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The Chan–Evans–Lam *N*-Arylation of 2-Imidazolines

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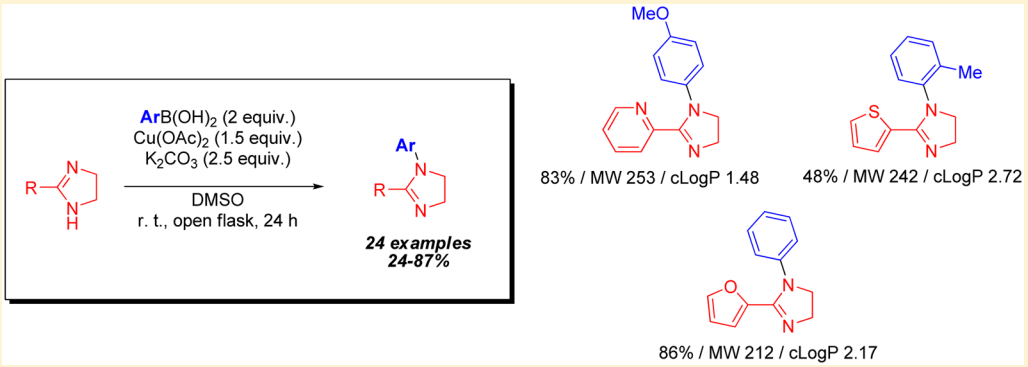
Supporting Information



ABSTRACT: *N*-Arylation of 2-imidazolines with arylboronic acids promoted by copper(II) acetate in DMSO provides an attractive alternative to the earlier reported transition metal-catalyzed approaches employing (hetero)aryl halides as it taps into the vast reagent space of commercially available boronic acids and proceeds at ambient temperature. Many of the resulting compounds are distinctly lead-like, thus positioning the method developed well within the toolbox of lead-oriented synthesis.

Although 2-imidazolines are traditionally considered pharmacological tools for modulating imidazoline receptors,[1] they are, in fact, truly privileged motifs[2] as the range of biological activities displayed by these compounds extends far beyond modulating the class of targets which was named after them.[3] Selected illustrative examples include $P2X_7$ ion channel blocker **1** for the treatment of inflammatory conditions,[4] proteasome inhibitor **2** for multiple myeloma,[5] estrogen receptor modulator **3** for oncology applications,[6] and nutlin-3 (**4**),[7] which disrupts the oncogenic p53-mdm2 protein–protein interactions (Figure 1).

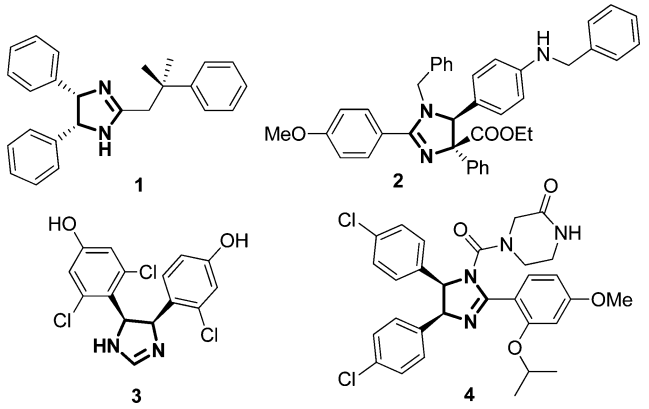


Figure 1. Examples of biologically active imidazolines.

N-(Hetero)aryl-substituted 2-imidazolines had been scarce in the medicinal chemistry literature prior to the introduction of efficient metal-catalyzed methods for 2-imidazoline *N*-arylation with (hetero)aryl halides by us[8] and the Bull group[9] in 2012 and 2013, respectively. Subsequently, we have validated *N*-(hetero)-aryl 2-imidazolines as a privileged motif on its own by discovering selective cyclooxygenase-2 inhibitors,[10] selective kinase inhibitors,[11] antitubercular agents,[12] and isoform-selective carbonic anhydrase inhibitors[13] based on this scaffold (Figure 2).

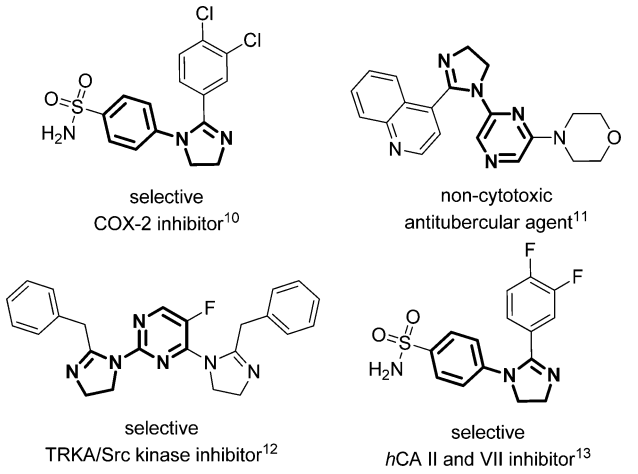


Figure 2. Examples of biologically active *N*-(hetero)aryl 2-imidazolines.

This is a particularly encouraging development in light of a strong emphasis recently put on the nonflat,[14] more saturated

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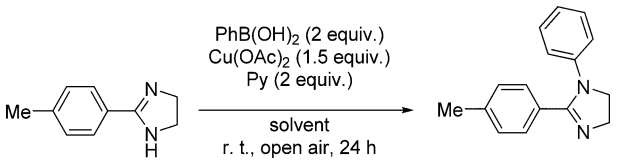
(higher-Fsp^3)[15] scaffolds in the development of small-molecule libraries for early drug discovery. Moreover, the hydrophilic-core *N*-(hetero)aryl imidazolines are distinctly lead-like,[16] allowing ample room for medicinal chemistry optimization in terms of both lipophilicity and molecular weight.[8] The readily available (hetero)aryl halides correspond to a significant chemistry space that can be accessed via the direct 2-imidazoline *N*-arylation methods employing palladium[8] and copper[9] catalysts. However, the complementary copper-catalyzed approach to *N*-arylation using arylboronic acids (the Chan–Evans–Lam coupling[17]) has not been described in the literature for 2-imidazolines.[18] We thought it particularly worthwhile to test the applicability of the Chan–Evans–Lam (CEL) protocol to these heterocycles as substrates as it would allow tapping into the boronic acid reagent space, which is particularly desired when the respective electron-neutral or electron-rich aryl halides are not available or fail to participate in the metal-catalyzed reaction. Moreover, the CEL coupling is generally known to proceed at ambient temperature as opposed to 100–150 °C range employed in the current procedures[8,9] for *N*-arylation of 2-imidazolines, therefore making CEL reaction the only practical option for the thermally prone substrates. Herein, we disclose the CEL protocol for *N*-arylation of 2-imidazolines, which specifically caters to the above needs.

Aiming to identify the optimal protocol for the *N*-arylation of 2-imidazolines with boronic acids, we chose not to alter the 1:2:1.5 molar ratio of the substrate, boronic acid, and Cu(II) acetate promoter originally reported by Chan[17a] and Lam[17c] and focus on finding the best practical combination of the solvent and the base. Notably, using 1.0 and 1.5 equiv of boronic acid incomplete conversions, most likely due the competing boronic acid homocoupling and phenol formation.[19] The initial solvent optimization for the model reaction involving 2-(*p*-tolyl)-4,5-dihydro-1*H*-imidazole (**5a**)[20] and phenylboronic acid in the presence of pyridine (2 equiv) revealed that the best isolated yield was obtained in DMSO (Table 1).

Table 1. Solvent Optimization for the CEL *N*-Arylation of 5a



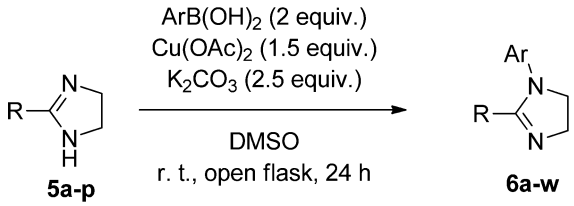
5a **6a**

entry	solvent[a]	isolated yield (%)
1	dichloromethane	34
2	toluene	23
3	MeOH	13
4	acetonitrile	35
5	1,4-dioxane	13
6	1,2-dichloroethane	39 (33[b])
7	ethyl acetate	27
8	NMP	trace
9	DMF	29
10	*i*-PrOH	30
11	pyridine	28
12	DMSO	57[c]
13	$EtOCH_2CH_2OH/H_2O$ (1:1)	trace

[a]0.025M. [b]Air was bubbled through the reaction mixture. [c]Using activated 4 Å molecular sieves[17b,c] did not alter the reaction yield.

However, we found it particularly cumbersome to purify polar 1-phenyl-2-(*p*-tolyl)-4,5-dihydro-1*H*-imidazole (**6a**) from traces of pyridine. Therefore, it was decided to test the anhydrous potassium carbonate (2.5 equiv) as a base in this reaction, which simplified the isolation of the product (**6a**) and led to a marked improvement of the yield (83%) (Scheme 1). This was adopted as a general protocol and applied to an extended range of 2-imidazoline CEL *N*-arylation reactions with results presented in Table 2.

Scheme 1. CEL *N*-Arylation of 2-Imidazolines Developed in This Work



5a-p **6a-w**

From the data presented in Table 2, it is evident that the method is perfectly suitable for introducing various aromatic groups at the nitrogen atom of the 2-imidazoline nucleus. Preliminarily, there appears to be a weak electronic influence from the substituents in position 2 as electron-neutral and electron-rich aromatic groups (e. g., in **5a**, **5c**, or **5m**) generally lead to somewhat higher reaction yields compared to electron-poor aromatics (as in **5n**); however, 3-pyridyl-substituted imidazoline **5k** acted as a perfectly competent substrate in this reaction. As expected, steric encumbrance in the boronic acid exerts some influence on the product yield (**6p** and **6r**).

The sensitivity of the reaction to the steric effects prompted us to compare the regioselectivity of the CEL *N*-arylation of unsymmetrical, 4-methyl-substituted imidazoline **5q**[21a,b] with that reported for $Pd(OAc)_2$-catalyzed (>9:1)[10,22] and CuI-catalyzed procedure (6.4:1).[9] The CEL reaction wth **5q** proved somewhat less regioselective delivering 3.6:1 ratio of regioisomers **6x** and **6x′** (according to ^{1}H NMR analysis of the crude reaction mixture). The latter have been isolated as individual compounds using column chromatography and their regiochemistry unequivocally established from their NOESY spectra (Scheme 2).

From their reactivity prospective, we consider 2-imidazolines a standalone class of heterocycles rather than a mere version of a cyclic amidine. Indeed, as we observed earlier, their "homologues" 1,4,5,6-tetrahydropyrimidines are (somewhat surprisingly) much poorer substrates for Pd-catalyzed *N*-arylation even with a highly reactive 2-chloro-3-nitropyridine.[23] In this work, too, 1,4,5,6-tetrahydropyrimidine **7**[24] turned out to be completely inert under the CEL conditions (Scheme 3).

2-Methythio and 2-amino imidazolines **5o** and **5p** can also be arylated under the CEL conditions, however, the yield of cyclic guanidine **6t** was less satisfactory. 2-Methylthio imidazoline **6q**, however, can be considered as a synthetic precursor that can be elaborated into a range of diversely substituted guanidines **9a–c** akin to **6t** via a direct substitution of methyl mercaptan with primary and secondary amines under conventional heating in 1,4-dioxane (Scheme 4). In conjunction with the CEL *N*-arylation protocol reported herein, this approach provides a streamlined entry into polysubstituted 2-aminoimidazolines which are usually obtained by the multistep synthesis.[25]

In summary, we have developed a convenient, amibient-temperature procedure for *N*-arylation of 2-imidazolines.

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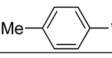
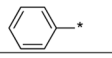
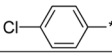
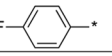
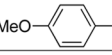
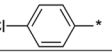
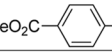
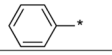
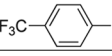
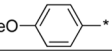
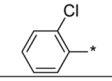
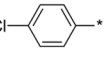
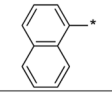
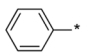
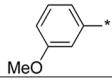
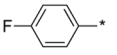
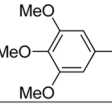
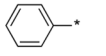
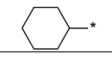
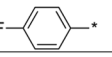
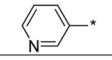
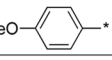
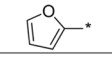
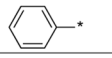
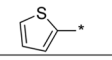
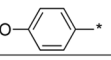
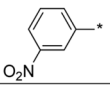
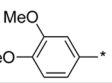
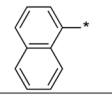
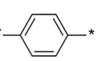
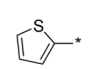
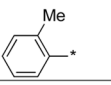
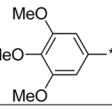
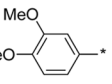
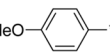
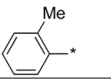
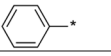
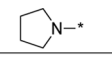
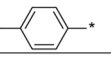
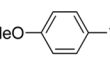
Table 2. *N*-Aryl 2-Imidazolines 6a–w Accessed via the CEL Protocol in This Work

Product	R	Starting 2-imidazoline	Ar	Isolated yield (%)
6a		**5a**		83
6b		**5b**		78
6c		**5c**		84
6d		**5d**		81
6e		**5e**		58
6f		**5f**		76
6g		**5g**		83
6h		**5h**		87
6i		**5i**		74
6j		**5j**		55
6k		**5k**		83
6l		**5l**		86
6m		**5m**		85
6n		**5n**		45[a]
6o		**5g**		79
6p		**5m**		48[b]
6q		**5i**		46[a]
6r		**5c**		24[c]
6s	MeS	**5o**		59
6t		**5p**		31
6u		**5c**		63
6v		**5a**		51[a]
6w		**5d**		69

[a]Conversion after 2 days was about 70%. [b]Conversion after 3 days was about 60%. [c]Conversion after 5 days was about 50%.

Scheme 2. *N*-Arylation Regioselectivity for 4-Methyl-4,5-dihydro-1*H*-imidazole 5q[a]

[a]Arrows indicate the through-space interactions observable in the NOESY spectrum.

Scheme 3. Attempted CEL *N*-Arylation of 1,4,5,6-Tetrahydropyrimidine 7

Scheme 4. Synthesis of 2-Alkylamino-1-phenyl-4,5-dihydro-1*H*-imidazoles 9a–c

Considering the scope of the appendage variations around the 2-imidazoline core achievable with the aid of this protocol, the method clearly belongs to the toolbox of lead-oriented synthesis.[16]

EXPERIMENTAL SECTION

General. NMR spectroscopic data were recorded with a 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ and were referenced to residual solvent proton signal (δ_H = 7.26 ppm) and solvent carbon signal (δ_C = 77.00 ppm).

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Mass spectra were recorded with a an ESI-qTOF spectrometer (electrospray ionization mode). Column chromatography was performed on 230−400 mesh silica gel.

Imidazolines 5. Imidazolines **5a**,[20] **5b−d**,[26] **5e**,[27] **5f**,[26] **5g**,[21b] **5h**,[28] **5i**,[29] **5j**,[21] **5k−l**,[8] **5m**,[21a] **5n**,[21b] and **5q**[21a,b] are known compounds and were prepared from the respective aldehydes according to the literature protocol[26] employing NBS as an oxidant. Compounds **5o** and **5p** were acquired from commercial sources.

General Experimental Procedure for the CEL *N*-Arylation of Imidazolines 5. A mixture of imidazoline **5** (1.0 mmol), $ArB(OH)_2$ (2.0 mmol), $Cu(OAc)_2$ (1.5 mmol), K_2CO_3 (2.5 mmol), and DMSO (3 mL) was stirred in an open flask at ambient temperature for 20−24 h (reaction progress was controlled by TLC). Reaction mixture was diluted with EtOAc (60 mL) containing Et_3N (2 mL), stirred for 10 min, and filtered through a pad of Celite. The filtrate was washed with water (20 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude material was subjected to column chromatography on silica gel to afford pure compound **6**. Eluent for compounds **6a−s**: EtOAc/MeOH/Et_3N system (from 100:0:0 to 94:5:1); eluent for compound **6t**: EtOAc/MeOH/Et_3N system (from 50:40:10 to 45:45:10); eluent for separation of isomers **6u** and **6u′**: EtOAc/Et_3N (from 99:1 to 98:2).

*1-Phenyl-2-(p-tolyl)-4,5-dihydro-1H-imidazole (**6a**).*[9] Yield 197 mg (83%); pale beige solid, mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.18 (t, J = 7.9 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 7.6 Hz, 2H), 4.05 (s, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 143.4, 140.0, 128.8, 128.7, 128.6, 128.3, 123.2, 122.6, 54.1, 53.0, 21.4. HRMS m/z $[M+H]^+$ calcd for $C_{16}H_{17}N_2$ 237.1386, found 237.1382.

*2-(4-Chlorophenyl)-1-(4-fluorophenyl)-4,5-dihydro-1H-imidazole (**6b**).* Yield 214 mg (78%); colorless solid, mp 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 8.6 Hz, 2H), 6.87−6.79 (m, 2H), 4.13−3.94 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 159.5 (d, $^1J_{CF}$ = 244.7 Hz), 139.1 (d, $^4J_{CF}$ = 2.9 Hz), 136.3, 130.1, 128.8, 128.5, 125.1 (d, $^3J_{CF}$ = 8.2 Hz), 115.8 (d, $^2J_{CF}$ = 22.6 Hz), 54.8, 52.8. HRMS m/z $[M+H]^+$ calcd for $C_{15}H_{13}N_2ClF$ 275.0746, found 275.0739.

*1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole (**6c**).* Yield 242 mg (84%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 4.10−3.97 (m, 4H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.2, 141.8, 130.3, 128.8, 128.6, 123.8, 122.6, 113.7, 55.3, 54.0, 52.5. HRMS m/z $[M+H]^+$ calcd for $C_{16}H_{16}ClN_2O$ 287.0946, found 287.0957.

*Methyl 4-(1-Phenyl-4,5-dihydro-1H-imidazol-2-yl)benzoate (**6d**).*[30] Yield 226 mg (81%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.9 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.7 Hz, 2H), 4.13−4.06 (m, 4H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.1, 142.6, 135.2, 131.4, 129.4, 128.9, 128.7, 124.0, 122.9, 54.2, 52.9, 52.2. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1285, found 281.1275.

*1-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-imidazole (**6e**).* Yield 186 mg (58%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 6.86−6.80 (m, 2H), 6.79−6.73 (m, 2H), 4.14−4.05 (m, 2H), 4.02−3.94 (m, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 156.9, 136.1, 134.3, 131.6 (q, $^2J_{CF}$ = 32.6 Hz), 129.1, 125.5, 125.0 (q, $^3J_{CF}$ = 3.8 Hz), 123.8 (d, $^1J_{CF}$ = 272.4 Hz), 114.4, 55.4, 55.3, 53.0. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{16}F_3N_2O$ 321.1209, found 321.1213.

*2-(2-Chlorophenyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-imidazole (**6f**).* Yield 221 mg (76%); colorless solid, mp 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.48 (m, 1H), 7.40−7.29 (m, 3H), 7.07 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 4.17−3.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 139.4, 132.7, 131.1, 131.1, 130.8, 130.0, 128.8, 128.0, 127.1, 120.7, 52.9, 51.5. HRMS m/z $[M+H]^+$ calcd for $C_{15}H_{13}Cl_2N_2$ 291.0450, found 291.0458.

*2-(Naphthalen-1-yl)-1-phenyl-4,5-dihydro-1H-imidazole (**6g**).*[31] Yield 226 mg (83%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.13 (m, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.87−7.83 (m, 1H), 7.53 (dd, J = 7.1, 1.3 Hz, 1H), 7.51−7.45 (m, 2H), 7.42 (dd, J = 8.2, 7.1 Hz, 1H), 7.00 (t, J = 7.9 Hz, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.69−6.63 (m, 2H), 4.28−4.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 141.5, 133.6, 131.0, 130.0, 129.2, 128.6, 128.2, 127.5, 126.8, 126.1, 125.5, 125.0, 122.7, 120.3, 53.1, 52.1. HRMS m/z $[M+H]^+$ calcd for $C_{19}H_{17}N_2$ 273.1386, found 273.1392.

*1-(4-Fluorophenyl)-2-(3-methoxyphenyl)-4,5-dihydro-1H-imidazole (**6h**).* Yield 236 mg (87%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 7.9 Hz, 1H), 7.08 (dd, J = 2.6, 1.6 Hz, 1H), 6.99 (dt, J = 7.6, 1.2 Hz, 1H), 6.94−6.86 (m, 3H), 6.85−6.80 (m, 2H), 4.20−3.90 (m, 4H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 159.3 (d, $^1J_{CF}$ = 244.0 Hz), 159.3, 139.3 (d, $^4J_{CF}$ = 2.9 Hz), 131.7, 129.2, 124.9 (d, $^3J_{CF}$ = 8.2 Hz), 121.2, 116.7, 115.6 (d, $^2J_{CF}$ = 22.6 Hz), 113.5, 55.3, 54.6, 52.7. HRMS m/z $[M+H]^+$ calcd for $C_{16}H_{16}FN_2O$ 271.1241, found 271.1248.

*1-Phenyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-imidazole (**6i**).* Yield 230 mg (74%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 2H), 6.74 (s, 2H), 4.07 (s, 4H), 3.85 (s, 3H), 3.68 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 152.7, 143.1, 139.6, 128.8, 125.6, 124.0, 123.2, 106.3, 60.9, 56.0, 54.2, 52.6. HRMS m/z $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_3$ 313.1547, found 313.1552.

*2-Cyclohexyl-1-(4-fluorophenyl)-4,5-dihydro-1H-imidazole (**6j**).* Yield 136 mg (55%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.02 (m, 4H), 3.87−3.78 (m, 2H), 3.76−3.67 (m, 2H), 2.22−2.13 (m, 1H), 1.80−1.67 (m, 4H), 1.66−1.57 (m, 1H), 1.56−1.42 (m, 2H), 1.28−1.01 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 160.4 (d, $^1J_{CF}$ = 245.5 Hz), 138.3 (d, $^4J_{CF}$ = 2.9 Hz), 126.8 (d, $^3J_{CF}$ = 8.3 Hz), 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 54.1, 52.0, 36.2, 30.9, 26.0, 25.8. HRMS m/z $[M+H]^+$ calcd for $C_{15}H_{20}FN_2$ 247.1605, found 247.1616.

*3-(1-(4-Methoxyphenyl)-4,5-dihydro-1H-imidazol-2-yl)-pyridine (**6k**).* Yield 209 mg (83%); colorless solid, 73−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 2.0 Hz, 1H), 8.56 (dd, J = 4.8, 1.7 Hz, 1H), 7.82 (dt, J = 7.9, 2.0 Hz, 1H), 7.21 (dd, J = 7.9, 4.8 Hz, 1H), 6.90−6.81 (m, 2H), 6.81−6.72 (m, 2H), 4.14−4.04 (m, 2H), 4.03−3.93 (m, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 157.1, 150.7, 149.7, 136.1, 135.7, 126.7, 125.8, 122.9, 114.5, 55.4, 55.2, 52.9. HRMS m/z $[M+H]^+$ calcd for $C_{15}H_{16}N_3O$ 254.1288, found 254.1281.

*2-(Furan-2-yl)-1-phenyl-4,5-dihydro-1H-imidazole (**6l**).*[31] Yield 183 mg (86%); pale beige solid, mp 75−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.0 Hz, 1H), 7.31 (t, J = 7.9 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.05−7.01 (m, 2H), 6.37 (d, J = 3.5 Hz, 1H), 6.34 (dd, J = 3.5, 2.0 Hz, 1H), 4.12−4.04 (m, 2H),

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4.00−3.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 144.6, 144.0, 142.9, 129.0, 125.1, 124.2, 113.8, 111.1, 54.7, 53.1. HRMS m/z $[M+Na]^+$ calcd for $C_{13}H_{12}N_2NaO$ 235.0842, found 235.0842.

*1-(4-Methoxyphenyl)-2-(thiophen-2-yl)-4,5-dihydro-1H-imidazole (**6m**).* Yield 221 mg (85%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 3.9, 2.3 Hz, 1H), 7.11−7.06 (m, 2H), 6.89−6.84 (m, 4H), 4.07−4.00 (m, 2H), 3.93−3.86 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.0, 136.1, 132.8, 129.8, 128.6, 127.6, 127.0, 114.5, 56.4, 55.4, 52.8. HRMS m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2OS$ 259.0900, found 259.0888.

*1-(3,4-Dimethoxyphenyl)-2-(3-nitrophenyl)-4,5-dihydro-1H-imidazole (**6n**).* Yield 146 mg (45%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (t, J = 2.2 Hz, 1H), 8.20 (ddd, J = 8.2, 2.2, 1.1 Hz, 1H), 7.83 (dt, J = 7.8, 1.1 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 6.50−6.44 (m, 2H), 4.16−4.09 (m, 2H), 4.06−3.99 (m, 2H), 3.83 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 149.3, 147.9, 146.9, 135.9, 134.5, 132.5, 129.2, 124.6, 123.8, 116.8, 111.4, 108.7, 56.0, 55.9, 55.5, 53.0. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_4$ 328.1292, found 328.1281.

*1-(4-Fluorophenyl)-2-(naphthalen-1-yl)-4,5-dihydro-1H-imidazole (**6o**).* Yield 146 mg (79%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.15 (m, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.87−7.82 (m, 1H), 7.51 (dd, J = 7.1, 1.3 Hz, 1H), 7.49−7.45 (m, 2H), 7.41 (dd, J = 8.2, 7.1 Hz, 1H), 6.73−6.61 (m, 4H), 4.26−4.19 (m, 2H), 4.16−4.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 158.7 (d, $^1J_{CF}$ = 243.0 Hz), 138.0 (d, $^4J_{CF}$ = 2.8 Hz), 133.6, 130.9, 130.1, 128.8, 128.3, 127.6, 126.8, 126.2, 125.4, 124.9, 122.5 (d, $^3J_{CF}$ = 8.0 Hz), 115.4 (d, $^2J_{CF}$ = 22.6 Hz), 53.2, 52.7. HRMS m/z $[M+H]^+$ calcd for $C_{19}H_{16}FN_2$ 291.1292, found 291.1282.

*2-(Thiophen-2-yl)-1-(o-tolyl)-4,5-dihydro-1H-imidazole (**6p**).* Yield 117 mg (48%); reddish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 2H), 7.24 (td, J = 7.3, 1.6 Hz, 1H), 7.18 (td, J = 7.5, 2.0 Hz, 1H), 7.10 (dd, J = 7.7, 1.6 Hz, 1H), 6.81 (dd, J = 5.1, 3.7 Hz, 1H), 6.72 (dd, J = 3.8, 1.1 Hz, 1H), 4.21−3.93 (m, 3H), 3.75−3.58 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 141.8, 136.6, 133.1, 131.2, 129.2, 128.6, 128.1, 127.6, 127.2, 127.1, 54.9, 53.3, 17.8. HRMS m/z $[M+H]^+$ calcd for $C_{14}H_{14}N_2S$ 243.0950, found 243.0945.

*1-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-imidazole (**6q**).* Yield 171 mg (46%); dark red viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (br.s, 1H), 6.73 (d, J = 8.5 Hz, 2H), 6.50 (dd, J = 8.5, 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 4.12−3.94 (m, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 3.69 (s, 6H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 152.7, 149.0, 146.3, 139.5, 136.7, 125.5, 116.1, 111.3, 108.4, 106.2, 60.9, 56.1, 56.0, 55.8, 55.0, 52.3. HRMS m/z $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_5$ 373.1758, found 373.1756.

*2-(4-Methoxyphenyl)-1-(o-tolyl)-4,5-dihydro-1H-imidazole (**6r**).* Yield 63 mg (24%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.20 (dd, J = 7.4, 1.9 Hz, 1H), 7.08 (td, J = 7.4, 1.5 Hz, 1H), 7.02 (td, J = 7.7, 1.9 Hz, 1H), 6.82 (dd, J = 7.7, 1.5 Hz, 1H), 6.74−6.67 (m, 2H), 4.23−3.92 (br.s, 3H), 3.74 (s, 3H), 3.68−3.42 (br.s, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 160.7, 143.3, 135.0, 131.1, 130.0, 127.3, 126.8, 126.3, 123.1, 113.3, 55.1, 54.4, 53.5, 18.1. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1499.

*2-(Methylthio)-1-phenyl-4,5-dihydro-1H-imidazole (**6s**).*[32] Yield 114 mg (59%); colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.26 (d, J = 7.6 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 3.94 (s, 4H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 140.4, 129.1, 124.9, 122.7, 53.5, 52.9, 14.6. HRMS m/z $[M+H]^+$ calcd for $C_{10}H_{13}N_2S$ 193.0794, found 193.0793.

*1-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)-4,5-dihydro-1H-imidazole (**6t**).* Yield 78 mg (31%); colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.21 (m, 2H), 7.09−6.98 (m, 2H), 3.87−3.80 (m, 2H), 3.80−3.73 (m, 2H), 3.25−3.17 (m, 4H), 1.84−1.75 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 143.5, 129.1, 128.6, 123.8, 55.7, 50.6, 48.9, 25.4. HRMS m/z $[M+H]^+$ calcd for $C_{13}H_{17}ClN_3$ 250.1106, found 250.1103.

*5-(2-(4-Methoxyphenyl)-4,5-dihydro-1H-imidazol-1-yl)-pyrimidine (**6u**).* Yield 161 mg (63%); colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.18 (s, 2H), 6.41 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.20−3.98 (m, 4H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 160.4, 152.2, 148.5, 138.1, 129.9, 122.0, 114.3, 55.3, 53.5, 52.4. HRMS m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_4O$ 255.1240, found 255.1234.

*1-(Thiophen-3-yl)-2-(p-tolyl)-4,5-dihydro-1H-imidazole (**6v**).* Yield 124 mg (51%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 5.2, 3.2 Hz, 1H), 6.51 (dd, J = 5.2, 1.5 Hz, 1H), 6.33 (dd, J = 3.2, 1.5 Hz, 1H), 4.10−4.02 (m, 2H), 4.01−3.91 (m, 2H), 2.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 141.9, 140.1, 128.9, 128.5, 128.3, 124.4, 123.0, 109.8, 53.6, 53.2, 21.4. HRMS m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2S$ 243.0950, found 243.0950.

*Methyl 4-(1-(Pyridin-3-yl)-4,5-dihydro-1H-imidazol-2-yl)-benzoate (**6w**).* Yield 203 mg (69%); colorless solid, mp 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 4.7, 1.4 Hz, 1H), 8.18 (d, J = 2.7 Hz, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.08 (dd, J = 8.3, 4.7 Hz, 1H), 6.99 (ddd, J = 8.3, 2.7, 1.5 Hz, 1H), 4.20−4.03 (m, 4H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.1, 144.5, 143.7, 139.3, 134.9, 131.7, 129.7, 128.8, 128.6, 123.2, 53.8, 53.5, 52.3. HRMS m/z $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_2$ 282.1237, found 282.1228.

*4-Methyl-1-phenyl-2-(p-tolyl)-4,5-dihydro-1H-imidazole (**6x**).* Yield 161 mg (64%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.23−7.15 (m, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.99 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.6 Hz, 2H), 4.39−4.28 (m, 1H), 4.16 (dd, J = 9.9, 9.1 Hz, 1H), 3.64 (dd, J = 9.1, 8.0 Hz, 1H), 2.34 (s, 3H), 1.43 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 143.2, 140.2, 128.8, 128.8, 128.7, 128.0, 123.2, 122.4, 60.8, 59.3, 22.2, 21.4. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2$ 251.1543, found 251.1539.

*5-Methyl-1-phenyl-2-(p-tolyl)-4,5-dihydro-1H-imidazole (**6x′**).* Yield 43 mg (17%); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.2 Hz, 2H), 7.21 (t, J = 7.8 Hz, 2H), 7.11−7.02 (m, 3H), 6.94−6.87 (m, 2H), 4.28−4.10 (m, 2H), 3.64 (dd, J = 13.7, 6.7 Hz, 1H), 2.30 (s, 3H), 1.37 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 142.9, 139.9, 128.9, 128.70, 128.69, 128.3, 125.1, 124.7, 61.6, 61.2, 21.4, 20.9. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2$ 251.1543, found 251.1530.

*2-(p-Tolyl)-1,4,5,6-tetrahydropyrimidine (**7**).* 7 is a known compound and was prepared as reported in the literature.[24]

*N-Isobutyl-1-phenyl-4,5-dihydro-1H-imidazol-2-amine (**9a**).* In a screw-capped tube a solution of compound **6s** (96 mg, 0.5 mmol) and isobutylamine (55 mg, 0.75 mmol) in dry *n*-butanol (1 mL) was stirred at 110 °C for 24 h. Volatiles were removed in vacuo and the crude residue was subjected to column chromatography on silica gel (eluent MeOH to MeOH-Et_3N (5:1)) to afford pure titled compound. Yield 67 mg (62%),

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colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 3.93 (br.s, 1H), 3.82−3.76 (m, 2H), 3.74−3.67 (m, 2H), 3.08 (d, J = 6.9 Hz, 2H), 1.90−1.74 (m, 1H), 0.91 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 141.4, 129.6, 123.9, 121.7, 52.0, 51.0, 48.8, 28.4, 20.3. HRMS m/z $[M+H]^+$ calcd for $C_{13}H_{20}N_3$ 218.1652, found 218.1655.

General Experimental Procedure for the Preparation of 2-Alkylaminoimidazolines 9b,c. In a screw-capped tube a solution of compound **6s** (96 mg, 0.5 mmol) and appropriate amine (0.6 mmol) in dry 1,4-dioxane (1 mL) was stirred at 110 °C during 7 days (for **9b**) or 3 days (for **9c**). Volatiles were removed in vacuo and the crude residue was subjected to column chromatography on silica gel (eluent EtOAc/MeOH/Et_3N from (94:5:1) to (88:10:2)) to afford pure compounds **9b,c**.

*2-(1-Phenyl-4,5-dihydro-1H-imidazol-2-yl)-1,2,3,4-tetrahydroisoquinoline (**9b**).* Yield 72 mg (54%); colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.19−7.14 (m, 2H), 7.13−7.03 (m, 3H), 4.46 (s, 2H), 4.00−3.91 (m, 2H), 3.85−3.76 (m, 2H), 3.37 (t, J = 5.9 Hz, 2H), 2.78 (t, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 144.6, 134.2, 133.6, 129.1, 128.7, 126.5, 126.4, 126.0, 123.1, 121.3, 54.8, 50.0, 49.7, 45.6, 28.3. HRMS m/z $[M+H]^+$ calcd for $C_{18}H_{20}N_3$ 278.1652, found 278.166.

*N-(4-Methoxybenzyl)-1-phenyl-4,5-dihydro-1H-imidazol-2-amine (**9c**).* Yield 103 mg (73%); colorless solid, mp 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 7.8 Hz, 2H), 7.30−7.23 (m, 4H), 7.11 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.90−3.85 (m, 2H), 3.83 (br.s, 1H), 3.80 (s, 3H), 3.78−3.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 157.1, 140.8, 131.1, 129.6, 128.9, 124.2, 121.9, 114.0, 55.3, 51.9, 47.8, 47.4. HRMS m/z $[M+H]^+$ calcd for $C_{17}H_{20}N_3O$ 282.1601, found 282.1612.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02404.

Copies of ^{1}H and ^{13}C NMR (as well as NOESY) spectra (PDF)

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Notes

The authors declare no competing financial interest.

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