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Copper-Catalyzed *N*-Arylation of 2-Imidazolines with Aryl Iodides

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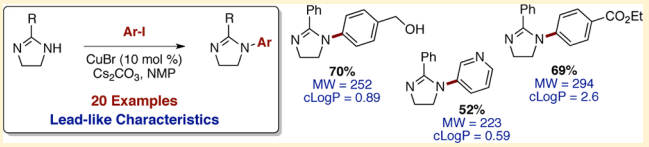
Supporting Information

ABSTRACT: The first copper-catalyzed *N*-arylation of 2-imidazolines is described. The reaction affords compounds with desirable lead-like characteristics in high yield with practical simplicity under inexpensive, "ligand-free" conditions. The cross coupling was successful with electron-rich and electron-poor aromatic iodides. Substrates bearing halides, esters, nitriles, and free hydroxyls are well tolerated, providing reactive handles for further functionalization, as are pyridines. In addition, the regioselective *N*-arylation of a 4-substituted imidazoline is reported.



Imidazolines are prominent motifs in biologically active natural products and medicinal compounds (Figure 1).[1] Perhaps most notably, Nutlin-3 has received considerable attention as an inhibitor of the interaction between tumor suppressor protein p53 and its regulator mdm2, which is overexpressed in many cancer types.[2] Consequently, there has been significant recent interest in the preparation of novel imidazoline analogues.[3,4]

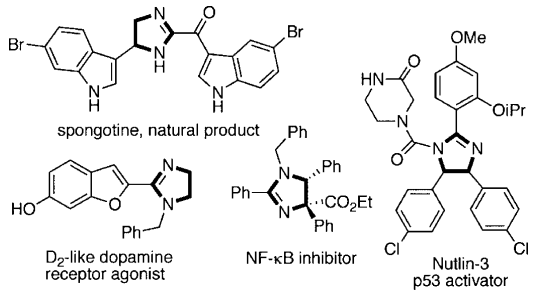
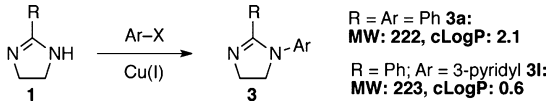


Figure 1. Biologically active imidazoline-containing compounds.

Early-stage drug discovery can benefit from lead compounds possessing inherently desirable physical properties, often characterized through molecular weight and lipophilicity parameters.[5] It can also be desirable to incorporate more three-dimensional shape and saturated carbon atoms into lead-like and fragment-like compounds.[5a,6] This disruption of planarity can afford improvements in aqueous solubility[7] and can lead to improved selectivity and toxicity profiles relative to highly aromatic compounds.[6,8] Consequently, as an approach to novel nonplanar lead-like compounds, we are interested in synthetic methods for the functionalization of intact non-aromatic heterocycles. The *N*-functionalization of imidazolines would offer an attractive approach to lead-like compounds as they provide low MW, high polarity, and a cyclic structure appropriate for molecular scaffolds. Furthermore, 2-substituted-*N*-arylimidazolines have been shown to be nonplanar due to sp^3 puckering of the ring and the out-of-plane orientation of the substituents.[9,10]

Despite the number of methods to prepare *N*-unfunctionalized imidazolines,[11,12] approaches to further derivatize these units by formation of C−N bonds are limited to reactions with activated alkylating agents and carbonyl derivatives. To date there are only two reports of C(sp^2)−N cross coupling involving imidazolines, both using Pd catalysis, and these are limited to very electron-poor aryl halides.[13,14] The ability to efficiently link (hetero)aromatics to imidazolines in this manner would allow rapid access to a wider range of derivatives, thus opening up new areas of lead-like or fragment chemical space (Scheme 1). Here we report the development of the first *N*-arylation of substituted 2-imidazolines using inexpensive copper catalysis, under 'ligand-free' reaction conditions, to afford compounds with lead-like properties.

Scheme 1. Proposed *N*-Arylation of Imidazolines and Possible Lead-like Characteristics[10,15]



Recent years have seen many important advances in the use of transition metals for the formation of C−N bonds, notably the Pd-catalyzed Buchwald−Hartwig coupling.[16] Copper-catalyzed *N*-arylation (Ullman condensation) has been increasingly well developed utilizing a range of nitrogen-containing functional groups.[17] However, while protocols have been developed for the copper-catalyzed *N*-arylation of amidines,[18] there are no examples involving imidazolines, important cyclic variants. Surprisingly, no reaction was observed between 2-phenyl imidazoline and PhBr when applying conditions developed by Antilla for the copper-catalyzed *N*-arylation of *N,N′*-unsubstituted amidines.[19] Like-

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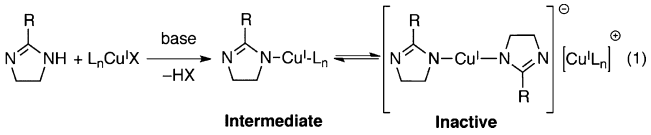
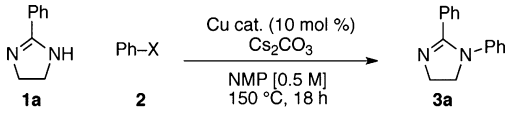
wise, protocols developed for other related substrates were also unsuccessful.[10]

We noted that in the related *N*-arylation of amides (Goldberg reaction), formation of the intermediate copper(I) amidate occurs prior to activation of the aryl halide.[20] Diamine ligands have been shown to limit the coordination of a second amide to form an inactive anionic bis(amido)-Cu^{I} complex, which is the resting state in their absence.[20] Relative to amide substrates, imidazolines have strong coordinating properties, and so have wide ranging uses as ligands for metal complexes.[21,11,14b] We hypothesized that the desired *N*-arylation reaction was prevented due to powerful coordination to Cu, affording a stable bis(imidazolino)Cu complex that was not catalytically active (eq 1). Indeed the product of *N*-arylation would remain a strong ligand and may prevent turnover.



To disrupt coordination of this substrate, we chose to elevate the temperature (150 °C) and examined a range of solvents and ligands.[10] Employing NMP as solvent without an exogenous ligand gave 5% conversion to the desired product. Presumably the NMP has a dual role as a ligand for the Cu species, and as such we proceeded without the inclusion of an external ligand (Table 1). The use of NMP was critical through the optimization, DMA and DMF showed significantly poorer conversion and no conversion was observed with other solvents tested. Using PhI in place of PhBr gave a significant increase in yield (to 29%, entry 2). The copper salt was examined next (entries 3–4); CuTC provided an improved yield relative to CuI, but the inexpensive CuBr was preferable. Several inorganic and amine bases were screened, but Cs_2CO_3 remained the most effective, at a loading of 1.5 equiv (entry 5). Notably, the use of Ag_2CO_3 did not afford the product of *N*-arylation; rather oxidation to 2-phenyl-imidazole (**4**, not shown) occurred cleanly in 69% yield.

Table 1. Selected Optimization of Reaction Conditions[a]



entry	PhX (equiv)	Cu cat.	Cs_2CO_3 (equiv)	yield[b] (%)
1	PhBr (1.0)	CuI	2.0	<5
2	PhI (1.0)	CuI	2.0	29
3	PhI (1.0)	CuTC	2.0	37
4	PhI (1.0)	CuBr	2.0	43
5	PhI (1.0)	CuBr	1.5	59
6	PhI (1.5)	CuBr	1.5	70
7	PhI (2.0)	CuBr	1.5	84 (74)

[a]Conditions: **1a** (0.3 mmol), PhX, Cu cat. (10 mol %), Cs_2CO_3, NMP (0.5 M), 18 h. [b]Yield determined by ^{1}H NMR with an internal standard (1,3,5-trimethoxybenzene) except where shown in parentheses. CuTC = copper(I) thiophene-2-carboxylate.

A reaction concentration of 0.5 M was found to give reproducible results. Attempts to reduce the temperature led to a decrease in yield, whereas raising the temperature further gave decomposition products. The reaction was moderately sensitive to water with the addition of 1 equiv resulting in a drop in yield (28% by ^{1}H NMR). Performing the reaction under an inert atmosphere proved to be vital for the reaction to occur as 2-phenylimidazole **4** formed when O_2 was present.[22] Finally, the yield was maximized by employing 2 equiv of iodobenzene (Table 1, entries 5–7), but increasing to 3 equiv of PhI did not afford a significant further increase (86% by ^{1}H NMR).[23] The reaction required 18 h to achieve maximum conversion. The reaction was successful for reduced copper loadings (76% with 5 mol %; 39% with 1 mol %), though we proceeded with 10 mol % of CuBr for convenience. Under these optimized conditions, a yield of 74% was obtained for **3a** (Table 2, entry 1). The reaction gave a higher yield when performed on a 5 mmol scale (entry 2). Moreover, the reaction time could be reduced using microwave heating, which afforded a comparable yield of **3a** after 60 min at 180 °C (entry 3).[10]

The reaction displayed wide substrate scope upon variation of the aryl iodide (Table 2). *p*-Iodotoluene gave a high yield of **3b** (entry 4); however, using *o*-iodotoluene gave a somewhat reduced yield due to unfavorable steric interactions in forming the more hindered C–N bond (entry 5). Increasing the reaction time to 72 h raised the yield of **3c** to 52% (entry 6). The reaction was successful with both electron-rich (entry 7) and electron-poor substrates (entries 8–12). Compatibility with functional groups is a desirable feature in lead-oriented synthesis to allow further derivatization. Ethyl esters were tolerated, though competitive hydrolysis afforded a reduced yield due to the action of water or hydroxide generated in the decomposition of $CsHCO_3$ following deprotonation of the imidazoline (entry 9).[24,25] Performing the reaction in the presence of 4 Å molecular sieves, to circumvent this, improved the yield significantly (entry 10). Under these conditions, even the corresponding methyl ester was successful, as was the nitrile functional group (entries 11 and 12). Halides were well tolerated (entries 13–15), providing reactive handles for further functionalization. Pleasingly, iodide **2j** bearing an unprotected hydroxyl group was successfully cross-coupled in high yield (entry 16), and heterocycles in the form of pyridine rings could also be readily introduced (entries 17 and 18).

Next the 2-substituent of the imidazoline was varied (Table 3). A variety of 2-arylimidazolines were successfully applied, with various electronic demands tolerated (entries 1–3) as was 2-(4-pyridyl)imidazoline (entry 4). The use of 2-methylimidazoline was successful (entry 5), which is notable due to the introduction of relatively acidic protons and the reduction in the aromatic ring count.

The introduction of a substituent at the 4-position of the imidazoline provides an additional nonplanar element but introduces a question of regiochemistry in the arylation. The arylation of 4-methyl-2-phenylimidazoline **1g** displayed a >6:1 regioselectivity in favor of the less hindered position, affording **10a** as the major product (entry 6). We propose this is due to the reacting nitrogen in the minor diastereoisomer **10b** being more sterically crowded.

In summary, we have described the first *N*-arylation of imidazolines using inexpensive Cu catalysis under convenient "ligand-free" conditions. The reaction is tolerant of a range of electron-rich and electron-poor aromatics and heteroaromatics as well as various functional groups, including halides, esters, and free hydroxyls. The methodology allows rapid diversification to novel imidazoline containing structures that are compliant with lead-like and fragment guideline criteria.[10]

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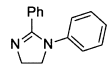
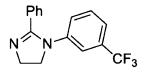
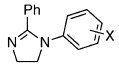
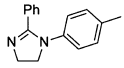
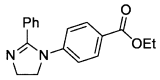
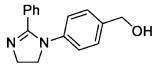
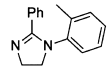
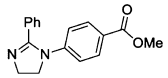
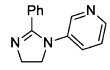
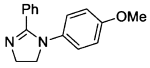
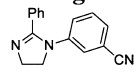
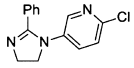
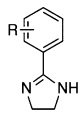
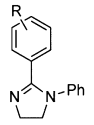
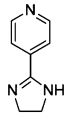
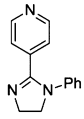
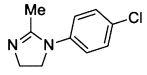
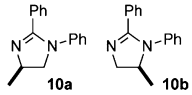
Table 2. Reaction Scope Varying the Aryl Halide in the Cu-Catalyzed Arylation of 1a[a]

entry	*N*-Ar-imidazoline	yield (%)	entry	*N*-Ar-imidazoline	yield (%)	entry	*N*-Ar-imidazoline	yield (%)
1		74	8		67	13	 X = 3-F **3i**	67
2		87[b]				14	X = 4-Cl **3j**	70
3	**3a**	66[c]		**3e**		15	X = 4-Br **3k**	71[f]
4	 **3b**	65	9 10	 **3f**	42 69[e]	16	 **3l**	70
5		32	11		42[e]	17		52
6	**3c**	52[d]		**3g**			**3m**	
7	 **3d**	67	12	 **3h**	55[e]	18	 **3n**	40

[a]Conditions: **1a** (1 equiv, 0.5 mmol), Ar-I **2a–n** (2.0 equiv), CuBr (10 mol %), Cs_2CO_3 (1.5 equiv), NMP (0.5 M), 150 °C, 18 h. [b]Reaction on 5 mmol scale. [c]Microwave heating, 180 °C, 60 min. [d]Reaction time of 72 h. [e]Powdered 4 Å molecular sieves (250 mg) added. [f]Isolated with an inseparable minor impurity derived from ArI.

Table 3. Scope of the Imidazoline in Reaction with Iodobenzene 2a[a]

entry	imidazoline	*N*-Ar-imidazoline	yield (%)
1	 R = 4-Me **1b**	 **5**	52
2	R = 3-OMe **1c**	**6**	78
3	R = 4-Cl **1d**	**7**	47
4	 **1e**	 **8**	37
5[b]	 **1f**	 **9**	41
6	 **1g**	 **10a:10b** (6.4:1)	59[c]

[a]Conditions: **1b–g** (1 equiv, 0.5 mmol), **2a** (2.0 equiv), CuBr (10 mol %), Cs_2CO_3 (1.5 equiv), NMP (0.5 M), 150 °C, 18 h. [b]4-Chloroiodobenzene **2j** employed in place of **2a**. [c]Combined yield of isomers. Isomers separable by flash chromatography. Structures determined by NOE studies.[10]

EXPERIMENTAL SECTION

General Consideration. All nonaqueous reactions were run under an inert atmosphere (argon) atmosphere with oven-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (toluene) or used as supplied (DMF, 1,4-dioxane, NMP). Flash column chromatography was performed using 230–400 mesh silica with the indicated solvent system. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and potassium permanganate stain. Infrared spectra (FTIR) were recorded in reciprocal centimeters (cm^{-1}) using a FT-IR ATR spectrometer. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: 7.27 ppm). Data were reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant, integration and assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm). *J* values are reported in Hz. Assignments of ^1H NMR spectra were made by analysis of the δ/J values and COSY experiments as appropriate. Selective NOE experiments were employed to establish the identity of compounds **10a**/**10b**.[10] In some examples, the resonance from the fully substituted imidazoline NC=N carbon in the ^{13}C NMR was very broad due to quadrupole coupling to ^{14}N nuclei, and thus very difficult to observe. In these cases, the carbon resonance is not reported. Melting points are uncorrected. Reactions with microwave heating were performed using a Biotage Initiator 2.0 Microwave Synthesizer with an external IR temperature sensor. **Reagents:** Commercial reagents were used as supplied or purified by standard techniques where necessary. Purity of the CuBr ≥98.0% (RT, $CuBr_2$ ≤3%). Purity of the Cs_2CO_3, 99%.

Imidazolines 1. Imidazolines **1a** and **1f** were purchased from commercial suppliers and used as supplied. Imidazolines **1b**,[12b] **1c**,[12a] **1d**,[12a] and **1e**,[12b] were prepared according to the referenced literature procedures.

(±)-4-Methyl-2-phenyl-4,5-dihydro-1*H*-imidazole (1g). Procedure adapted from that reported by Togo.[26] 1,2-Diaminopropane (0.47 mL, 5.5 mmol) was added to a solution of benzaldehyde (0.51 mL, 5.0 mmol) in *tert*-butyl alcohol (45 mL). After the mixture was stirred for 30 min at rt, potassium carbonate (2.17 g, 16 mmol) and iodine (2.47 g, 10 mmol) were added. The mixture was stirred at 70 °C for 3 h and then quenched with saturated aqueous Na_2SO_3 until the iodine color had dispersed and then extracted with chloroform (4 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 4-methyl-2-phenylimidazoline **1g** as a dark brown oil (382 mg, 48%): IR (film) cm^{-1} 3196 (br NH), 3060, 2968, 2928, 1616, 1564, 1510, 1460, 1376, 1272, 784, 695; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.03–7.94 (m, 2 H, 2 × Ph-H), 7.56–7.48 (m, 1 H, Ph-H), 7.45–7.37 (m, 2 H, 2 × Ph-H), 4.33–4.21 (m, 1 H, NC*H*(Me)), 3.99 (dd, *J* = 11.6, 10.4 Hz, 1 H, C*H*H), 3.45 (dd, *J* = 11.7, 7.7 Hz, 1 H, CH*H*), 1.37 (d, *J* = 6.4 Hz, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 132.5, 128.8, 128.1, 126.7, 55.4, 55.1, 21.6; HRMS (ESI/TOF) *m*/*z* calcd for $C_{10}H_{13}N_2^+$ $[M + H]^+$ 161.1073, found 161.1071. Compound previously reported.[27]

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General Experimental Procedure for the *N*-Arylation of Imidazolines. *Conventional Heating.* A microwave vial (2−5 mL volume) was charged with imidazoline (0.50 mmol), cesium carbonate (244 mg, 0.75 mmol), and copper(I) bromide (7.2 mg, 0.05 mmol). The reaction vial was sealed with a cap and flushed with argon for approx 15 min. Anhydrous *N*-methyl-2-pyrrolidone (1.0 mL) was added to the sealed vial followed by the aryl iodide (1.00 mmol). The stirred mixture was heated in an oil bath at 150 °C for 18 h and then cooled to rt, diluted with water (15 mL), and extracted with EtOAc (1 × 4 mL, 5 × 2 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography. Where necessary, residual NMP was removed by warming under vacuum (60 °C, up to 2 h, 0.5−1 mbar).

Microwave Heating. As for general procedure above, but the reaction was heated under microwave irradiation at 180 °C for 60 min.

In the Presence of Molecular Sieves. As for the general procedure above except that the reaction vial was charged with flame-activated 4 Å powdered molecular sieves followed by other solid reagents prior to sealing the vial.

1,2-Diphenyl-4,5-dihydro-1*H*-imidazole (3a). Purification by flash chromatography (10% MeOH in EtOAc): dark brown crystalline solid (82.0 mg, 74%); R_f = 0.04 (10% MeOH in EtOAc); mp = 72−76 °C (lit.[28] mp 74 °C); IR (film) cm^{-1} 3061, 2934, 2866, 1586, 1572, 1496, 1379, 1271, 758, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 2 H, Ph-H), 7.36 (t, J = 7.3 Hz, 1 H, Ph-H), 7.28 (t, J = 7.2 Hz, 2 H, Ph-H), 7.17 (t, J = 7.7 Hz, 2 H, Ph-H), 6.99 (t, J = 7.4 Hz, 1 H, Ph-H) 6.80 (d, J = 7.9 Hz, 2 H, Ph-H), 4.07 (br s, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 131.1, 129.8, 128.6, 128.5, 128.0, 123.2, 122.4, 53.9, 53.0; HRMS (ESI/TOF) m/z calcd for $C_{15}H_{15}N_2^+$ $[M + H]^+$ 223.1230, found 223.1233. Observed data (^1H, ^{13}C, mp) consistent with those previously reported.[28,29]

2-Phenyl-1-(4-methylphenyl)-4,5-dihydro-1*H*-imidazole (3b). Purification by flash chromatography (10% MeOH in EtOAc): dark brown oil (76 mg, 65%); R_f = 0.09 (20% MeOH in EtOAc); IR (film) cm^{-1} 3061, 2925, 2864, 1596, 1512, 1499, 1377, 1271, 816, 773, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (br m, 2 H, Ph-H), 7.33 (br m, 1 H, Ph-H), 7.26 (br m, 2 H, Ph-H), 6.96 (d, J = 7.8 Hz, 2 H, Ar−H), 6.70 (d, J = 7.8 Hz, 2 H Ar-H), 4.01 (br s, 4 H, 2 × CH_2), 2.24 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 133.1, 131.2, 129.7, 129.2, 128.4, 128.0, 122.8 53.1, 20.6; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1388. Observed data (^1H, ^{13}C) consistent with that previously reported.[29]

2-Phenyl-1-(2-methylphenyl)-4,5-dihydro-1*H*-imidazole (3c). Reaction time of 72 h. Purification by flash chromatography (1−10% MeOH in EtOAc): pale brown crystalline solid (61.6 mg, 52%); R_f = 0.05 (10% MeOH in EtOAc); mp = 86 °C (lit.[30] mp 85 °C); IR (film) cm^{-1} 3060, 2937, 2864, 1598, 1571, 1491, 1369, 1272, 764, 724, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2 H, Ph-H), 7.26 (m, 1 H, Ar-H), 7.19 (m, 3 H, Ph-H), 7.07 (td, J = 7.5, 1.4 Hz, 1 H, Ar-H), 6.99 (td, J = 7.6, 1.5 Hz, 1 H, Ar-H), 6.81 (dd, J = 7.8, 1.1 Hz, 1 H, Ar-H), 4.10 (br s, 3 H, CH_2 + CH) 3.59 (br s, 1 H, CH), 2.34 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 142.7, 134.9, 131.0, 130.5, 129.8, 128.4, 127.9, 127.2, 126.7, 126.4, 54.3, 53.4, 18.1; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1377. Compound previously reported.[30]

1-(4-Methoxyphenyl)-2-phenyl-4,5-dihydro-1*H*-imidazole (3d). Purification by flash chromatography (5−10% MeOH in EtOAc). Dark yellow amorphous solid (84.1 mg, 67%): mp = 70 °C (9:1 EtOAc/MeOH) (lit.[30] mp 78 °C (hexane)); R_f = 0.02 (10% MeOH in EtOAc); IR (film) cm^{-1} 3060, 2935, 2868, 1611, 1596, 1570, 1508, 1496, 1241, 1039, 830, 774, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.2 Hz, 2 H, Ph-H), 7.31−7.34 (m, 1 H, Ph-H), 7.23−7.28 (m, 2 H, Ph-H), 6.86−6.78 (m, 2 H, Ar-H), 6.76−6.69 (m, 2 H, Ar-H), 4.10−4.00 (m, 2 H, CH_2), 4.00−3.92 (m, 2 H, CH_2), 3.73 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.3, 136.5, 130.7, 129.8, 128.6, 128.0, 125.1, 114.0, 55.3, 55.0, 52.7; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2O^+$ $[M + H]^+$ 253.1335, found 253.1331. Observed data (^1H, ^{13}C, mp) consistent with those previously reported.[29,30]

2-Phenyl-1-(3-trifluoromethylphenyl)-4,5-dihydro-1*H*-imidazole (3e). Purification by flash chromatography (5−10% MeOH in EtOAc). Dark yellow oil (97 mg, 67%): R_f = 0.15 (10% MeOH in EtOAc); IR (film) cm^{-1} 3065, 2948, 2873, 1597, 1495, 1453, 1324, 1268, 1164, 1118, 1071, 1026, 770, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2 H, Ph-H), 7.38 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ar-H), 7.24−7.18 (m, 2 H, Ph-H), 7.00 (br s, 1 H, Ar-H), 6.84 (m, 1 H, Ar-H), 4.09 (br s, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 143.3, 131.0 (q, J_{CF} = 33 Hz), 130.8, 130.1, 129.0, 127.7, 124.6, 123.6 (q, J_{CF} = 273 Hz), 119.1 (q, J_{CF} = 4 Hz), 118.0 (q, J_{CF} = 4 Hz), 53.3; ^{19}F NMR (375 MHz, $CDCl_3$) δ −63.0; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{14}F_3N_2^+$ $[M + H]^+$ 291.1104, found 291.1101.

1-(4-Benzoic acid ethyl ester)-2-phenyl-4,5-dihydro-1*H*-imidazole (3f). Molecular sieves (4 Å) added. Purification by flash chromatography (1−10% MeOH in EtOAc). Pale brown oil (101.5 mg, 69%): R_f = 0.39 (10% MeOH in EtOAc); IR (film) cm^{-1} 3059, 2980, 2930, 2918, 2873, 1651, 1704, 1604, 1530, 1516, 1367, 1268, 1174, 1102; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2 H, Ar-H), 7.47 (d, J = 7.4 Hz, 2 H, Ph-H), 7.41 (t, J = 7.4 Hz, 1 H, Ph-H), 7.32 (t, J = 7.3 Hz, 2 H, Ph-H), 6.72 (d, J = 8.7 Hz, 2 H, Ar-H), 4.31 (q, J = 7.1 Hz, 2 H, Et), 4.17−4.08 (m, 4 H, 2 × CH_2), 1.34 (t, J = 7.1 Hz, 3 H, Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 146.1, 130.8, 130.5, 130.3, 128.5, 124.1, 120.2, 60.8, 53.0, 52.8, 14.4; HRMS (ESI/TOF) m/z Calcd for $C_{18}H_{19}N_2O_2^+$ $[M + H]^+$ 295.1441, found 295.1438.

1-(4-Benzoic acid methyl ester)-2-phenyl-4,5-dihydro-1*H*-imidazole (3g). Molecular sieves (4 Å) added. Purification by flash chromatography (10% MeOH in EtOAc). Brown oil (58.8 mg, 42%): R_f = 0.12 (10% MeOH in EtOAc); IR (film) cm^{-1} 2949, 2872, 1701, 1596, 1514, 1496, 1435, 1376, 1269, 1180, 1113, 770, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2 H, Ar-H), 7.47 (d, J = 7.6 Hz, 2 H, Ph-H), 7.42 (t, J = 7.6 Hz, 1 H, Ph-H), 7.33 (t, J = 7.6, 2 H, Ph-H), 6.73 (d, J = 8.6 Hz, 2 H, Ar-H), 4.21−4.04 (m, 4 H, 2 × CH_2), 3.85 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 161.5, 146.0, 130.6, 130.4, 130.3, 128.51, 128.45, 123.7, 120.2, 53.0, 52.6, 51.9; HRMS (ESI/TOF) m/z calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$ 281.1285, found 281.1283.

3-(2-Phenyl-4,5-dihydro-1*H*-imidazol-1-yl)benzonitrile (3h). Molecular sieves (4 Å) added. Purification by flash chromatography (10% MeOH in EtOAc). Pale brown oil (67.1 mg, 55%): R_f = 0.11 (10% MeOH in EtOAc); IR (film) cm^{-1} 3063, 2949, 2870, 2229, 1593, 1573, 1483, 1373, 1270, 1131, 1003, 772, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.37 (m, 3 H, Ph-H), 7.33 (t, J = 7.5 Hz, 2 H, Ph-H), 7.24−7.15 (m, 2 H, Ar-H), 7.02 (s, 1 H, Ar-H), 6.92−6.87 (m, 1 H, Ar-H), 4.08 (s, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 143.2, 130.6, 130.1, 129.4, 128.5, 128.4, 126.1, 125.8, 124.3, 118.3, 112.7, 53.2, 52.8; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{14}N_3^+$ $[M + H]^+$ 248.1182, found 248.1180.

2-Phenyl-1-(3-fluorophenyl)-4,5-dihydro-1*H*-imidazole (3i). Purification by flash chromatography (5−10% MeOH in EtOAc). Brown oil (81 mg, 67%): R_f = 0.12 (10% MeOH in EtOAc); IR (film) cm^{-1} 3060, 2946, 2875, 1608, 1592, 1493, 1378, 1266, 1155, 853, 770, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 2 H, Ph-H), 7.41 (t, J = 7.3 Hz, 1 H, Ph-H), 7.33 (t, J = 7.4 Hz, 2 H, Ph-H), 7.15−7.04 (m, 1 H, Ar-H), 6.68 (td, J = 8.2, 2.3 Hz, 1 H, Ar-H), 6.59−6.44 (m, 2 H, 2 × Ar-H), 4.07 (br s, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{CF} = 246 Hz), 144.3, 130.8, 130.2, 129.6 (d, J_{CF} = 10 Hz), 128.5, 128.3, 117.5, 109.7 (d, J_{CF} = 21 Hz), 109.0 (d, J_{CF} = 24 Hz), 53.5, 53.0. ^{19}F NMR (375 MHz, $CDCl_3$) δ −111.8; HRMS (ESI/TOF) m/z calcd for $C_{15}H_{14}FN_2^+$ $[M + H]^+$ 241.1136, found 241.1138.

2-Phenyl-1-(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole (3j). Purification by flash chromatography (10% MeOH in EtOAc). Yellow oil (91 mg, 70%): R_f = 0.06 (10% MeOH in EtOAc); IR (film) cm^{-1} 3062, 2936, 2870, 1612, 1592, 1571, 1491, 1376, 1271, 1093, 996, 824, 771, 726, 695, 566; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.41 (m, 2 H, Ph-H), 7.38−7.31 (m, 1 H, Ph-H), 7.27 (m, 2 H, Ph-H), 7.11−7.04 (m, 2 H, Ar-H), 6.72−6.62 (m, 2 H, Ar-H), 4.09−3.92 (m, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 141.4, 130.7, 129.9, 128.5, 128.4, 128.1, 123.3, 53.6, 52.9; HRMS (ESI/TOF) m/z calcd

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for $C_{15}H_{14}ClN_2^+$ $[M + H]^+$ 257.0840, found 257.0839. Observed data (^1H, ^{13}C) consistent with that previously reported.[29]

2-Phenyl-1-(4-bromophenyl)-4,5-dihydro-1*H*-imidazole (3k). Purification by flash chromatography (10% MeOH in EtOAc). Brown oil (107.4 mg, 71%): R_f = 0.12 (10% MeOH in EtOAc); IR (film) cm^{-1} 3059, 2937, 2868, 1612, 1588, 1488, 1376, 1272, 1001, 821, 772, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 2 H, Ph-H), 7.39 (t, J = 7.4 Hz, 1 H, Ph-H), 7.31 (t, J = 7.4 Hz, 2 H, Ph-H), 7.29–7.23 (m, 2 H, Ar-H), 6.65 (d, J = 8.7 Hz, 2 H, Ar-H), 4.04 (s, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 141.9, 132.0, 131.7, 130.2, 128.6, 128.3, 126.9, 123.8, 53.7, 52.8; HRMS (ESI/TOF) m/z calcd for $C_{15}H_{14}BrN_2^+$ $[M + H]^+$ 301.0335, found 301.0335.

[4-(2-Phenyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]methanol (3l). Purification by flash chromatography (5–10% MeOH in EtOAc). Pale yellow oil (88.4 mg, 70%): R_f = 0.04 (10% MeOH in EtOAc); IR (film) cm^{-1} 3190 br, 2937, 2867, 1594, 1568, 1512, 1386, 1271, 1002, 907, 772, 725, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 2 H, 2 × Ph-H), 7.38 (t, J = 7.6 Hz, 1 H, Ph-H), 7.29 (t, J = 7.6 Hz, 2 H, 2 × Ph-H), 7.18 (d, J = 8.0 Hz, 2 H, 2 × Ar-H), 6.78 (d, J = 8.0 Hz, 2 H, 2 × Ar-H), 4.58 (s, 2 H, CH_2OH), 4.06 (s, 4 H, 2 × CH_2N), 3.10 (br s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 142.2, 136.2, 130.8, 130.0, 128.6, 128.2, 127.5, 122.6, 64.5, 54.0, 52.6; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2O^+$ $[M + H]^+$ 253.1335, found 253.1330.

3-(2-Phenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (3m). Purification by flash chromatography (5–10% MeOH in EtOAc). Pale brown oil (58.3 mg, 52%): R_f = 0.05 (10% MeOH in EtOAc); IR (film) cm^{-1} 3035, 2947, 2868, 1568, 1481, 1426, 1374, 1270, 771, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–8.12 (m, 2 H, 2 × pyr-H), 7.45 (d, J = 7.6 Hz, 2 H, 2 × Ph-H), 7.37 (t, J = 7.3 Hz, 1 H, Ph-H), 7.29 (d, J = 7.3 Hz, 2 H, Ph-H), 7.04 (dd, J = 8.3, 4.5 Hz, 1 H, pyr-H), 6.98 (d, J = 8.1 Hz, 1 H, pyr-H), 4.06 (s, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 143.8, 143.3, 139.4, 130.4, 130.2, 128.5, 128.33, 128.26, 123.0, 53.2; HRMS (ESI/TOF) m/z calcd for $C_{14}H_{14}N_3^+$ $[M + H]^+$ 224.1182, found 224.1183.

2-Chloro-5-(2-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (3n). Purification by flash chromatography (5–10% MeOH in EtOAc). Brown oil (51.4 mg, 40%): R_f = 0.16 (10% MeOH in EtOAc); IR (film) cm^{-1} 3057, 2948, 2871, 1615, 1463, 1397, 1271, 1107, 907, 771, 735, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.9 Hz, 1 H, pyr-H), 7.50–7.40 (m, 3 H, Ph-H), 7.35 (t, J = 7.4 Hz, 2 H, Ph-H), 7.08 (d, J = 8.6 Hz, 1 H, pyr-H), 6.96 (dd, J = 8.6, 3.0 Hz, 1 H, pyr-H), 4.18–4.02 (m, 4H, 2 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 144.6, 142.3, 138.2, 131.2, 130.5, 129.9, 128.6, 128.3, 123.6, 53.1, 53.0; HRMS (ESI/TOF) m/z calcd for $C_{14}H_{13}ClN_3^+$ $[M + H]^+$ 258.0793, found 258.0789.

2-(4-Methylphenyl)-1-phenyl-4,5-dihydro-1*H*-imidazole (5). Purification by flash chromatography (5–10% MeOH in EtOAc). Yellow oil (62 mg, 52%): R_f = 0.02 (10% MeOH in EtOAc); IR (film) cm^{-1} 3034, 2925, 2865, 1594, 1497, 1375, 1270, 1130, 1001, 823, 756, 724, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.1 Hz, 2 H, Ar-H), 7.20–7.13 (m, 2 H, Ph-H), 7.08 (d, J = 8.0 Hz, 2 H, Ar-H), 6.96–7.00 (m, 1 H, Ph-H), 6.79–6.82 (m, 2 H, Ph-H), 4.04 (s, 4 H, 2 × CH_2), 2.33 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 143.2, 140.0, 128.7, 128.6, 128.5, 128.0, 123.2, 122.5, 54.0, 52.7, 21.3; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1384.

2-(3-Methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-imidazole (6). Purification by flash chromatography (5–10% MeOH in EtOAc). Dark brown oil (99 mg, 78%): R_f = 0.08 (10% MeOH in EtOAc); IR (film) cm^{-1} 2938, 2869, 1594, 1574, 1494, 1377, 1274, 1235, 1037, 909, 727, 709, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.09 (m, 3 H, Ar-H), 7.07 (br s, 1 H, Ar-H), 7.01–6.93 (m, 2 H, Ar-H), 6.88 (dd, J = 8.3, 2.5 Hz, 1 H, Ar-H), 6.79 (d, J = 7.3 Hz, 2 H, Ar-H), 4.03 (s, 4 H, 2 × CH_2), 3.69 (s, 3 H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 159.1, 142.8, 132.2, 129.0, 128.6, 123.3, 122.5, 121.0, 116.4, 113.2, 55.1, 53.9, 52.8; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2O^+$ $[M + H]^+$ 253.1335, found 253.1336.

2-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-imidazole (7). Purification by flash chromatography (5–10% MeOH in EtOAc). Dark brown oil (59 mg, 47%): R_f = 0.11 (10% MeOH in EtOAc); IR (film) cm^{-1} 3062, 2936, 2868, 1590, 1492, 1377, 1269, 1089, 1014, 833, 824, 771, 724, 694, 558; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2 H, Ar-H), 7.29–7.21 (m, 2 H, Ar-H), 7.19 (dd, J = 8.5, 7.3 Hz, 2 H, Ph-H), 7.02 (t, J = 7.4 Hz, 1 H, Ph-H), 6.84–6.75 (m, 2 H, Ph-H), 4.04 (br s, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 142.8, 135.8, 129.9, 129.5, 128.8, 128.3, 123.6, 122.7, 54.1, 53.0; HRMS (ESI/TOF) m/z calcd for $C_{15}H_{14}ClN_2^+$ $[M + H]^+$ 257.0840, found 257.0839.

4-(1-Phenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine (8). Purification by flash chromatography (1–10% MeOH in EtOAc). Pale yellow oil (40.8 mg, 37%): R_f = 0.05 (10% MeOH in EtOAc); IR (film) cm^{-1} 3042, 2935, 2872, 1591, 1495, 1410, 1386, 1275, 1137, 994, 830, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.6, 1.4 Hz, 2 H, pyr-H), 7.37 (dd, J = 4.6, 1.5 Hz, 2 H, pyr-H), 7.21 (t, J = 7.9 Hz, 2 H, Ph-H), 7.06 (t, J = 7.4 Hz, 1 H, Ph-H), 6.81 (d, J = 7.7 Hz, 2 H, Ph-H), 4.15–4.02 (m, 4 H, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 149.9, 142.4, 138.8, 129.1, 124.3, 123.0, 122.8, 54.3, 53.4; HRMS (ESI/TOF) m/z Calcd for $C_{14}H_{14}N_3^+$ $[M + H]^+$ 224.1182, found 224.1191.

1-(4-Chlorophenyl)-2-methyl-4,5-dihydro-1*H*-imidazole (9). Purification by flash chromatography (1–10% MeOH in CH_2Cl_2). Dark brown oil (42 mg, 41%): R_f = 0.32 (10% MeOH in CH_2Cl_2); IR (film) cm^{-1} 3091, 2936, 1647, 1599, 1492, 1292, 1091, 818; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.8 Hz, 2 H, Ar-H), 6.54 (d, J = 8.8 Hz, 2 H, Ar-H), 3.54–3.48 (m, 2 H, CH_2), 3.29–3.26 (m, 2 H, CH_2), 2.01 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 146.5, 129.0, 122.0, 113.7, 44.2, 39.1, 23.2; HRMS (CI) m/z Calcd for $C_{10}H_{15}ClN_3^+$ $[M + NH_4]^+$ 212.0949, found 212.0961. Compound previously reported.[31]

(±)-4-Methyl-1,2-diphenyl-4,5-dihydro-1*H*-imidazole (10a) and (±)-5-Methyl-1,2-diphenyl-4,5-dihydro-1*H*-imidazole (10b). Isomeric ratio in the crude product mixture = 6.4:1 **10a**:**10b** by ^1H NMR. Purification by flash chromatography (1–10% MeOH in EtOAc) afforded major product *N*-Ar imidazoline **10a** as a brown oil (60.6 mg, 51%) followed by minor product *N*-Ar imidazoline **10b** as a pale yellow oil (10.4 mg, 8%).

*Major product **10a**:* R_f = 0.21 (10% MeOH in CH_2Cl_2); IR (film) cm^{-1} 3061, 2963, 2924, 2866, 1591, 1569, 1493, 1382, 1267, 729, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.2 Hz, 2 H, Ph-H), 7.37 (t, J = 7.4 Hz, 1 H, Ph-H), 7.28 (t, J = 7.5 Hz, 2 H, Ph-H), 7.18 (t, J = 7.9 Hz, 2 H, Ph-H), 7.02 (t, J = 7.4 Hz, 1 H, Ph-H), 6.83 (d, J = 7.5 Hz, 2 H, Ph-H), 4.48–4.31 (m, 1 H, CHCH$_3$), 4.25 (t, J = 9.7 Hz, 1 H, CHH′), 3.69 (dd, J = 9.3, 8.0 Hz, 1 H, CHH′), 1.42 (d, J = 6.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 141.8, 130.5, 129.5, 128.84, 128.77, 128.2, 124.0, 122.7, 60.7, 58.2, 21.9; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1387.

*Minor product **10b**:* R_f = 0.12 (10% MeOH in CH_2Cl_2); IR (film) cm^{-1} 3061, 2967, 2925, 2864, 1592, 1571, 1493, 1376, 1267, 768, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.6 Hz, 2 H, Ph-H), 7.32 (t, J = 7.3 Hz, 1 H, Ph-H), 7.23 (dt, J = 13.3, 7.7 Hz, 4 H, Ph-H), 7.08 (t, J = 7.4 Hz, 1 H, Ph-H), 6.90 (d, J = 7.1 Hz, 2 H, Ph-H), 4.31–4.13 (m, 2 H, CH and CHH′), 3.66 (dd, J = 13.2, 6.7 Hz, 1 H, CHH′), 1.38 (d, J = 5.8 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 142.4, 130.9, 129.9, 129.0, 128.7, 128.0, 125.1, 124.8, 61.6, 61.0, 20.8; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1388. Observed data (^1H NMR) consistent with those previously reported.[32]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization of reaction conditions; microwave heating; analysis of calculated lead-like and fragment characteristics of imidazolines **3** and **5**–**10**; DFT geometry optimization for **3a**; NOE studies on compounds **10a**/**b**; copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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