.3 Hz, 1 H), 7.74 (s, 1 H), 7.93 (d, *J* = 7.6 Hz, 2 H), 7.97 (s, 1 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 40.4, 108.2, 115.5 [d, *J*(CF_3) = 21.5 Hz, 2 × CH)], 117.5, 118.8, 126.20 (2 × CH), 128.4, 128.9 (2 × CH), 129.2, 130.1, 130.64 [d, *J*(CF_3) = 8.1 Hz, 2 × CH], 133.3 [d, *J*(CF_3) = 3.2 Hz], 133.5, 144.9, 146.7, 162.19 [d, *J*(CF_3) = 246.3 Hz].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.67 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}FN_2S$: 335.1013; found: 335.1015.

6-(Benzylthio)-2-phenylimidazo[1,2-*a*]pyridine (16)

Prepared from benzyl mercaptan (73 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (1:1); yield: 58 mg (60%); brown solid; mp 149–150 °C.

IR (neat): 688, 699, 719, 770, 813, 1083, 1338, 1419, 1674 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.99 (s, 2 H), 7.14 (t, *J* = 7.7 Hz, 3 H), 7.25 (d, *J* = 7.0 Hz, 3 H), 7.32 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.54 (d, *J* = 9.3 Hz, 1 H), 7.69 (s, 1 H), 7.91 (d, *J* = 8.2 Hz, 3 H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 41.0, 108.3, 117.3, 119.4, 126.2 (2 × CH), 127.5, 128.3, 128.7 (2 × CH), 128.9 (2 × CH), 128.9, 129.0 (2 × CH), 130.3, 133.4, 137.4, 144.7, 146.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_2S$: 317.1107; found: 317.1110.

6-(Ethylthio)-2-phenylimidazo[1,2-*a*]pyridine (17)[16]

Prepared from ethanethiol (46 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (1:9); yield: 58 mg (73%); beige solid; mp 134–135 °C.

IR (neat): 688, 762, 772, 816, 1073, 1243, 1418, 1619 cm^{-1}.

^{1}H NMR (400.13 MHz, acetone-d_6): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 2.94 (q, *J* = 7.3 Hz, 2 H), 7.21–7.40 (m, 2 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.53 (d, *J* = 9.4 Hz, 1 H), 8.04 (d, *J* = 7.6 Hz, 2 H), 8.24 (s, 1 H), 8.54 (s, 1 H).

^{13}C NMR (100.62 MHz, acetone-d_6): δ = 14.0, 28.9, 108.8, 116.9, 119.6, 125.8 (2 × CH), 127.7, 127.9, 128.5 (2 × CH), 128.8, 134.3, 144.4, 145.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2S$: 255.0950; found: 255.0953.

6-(Isopropylthio)-2-phenylimidazo[1,2-*a*]pyridine (18)

Prepared from 2-propanethiol (57 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (3:7); yield: 43 mg (51%); beige solid; mp 136–137 °C.

IR (neat): 687, 817, 1027, 1208, 1237, 1418, 1619 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.24 (s, 3 H), 1.26 (s, 3 H), 3.37–3.45 (m, 1 H), 7.27–7.37 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.58 (d, *J* = 9.3 Hz, 1 H), 7.96 (d, *J* = 7.5 Hz, 2 H), 8.37 (s, 1 H), 8.68 (s, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 22.8 (2 × CH_3), 38.5, 109.2, 116.5, 117.9, 125.6 (2 × CH), 127.9, 128.7 (2 × CH), 129.8, 130.2, 133.6, 143.9, 144.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2S$: 269.1107; found: 269.1110.

6-(Cyclopentylthio)-2-phenylimidazo[1,2-*a*]pyridine (19)

Prepared from cyclopentanethiol (67 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (2:8); yield: 63 mg (69%); beige solid; mp 103–105 °C.

IR (neat): 689, 725, 798, 1070, 1414, 1519, 2937 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.48–1.60 (m, 4 H), 1.69–1.74 (m, 2 H), 1.93–2.00 (m, 2 H), 3.56–3.65 (m, 1 H), 7.25–7.36 (m, 2 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.55 (d, *J* = 9.4 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 2 H), 8.34 (s, 1 H), 8.64 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 24.2 (2 × CH_2), 32.8 (2 × CH_2), 46.7, 109.2, 116.5, 119.5, 125.6 (2 × CH), 127.9, 128.4, 128.8 (2 × CH), 129.4, 133.5, 143.7, 144.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2S$: 295.1263; found: 295.1264.

6-(*tert*-Butylthio)-2-phenylimidazo[1,2-*a*]pyridine (20)[15]

Prepared from *tert*-butylthiol (70 μL, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (2:8); yield: 32 mg (36%); beige solid; mp 148–149 °C.

IR (neat): 672, 726, 807, 1163, 1320, 1367, 1412, 1471, 1623 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 7.28 (d, *J* = 10.6 Hz, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 9.3 Hz, 1 H), 7.86 (s, 1 H), 7.95 (d, *J* = 7.4 Hz, 2 H), 8.30 (s, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 30.8 (3 × CH_3), 46.3, 108.2, 116.6, 117.7, 126.3 (2 × CH), 128.3, 128.9 (2 × CH), 132.2, 133.47, 133.6, 145.1, 146.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2S$: 283.1263; found: 283.1267.

2-[(2-Phenylimidazo[1,2-*a*]pyridin-6-yl)thio]benzo[*d*]thiazole (21)

Prepared from 2-mercaptobenzothiazole (104 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (1.9); yield: 105 mg (94%); beige solid; mp 181–182 °C.

IR (neat): 750, 720, 814, 1020, 1422, 1459, 1617 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.32–7.35 (m, 2 H), 7.42–7.46 (m, 4 H), 7.77 (d, *J* = 9.4 Hz, 1 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 8.00 (d, *J* = 7.6 Hz, 2 H), 8.50 (s, 1 H), 9.21 (s, 1 H).

^{13}C NMR (62.9 MHz DMSO-d_6): δ = 110.2, 169.0, 153.5, 145.8, 144.3, 135.0, 133.7, 113.3, 117.7, 121.6, 121.9, 124.7, 125.9 (2 × CH), 126.7, 128.4 (2 × CH), 129.0, 130.7, 133.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{14}N_3S_2$: 360.0624; found: 360.0627.

6-Nitro-2-[(2-phenylimidazo[1,2-*a*]pyridin-6-yl)thio]benzo[*d*]thiazole (22)

Prepared from 6-nitro-2-mercaptanbenzothiazole (132 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (1:9); yield: 75 mg (60%); yellow solid; mp 239–240 °C.

IR (neat): 683, 722, 813, 883, 1022, 1275, 1510 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.38 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.57 (dd, *J* = 9.1, 1.9 Hz, 1 H), 7.82 (d, *J* = 9.3 Hz, 1 H), 7.97–8.07 (m, 3 H), 8.30 (dd, *J* = 9.1, 2.5 Hz, 1 H), 8.53 (s, 1 H), 8.98 (d, *J* = 2.4 Hz, 1 H), 9.27 (s, 1 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 110.1, 112.3, 118.0, 118.8, 121.7, 122.1, 125.9 (2 × CH), 128.3, 128.9 (2 × CH), 130.2, 133.1, 134.2, 135.4, 143.7, 144.3, 146.1, 157.4, 177.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{13}N_4O_2S_2$: 405.0474; found: 405.0474.

6-Ethoxy-2-[(2-phenylimidazo[1,2-*a*]pyridin-6-yl)thio]benzo[*d*]thiazole (23)

Prepared from 6-ethoxy-2-mercaptanbenzothiazole (132 mg, 0.624 mmol) and purified by column chromatography eluting with EtOAc–PE (1:9); yield: 115 mg (92%); beige solid; mp 164–165 °C.

IR (neat): 724, 818, 936, 1218, 1256, 1446, 1599 cm^{-1}.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 7.0 Hz, 3 H), 4.01 (q, *J* = 6.9 Hz, 2 H), 7.04 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.37 (t, *J* = 7.3 Hz, 1 H), 7.42–7.57 (m, 4 H), 7.75 (dd, *J* = 9.2, 3.3 Hz, 2 H), 8.00 (d, *J* = 7.6 Hz, 2 H), 8.49 (s, 1 H), 9.17 (s, 1 H).

^{13}C NMR (100.62 MHz DMSO-d_6): δ = 14.5, 63.7, 105.5, 110.0, 113.5, 115.6, 117.6, 122.1, 125.8 (2 × CH), 128.2, 128.8 (2 × CH), 130.4, 133.2, 133.3, 136.5, 144.2, 145.7, 147.7, 156.0, 164.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}N_3OS_2$: 404.0886; found: 404.0883.

Acknowledgment

We acknowledge the OMJ (Office Mediterranéen de la Jeunesse) for financial support to Zahira Tber.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380383.

References

(1) For latest articles, see: (a) Miller, J. F.; Chong, P. K.; Shotwell, J. B.; Catalano, J. G.; Tai, V. W.-F.; Fang, J.; Banka, A. L.; Roberts, C. D.; Youngman, M.; Zhang, H.; Xiong, Z.; Mathis, A.; Pouliot, J. J.; Hamatake, R. K.; Price, D. P.; Seal, J. W. III.; Stroup, L. L.; Creech, K. L.; Carballo, L. H.; Todd, D.; Spaltenstein, A.; Furst, S.; Hong, Z.; Peat, A. J. *J. Med. Chem.* **2014**, *57*, 2107. (b) Hicken, E. J.; Marmsater, F. P.; Munson, M. C.; Schlachter, S. T.; Robinson, J. E.; Allen, S.; Burgess, L. E.; DeLisle, R. K.; Rizzi, J. P.; Topalov, G. T.; Zhao, Q.; Hicks, J. M.; Kallan, N. C.; Tarlton, E.; Allen, A.; Callejo, M.; Cox, A.; Rana, S.; Klopfenstein, N.; Woessner, R.; Lyssikatos, J. P. *ACS Med. Chem. Lett.* **2014**, *5*, 78. (c) Reutlinger, M.; Rodrigues, T.; Schneider, P.; Schneider, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 582. (d) Meng, T.; Wang, W.; Zhang, Z.; Ma, L.; Zhang, Y.; Miao, Z.; Shen, J. *Bioorg. Med. Chem.* **2014**, *22*, 848. (e) Gallud, A.; Vaillant, O.; Maillard, L. T.; Arama, D. P.; Dubois, J.; Maynadier, M.; Lisowski, V.; Garcia, M.; Martinez, J.; Masurier, N. *Eur. J. Med. Chem.* **2014**, *75*, 382. (f) Huang, S.; Qing, J.; Wang, S.; Wang, H.; Zhang, L.; Tang, Y. *Org. Biomol. Chem.* **2014**, *12*, 2344. (g) Denora, N.; Margiotta, N.; Laquintana, V.; Lopedota, A.; Cutrignelli, A.; Losacco, M.; Natile, F. G. *ACS Med. Chem. Lett.* **2014**, *5*, 685.

(2) For latest articles, see: (a) Cao, H.; Liu, X.; Zhao, L.; Cen, J.; Lin, J.; Zhu, Q.; Fu, M. *Org. Lett.* **2014**, *16*, 146. (b) Sanaeishoar, T.; Tavakkoli, H.; Mohave, F. *Appl. Catal. A: Gen.* **2014**, *470*, 56. (c) Siddiqui, I. R.; Rai, P.; Rahila, S.; Anushree, A.; Shamim, S. *Tetrahedron Lett.* **2014**, *55*, 1159. (d) Wang, Y.; Saha, B.; Li, F.; Frett, B.; Li, H.-Y. *Tetrahedron Lett.* **2014**, *55*, 1281. (e) Wang, S.; Liu, W.; Cen, J.; Liao, J.; Huang, J.; Zhan, H. *Tetrahedron Lett.* **2014**, *55*, 1589. (f) Maleki, A.; Rezayan, A. H. *Tetrahedron Lett.* **2014**, *55*, 1848. (g) Vidyacharan, S.; Shinde, A. H.; Satpathi, B.; Sharada, D. S. *Green Chem.* **2014**, *16*, 1168. (h) Chen, C.; Shang, G.; Zhou, J.; Yu, Y.; Li, B.; Peng, J. *Org. Lett.* **2014**, *16*, 1872. (i) Zheng, L.; Hua, R. *J. Org. Chem.* **2014**, *79*, 3930. (j) Gao, Z.; Zhu, X.; Zhang, R. *RSC Adv.* **2014**, *4*, 19891. (k) Wang, Y.; Frett, B.; Li, H. Y. *Org. Lett.* **2014**, *16*, 3016. (l) Xu, X.; Hu, P.; Yu, W.; Hong, G.; Tang, Y.; Fang, M.; Li, X. *Synlett* **2014**, *25*, 718.

(3) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (c) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.

(4) (a) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. French Patent 2840303, **2003**; *Chem. Abstr.* **2003**, *140*, 16744. (b) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695. (d) Taillefer, M.; Xia, N.; Ouali, A. WO Patent 2008004088, **2008**; *Chem. Abstr.* **2008**, *148*, 144205.

(5) (a) Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 4367. (b) Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 5614. (c) Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042. (d) Bischoff, A.; Subramanya, H.; Sundaresan, K.; Sammeta, S. R.; Vaka, A. K. (Forest Laboratories Holdings Ltd) US Patent 201000160323, **2010**; *Chem. Abstr.* **2010**, *153*, 116278. (e) Terao, Y.; Suzuki, H.; Yoshikawa, M.; Yashiro, H.; Takekawa, S.; Fujitani, Y.; Okada, K.; Inoue, Y.; Yamamoto, Y.; Nakagawa, H.; Yao, S.; Kawamoto, T.; Uchikawa, O. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7326. (f) Ince, S.; Haegebarth, A.; Politz, O.; Neuhaus, R.; Boemer, U.; Scott, W. (Bayer Pharma Aktiengesellschaft) International Patent WO 2012007345, **2012**; *Chem. Abstr.* **2012**, *156*, 203296. (g) Enguehard-Gueiffier, C.; Musiu, S.; Henry, N.; Véron, J.-B.; Mavel, S.; Neyts, J.; Leyssen, P.; Paeshuyse, J.; Gueiffier, A. *Eur. J. Med. Chem.* **2013**, *64*, 448.

(6) For reviews and other recent articles on copper catalyst and heterocyclic compounds, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294. (e) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. (f) Bhadra, S.; Sreedhar, B.; Ranu, B. C. *Adv. Synth. Catal.* **2009**, *351*, 2369. (g) Bagley, M. C.; Davis, T.; Dix, M. C.; Fusillo, V.; Rokicki, M. J.; Kipling, D. *J. Org. Chem.* **2009**, *74*, 8336. (h) Fukuzawa, S.-I.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374. (i) Sahoo, S. K.; Jamir, L.; Guin, S.; Patel, B. K. *Adv. Synth. Catal.* **2010**, *352*, 2538. (j) Sperotto, H.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Tetrahedron* **2010**, *66*, 3478. (k) Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J.-E.; Zhang, P.; Huang, K.-W.; Liu, X. *J. Org. Chem.* **2011**, *76*, 8999.

(7) (a) Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (c) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502.

(8) (a) Su, Y.; Jia, W.; Jiao, N. *Synthesis* **2011**, 1678; and references cited therein. (b) Panda, N.; Jena, A. K.; Mohapatra, S.; Rout, S. R. *Tetrahedron Lett.* **2011**, *52*, 1924. (c) Kundu, D.; Chatterjee, T.; Ranu, B. C. *Adv. Synth. Catal.* **2013**, *355*, 2285; and references cited therein.

(9) Hiebel, M.-A.; Fall, Y.; Scherrmann, M.-C.; Berteina-Raboin, S. *Eur. J. Org. Chem.* **2014**, 4643.

(10) For our latest articles on imidazo[1,2-*a*]pyridine, see: (a) El Akkaoui, A.; Bassoude, I.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron* **2011**, *67*, 7128. (b) El Kazzouli, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Lett. Org. Chem.* **2012**, *9*, 118. (c) El Akkaoui, A.; Hiebel, M.-A.; Mouaddib, A.; Berteina-Raboin, S.; Guillaumet, G. *Tetrahedron* **2012**, *68*, 9131. (d) Arnould, A.; Hiebel, M.-A.; Massip, S.; Léger, J.-M.; Jarry, C.; Berteina-Raboin, S.; Guillaumet, G. *Chem. Eur. J.* **2013**, *19*, 12249.

(11) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(12) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936.

(13) Bogenteatter, M.; Carruthers, N. I.; Jablonowski, J. A.; Lovenberg, T. W.; Ly, K. S. (Ortho McNeil Pharmaceutical, Inc.) International Patent WO 02/079168, **2002**; *Chem. Abstr.* **2002**, *137*, 279192.

(14) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073.

(15) Barlin, G. B.; Davies, L. P.; Ireland, S. J.; Ngu, M. M. L.; Zhang, J. *Aus. J. Chem.* **1992**, *45*, 877.

(16) Gol'dfarb, Y.; Stoyanovich, F. M.; Show, A. *Chem. Heterocycl. Compd.* **1979**, *15*, 514.