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Acid-Catalyzed 1,3-Dipolar Cycloaddition of 2*H*-Azirines with Nitrones: An Unexpected Access to 1,2,4,5-Tetrasubstituted Imidazoles

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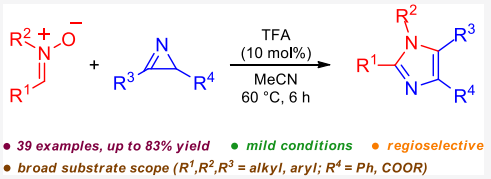
ABSTRACT: The first 1,3-dipolar cycloaddition of 2*H*-azirines with nitrones, a straightforward approach toward the regioselective synthesis of 1,2,4,5-tetrasubstituted imidazoles, is reported. This trifluoroacetic acid-catalyzed protocol tolerates a broad range of aliphatic and aromatic substrates, offering an efficient access to highly diverse, multisubstituted imidazoles in isolated yields up to 83% under mild conditions.



INTRODUCTION

2*H*-Azirines have received significant attention because of their wide applicability as building blocks in organic synthesis.[1] In addition to their ability to act as both nucleophiles and electrophiles,[2] 2*H*-azirines can also operate as dienophiles, dipolarophiles, and dipoles in cycloaddition reactions.[3] Furthermore, they can undergo selective ring cleavage on thermal or photochemical excitation to generate reactive vinyl nitrene, imino carbene, and nitrile ylide species.[4] By exploiting this versatile reactivity, efforts have been made over the past decades on the synthesis of *N*-heterocycles, such as pyrroles,[5] pyrazoles,[6] pyridines,[7] pyrazines,[8] and indoles,[9] from 2*H*-azirines.[1] In contrast, the azirine-based assembly of imidazoles has been less extensively explored.[10]

Looking at the 1,3-dipolar cycloaddition (1,3-DC) of 2*H*-azirines as dipolarophiles, the dipole scope of the reaction is almost exclusively limited to azomethine ylides (Scheme 1a).[11] To the best of our knowledge, there is no precedent for the utilization of nitrones in cycloaddition reactions involving azirines. Inspired by this information and the well-known dipolar cycloaddition reactions of the easily accessible nitrones[12] with alkenes,[13] alkynes,[14] and strained cyclopropenes[15] toward the synthesis of isoxazolidine and isoxazoline scaffolds (Scheme 1b,c), we envisioned a 1,3-DC approach for the construction of an unprecedented aziridine-fused bicyclic framework (Scheme 1d). Unexpectedly, the reaction between 2*H*-azirines and nitrones led to the discovery of a novel access to 1,2,4,5-tetrasubstituted imidazoles (Scheme 1e), which have drawn considerable attention owing to their wide range of biological and pharmacological properties including, among others,[16] p38α MAP kinase inhibitory,[17] antiviral,[18] antibacterial,[19] and anticancer[20] activities.

RESULTS AND DISCUSSION

We initiated our study by investigating the 1,3-DC of *C*-phenyl-*N*-methylnitrone **1a** and racemic ethyl 3-methyl-2*H*-azirine-2-carboxylate ((±)-**2a**) in anhydrous acetonitrile. However, no conversion was observed. In order to increase the reactivity of azirine (±)-**2a**, several Brønsted and Lewis acid catalysts were tested at room and elevated temperatures (60 °C) (Table 1, entries 2−31; see the Supporting Information for conversions and yields in 8 and 24 h). The

Scheme 1. 2*H*-Azirines and Nitrones in 1,3-DC

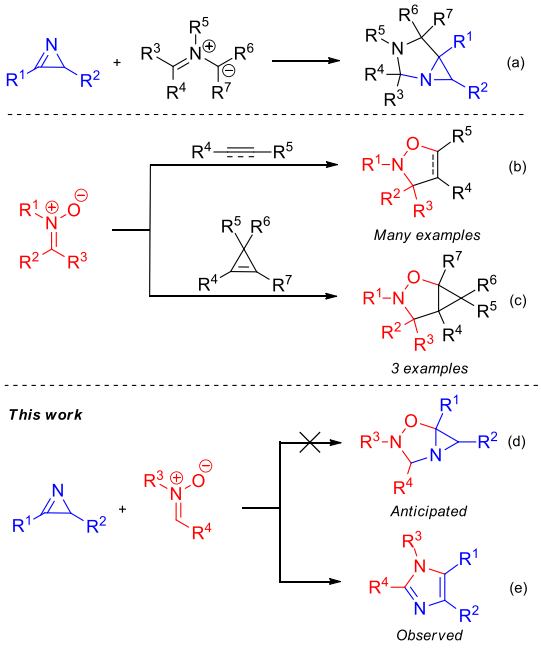


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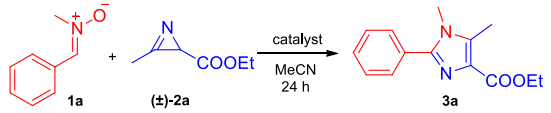
Table 1. Catalyst Screening[a]



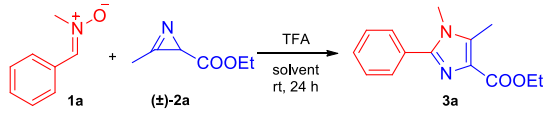
entry	catalyst	yield (%)[b]	yield (%)[c]
1		0	0
2	HCOOH	36	42
3	AcOH	0	17
4	**TFA**	**62**	**50**
5	$MeSO_3H$	52	42
6	PTSA × H_2O	57	44
7	$HClO_4$ (70%)	56	48
8	H_2SO_4	49	41
9	$NaHSO_4$	28	30
10	$B(OH)_3$	35	39
11	PTA[f]	54	49
12	BINOL-phosphoric acid[g]	52	43
13	silica gel[d,e]	16	41
14	Amberlyst 15[d]	1	1
15	montmorillonite K10[d]	22	22
16	$ZnCl_2$	8	22
17	$Zn(OAc)_2$	7	9
18	ZnF_2	0	22
19	$InCl_3$	12	21
20	$In(OAc)_3$	2	20
21	$In(OTf)_3$	39	35
22	$FeCl_2$ × $4H_2O$	4	31
23	$FeCl_3$ × $6H_2O$	7	20
24	CuCl	2	13
25	$CuCl_2$	3	16
26	$Cu(OAc)_2$	2	2
27	$Cu(OTf)_2$	12	23
28	$Mg(OTf)_2$	56	37
29	$Yb(OTf)_3$	57	39
30	$Sc(OTf)_3$	56	42
31	$Dy(OTf)_3$	59	39

[a]Reaction conditions: nitrone **1a** (0.10 mmol), 2*H*-azirine (±)-**2a** (0.10 mmol), anhydrous MeCN (0.3 mL), catalyst (10 mol %), 24 h. [b]Room temperature. Yields were determined by HPLC−MS analysis. [c]60 °C. Yields were determined by HPLC−MS analysis. [d]10 w/v % was applied. [e]60 Å, 70−230 mesh. [f]Phosphotungstic acid. [g]1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate.

reaction of **1a** and **2a** was readily promoted by most of the applied catalysts. Surprisingly, however, the regioselective formation of imidazole-4-carboxylate **3a** was observed instead of the expected cycloadduct. The best results were obtained when trifluoroacetic acid (TFA) was utilized at room temperature, affording **3a** in 62% high-performance liquid chromatography (HPLC) yield (Table 1, entry 4). Other Brønsted acids such as $HClO_4$ and *p*-toluenesulfonic acid (PTSA) gave similar yields (Table 1, entries 6 and 7), whereas AcOH and solid acids exhibited poor catalytic activity (Table 1, entries 3, 13−15). Among the tested Lewis acids, only $Mg(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $Dy(OTf)_3$ showed considerable efficiency (Table 1, entries 28−31), while zinc, indium, iron, and copper salts proved to be ineffective (Table 1, entries 16−27).

To further optimize the reaction conditions, various solvents were examined at room temperature in the presence of TFA (10 mol %) as a catalyst (Table 2, entries 1−13). However,

Table 2. Optimization of the Reaction Conditions[a]



entry	solvent	**2a** (equiv)	TFA (mol %)	yield (%)[b]
1	MeCN	1.0	10	62
2	MeOH	1.0	10	39
3	EtOH	1.0	10	46
4	IPA	1.0	10	33
5	TFE[c]	1.0	10	14
6	HFIP[c]	1.0	10	3
7	$CHCl_3$	1.0	10	39
8	CH_2Cl_2	1.0	10	55
9	Toluene	1.0	10	42
10	THF	1.0	10	54
11	dioxane	1.0	10	47
12	DMF	1.0	10	48
13	DMSO	1.0	10	13
14	MeCN	1.25	10	70
15	MeCN	1.5	10	74
16	MeCN	2.0	10	74
17	MeCN	1.5	1	43
18	MeCN	1.5	2.5	60
19	MeCN	1.5	5	73
20	MeCN	1.5	15	72
21	MeCN	1.5	20	68
22	MeCN	1.5	40	41
23[d]	MeCN	1.5	5	69
24[d]	MeCN	1.5	10	78 (72)[e]

[a]Reaction conditions: nitrone **1a** (0.10 mmol), 2*H*-azirine (±)-**2a** (0.10−0.20 mmol), anhydrous solvent (0.3 mL), TFA (1−40 mol %), rt, 24 h. [b]Yields were determined by HPLC−MS analysis. [c]Non-dried. [d]60 °C, 6 h. [e]Isolated yield. Nitrone **1a** (1 mmol), 2*H*-azirine (±)-**2a** (1.5 mmol), anhydrous MeCN (3 mL), TFA (10 mol %), 60 °C, 6 h.

none of the tested media proved superior to acetonitrile (62% HPLC yield, Table 2, entry 1). In general, the formation of **3a** was slightly more favored in aprotic solvents, while fluorinated alcohols (entries 5 and 6) and dimethyl sulfoxide (DMSO) were not tolerated. To our delight, by employing 1.5-fold excess of azirine **2a**, further improvement in the yield of **3a** could be achieved (74% HPLC yield, Table 2, entry 15). On the other hand, when lower or higher catalyst loadings in the range of 1−40 mol % were applied, a trend of decreasing yields was observed (Table 2, entries 17−22). Finally, the reaction performed at 60 °C in the presence of 10 mol % of TFA pleasingly furnished the product **3a** in 78% HPLC yield and 72% isolated yield in 6 h (Table 2, entry 24). It is noteworthy that HPLC−MS analysis of the crude reaction mixtures did not indicate the formation of the cycloadduct or other isomeric imidazoles.

To explore the scope of the reaction, a range of *N*-methylnitrones (**1a−r**) were reacted with azirine **2a** under optimized conditions [**2a** (1.5 equiv), TFA (10 mol %), anhydr. MeCN, 60 °C, 6 h] (Table 3, entries 1−13). The developed method was found to be facile with nitrones bearing both electron-donating (MeO) and electron-withdrawing (F, NO_2) substituents on the *C*-phenyl ring, affording **3b−d** in 68−78% isolated yields (entries 2−4). Moreover, the reaction could be readily extended to heteroaromatic *N*-methylnitrones, as exemplified by the synthesis of pyridyl and furyl imidazoles

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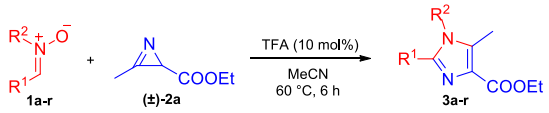
Table 3. Reactions of Various Nitrones 1 with 2*H*-Azirine (±)-2a[a]



entry	1	R^1	R^2	3	yield (%)
1	**1a**	C_6H_5	Me	**3a**	72
2	**1b**	4-$MeOC_6H_4$	Me	**3b**	68
3	**1c**	4-FC_6H_4	Me	**3c**	78
4	**1d**	4-$NO_2C_6H_4$	Me	**3d**	69
5	**1e**	2-pyridyl	Me	**3e**	82
6	**1f**	3-pyridyl	Me	**3f**	81
7	**1g**	5-Me-2-furyl	Me	**3g**	41
8	**1h**	Me	Me	**3h**	70
9	**1i**	*i*-Pr	Me	**3i**	53
10	**1j**	*t*-Bu	Me	**3j**	49
11	**1k**	*n*-heptyl	Me	**3k**	54
12	**1l**	*c*-Pr	Me	**3l**	72
13	**1m**	*c*-Hex	Me	**3m**	70
14	**1n**	*i*-Pr	*i*-Pr	**3n**	55
15	**1o**	C_6H_5	Bn	**3o**	63
16	**1p**	*i*-Pr	Bn	**3p**	71
17	**1q**	C_6H_5	*c*-Hex	**3q**	37
18	**1r**	C_6H_5	4-FC_6H_4	**3r**	42

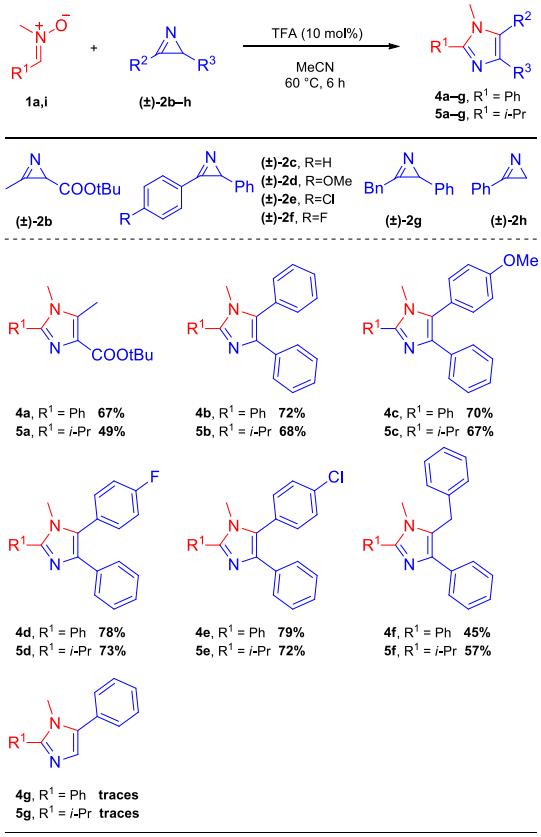
[a]Reaction conditions: nitrone **1a–r** (1 mmol), 2*H*-azirine (±)-**2a** (1.5 mmol), anhydrous MeCN (3 mL), TFA (10 mol %), 60 °C, 6 h.

3e–g (82, 81, and 41%, entries 5–7). Gratifyingly, C-aliphatic *N*-methylnitrones, including bulky substrate **1j** (R^1 = *t*-Bu), also underwent smooth transformation to furnish multisubstituted imidazoles **3h–m** in moderate to good yields (49–72%, entries 8–13). Subsequently, we examined the influence of the N-substituents (R^2) on the efficiency of the reaction (entries 14–18). Interestingly, while *N*-isopropyl- and *N*-benzylnitrones **1n–p** were well-tolerated (**3n–p**, 55–71%, entries 14–16), the corresponding *N*-cyclohexyl- and *N*-4-(fluorophenyl)imidazoles **3q** and **3r** were obtained in lower isolated yields (37 and 42%, entries 17 and 18).

Next, we focused on exploring the scope of the reaction with respect to azirine, using both a C-aromatic and a C-aliphatic *N*-methylnitrone (**1a** and **1i**) for a more reliable comparison (Table 4). As expected, transformations of azirine **2b** proceeded smoothly to give the corresponding imidazoles **4a** and **5a** in yields (Table 4, 67 and 49%) similar to those of ethoxycarbonyl analogue **2a** (Table 3, **3a**, 72% and **3i**, 53%). We were pleased to find that 2,3-diarylazirines **2c–f** were fully compatible with the reaction and could be efficiently converted to products **4b–e** and **5b–e** in good yields, regardless of the electronic nature of the azirine or the nitrone substrate (Table 4, 67–79%). Benzylazirine **2g** was also well-tolerated, albeit it provided lower isolated yields (**4f**, 45% and **5f**, 57%). Unfortunately, the application of monosubstituted azirine **2h** led to complex reaction mixtures and only trace amounts of the desired products.

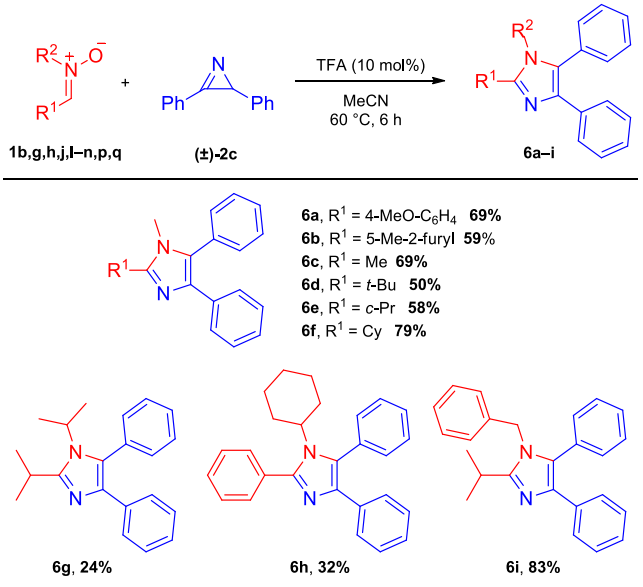
Finally, to give a comprehensive evaluation with respect to the generality, we briefly surveyed the reactivity of aromatic azirine **2c** toward some of the nitrones applied previously (Table 5). Pleasingly, both C-aromatic and C-aliphatic *N*-methylnitrones could be subjected to the reaction, delivering imidazoles **6a–f** in moderate to good yields (Table 5, 50–79%). It is notable that introducing the sterically demanding

Table 4. Scope of 2*H*-Azirines[a]



[a]Reaction conditions: nitrone **1a,i** (1 mmol), azirine **2b–h** (1.5 mmol), anhydrous MeCN (3 mL), TFA (10 mol %), 60 °C, 6 h.

Table 5. Scope of Nitrones with Aromatic 2*H*-Azirine 2c[a]



[a]Reaction conditions: nitrone **1** (1 mmol), azirine **2c** (1.5 mmol), anhydrous MeCN (3 mL), TFA (10 mol %), 60 °C, 6 h.

tert-butyl group as the R^1 substituent resulted again in a lower isolated yield (**6d**, 50%). On the other hand, nitrones possessing more electron-donating isopropyl and cyclohexyl substituents on the nitrogen (**1n** and **1q**) were less tolerated

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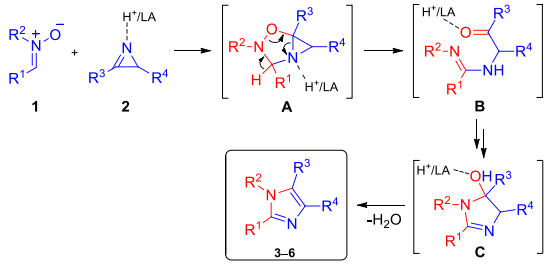
(**6g**, 24% and **6h**, 32%). In contrast, when *N*-benzylnitrone **1p** was employed, product **6i** was isolated in a superior yield of 83%.

Although the detailed reaction mechanism remains to be clarified, a plausible mechanism is proposed in Scheme 2.

Scheme 2. Plausible Mechanism for the Formation of Imidazoles



Initially, 1,3-DC between nitrone **1** and activated 2*H*-azirine **2** might occur to form cycloadduct **A**, which immediately rearranges to ketoamidine **B** in the presence of the acid catalyst. Following the intramolecular cyclization of intermediate **B**, the final product is achieved by the dehydration of hydroxyimidazoline **C**.

CONCLUSIONS

In summary, we have developed a novel procedure for the regioselective synthesis of 1,2,4,5-tetrasubstituted imidazoles through an unprecedented 1,3-DC of 2*H*-azirines with nitrones. This TFA-catalyzed cascade reaction is compatible with a variety of 2*H*-azirines and a wide range of C-aliphatic and C-aromatic as well as N-aliphatic and *N*-arylnitrones, offering a general and straightforward access to highly diverse multisubstituted imidazoles in isolated yields up to 83% under mild conditions.

EXPERIMENTAL SECTION

General Information. The NMR spectra were recorded at 298 K on a Bruker Ascend 500 with a 5 mm BBO Prodigy Probe in $CDCl_3$-d_1 or DMSO-d_6. The chemical shifts are reported in δ (ppm) relative to the internal standard (tetramethylsilane) or the residual solvent signal. In case of ^{19}F NMR, hexafluorobenzene was used as the reference compound. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, etc.), coupling constants, and integration. Coupling constants (J) are given in hertz (Hz). LC/MS analyses were carried out on an Agilent 1200 Series equipment with an Agilent G1946D MS detector (APCI, operated in a positive mode) with a Kinetex C18 column (100 Å, 5 μm, 250 × 4.6 mm, Phenomenex). High-resolution mass spectra (HRMS) were performed on a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer using an heated electrospray ionisation (HESI) ion source. Samples (5 μL from 1 μg/mL solution) were injected to the mass spectrometer using the flow injection method (200 μL/min, water/MeCN 1:1, 0.1% TFA). Melting points (mp) were recorded with a Digital Melting Point Apparatus (Electrothermal, IA 9000 Series). Chromatographic purification of the products was performed on Merck silica gel 60, particle size 0.063–0.200 mm. Thin-layer chromatography (TLC) was performed on fluorescent-indicating plates (aluminum sheets precoated with silica gel 60_{F254}, 1.05554, Merck), and visualization was achieved using UV light (254 nm) or by staining with basic potassium permanganate solution. Nitrones **1a–r** and racemic 2*H*-azirines **2a–h** were synthesized according to literature procedures.[21] All other reagents and solvents were commercially available and used without further purification.

General Procedure for the Synthesis of Imidazoles 3a–l, 4a–f, 5a–f, and 6a–i. To a solution of the corresponding nitrone **1** (1 mmol, 1.0 equiv) and 2*H*-azirine **2** (1.5 mmol, 1.5 equiv) in anhydrous MeCN (3 mL, 0.33 M), TFA (7.7 μL, 0.1 mmol, 10 mol %) was added at room temperature and stirred at 60 °C for 6 h on a heating block-mounted hot plate magnetic stirrer. After the reaction was complete (monitored by TLC), the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc or toluene/MeCN) to afford pure **3a–l**, **4a–f**, **5a–f**, and **6a–i**.

*Ethyl 1,5-Dimethyl-2-phenyl-1H-imidazole-4-carboxylate (**3a**).* White solid, 175 mg, 72% yield, mp 84–85 °C. Silica gel TLC R_f = 0.20 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, DMSO-d_6): δ 7.64 (d, J = 7.1 Hz, 2H), 7.57–7.46 (m, 3H), 4.24 (q, J = 7.1 Hz, 2H), 3.60 (s, 3H), 2.54 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 163.8, 146.9, 138.1, 130.6, 129.4, 129.2, 129.0, 128.0, 59.7, 32.5, 14.9, 10.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2$, 245.1285; found, 245.1284.

*Ethyl 2-(4-Methoxyphenyl)-1,5-dimethyl-1H-imidazole-4-carboxylate (**3b**).* White solid, 187 mg, 68% yield, mp 98–99 °C. Silica gel TLC R_f = 0.11 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.52 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.56 (s, 3H), 2.61 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 160.2, 147.4, 137.0, 130.7, 128.4, 122.6, 113.9, 60.2, 55.4, 31.9, 14.6, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3$, 275.1391; found, 275.1390.

*Ethyl 2-(4-Fluorophenyl)-1,5-dimethyl-1H-imidazole-4-carboxylate (**3c**).* White solid, 204 mg, 78% yield, mp 98–100 °C. Silica gel TLC R_f = 0.23 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.60–7.54 (m, 2H), 7.15 (t, J = 8.7 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.57 (s, 3H), 2.61 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 163.1 (d, J = 223.5 Hz), 146.5, 137.2, 131.2 (d, J = 8.3 Hz), 128.6, 126.3, 115.7 (d, J = 22.0 Hz), 60.3, 31.9, 14.6, 10.5. ^{19}F NMR (471 MHz, chloroform-d): δ −114.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}FN_2O_2$, 263.1191; found, 263.1191.

*Ethyl 1,5-Dimethyl-2-(4-nitrophenyl)-1H-imidazole-4-carboxylate (**3d**).* Yellow solid, 200 mg, 69% yield, mp 145–146 °C. Silica gel TLC R_f = 0.35 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 8.31 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H), 2.64 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 163.7, 147.9, 145.0, 138.3, 136.2, 129.9, 129.6, 123.8, 60.6, 32.3, 14.54, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_4$, 290.1136; found, 290.1138.

*Ethyl 1,5-Dimethyl-2-(pyridin-2-yl)-1H-imidazole-4-carboxylate (**3e**).* Light yellow solid, 201 mg, 82% yield, mp 114–115 °C. Silica gel TLC R_f = 0.13 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 8.61–8.56 (m, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.77 (dt, J = 7.8, 1.8 Hz, 1H), 7.26–7.22 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.04 (s, 3H), 2.62 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.0, 150.2, 148.1, 144.7, 138.8, 136.7, 128.6, 124.0, 123.0, 60.4, 33.0, 14.6, 10.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}N_3O_2$, 246.1238; found, 246.1237.

*Ethyl 1,5-Dimethyl-2-(pyridin-3-yl)-1H-imidazole-4-carboxylate (**3f**).* Orange oil, 198 mg, 81% yield. Silica gel TLC R_f = 0.52 (chloroform/MeOH = 19/1); ^1H NMR (500 MHz, chloroform-d): δ 8.84 (s, 1H), 8.68 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.41 (dd, J = 7.8, 4.8 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.63 (s, 3H), 2.64 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 163.8, 150.1, 149.6, 144.4, 137.7, 136.9, 129.4, 126.5, 123.5, 60.5, 32.0, 14.6, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}N_3O_2$, 246.1238; found, 246.1235.

*Ethyl 1,5-Dimethyl-2-(5-methylfuran-2-yl)-1H-imidazole-4-carboxylate (**3g**).* Yellow solid, 102 mg, 41% yield, mp 68–69 °C. Silica gel TLC R_f = 0.20 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 6.79 (d, J = 3.2 Hz, 1H), 6.15–6.04 (m, 1H),

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4.38 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.59 (s, 3H), 2.37 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.0, 153.1, 143.1, 139.4, 136.9, 128.6, 111.7, 107.6, 60.3, 31.8, 14.5, 13.8, 10.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_3$, 249.1234; found, 249.1233.

*Ethyl 1,2,5-Trimethyl-1H-imidazole-4-carboxylate (**3h**).* Light yellow oil, 127 mg, 70% yield. Silica gel TLC R_f = 0.41 (chloroform/MeOH = 19/1); ^1H NMR (500 MHz, chloroform-d): δ 4.35 (q, J = 7.2 Hz, 2H), 3.45 (s, 3H), 2.51 (s, 3H), 2.39 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.0, 144.4, 136.2, 127.1, 60.1, 30.3, 14.6, 13.5, 10.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{15}N_2O_2$, 183.1129; found, 183.1130.

*Ethyl 2-Isopropyl-1,5-dimethyl-1H-imidazole-4-carboxylate (**3i**).* Light yellow solid, 111 mg, 53% yield, mp 73−74 °C. Silica gel TLC R_f = 0.07 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.36 (q, J = 7.1 Hz, 2H), 3.48 (s, 3H), 3.02 (hept, J = 6.9 Hz, 1H), 2.51 (s, 3H), 1.46−1.27 (m, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 152.6, 136.1, 127.2, 60.2, 30.0, 26.6, 20.9, 14.6, 10.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{19}N_2O_2$, 211.1442; found, 211.1438.

*Ethyl 2-(tert-Butyl)-1,5-dimethyl-1H-imidazole-4-carboxylate (**3j**).* Light yellow oil, 110 mg, 49% yield. Silica gel TLC R_f = 0.38 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.34 (q, J = 7.1 Hz, 2H), 3.62 (s, 3H), 2.50 (s, 3H), 1.45 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.3, 154.0, 137.6, 126.3, 60.2, 33.3, 32.5, 29.1, 14.5, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{21}N_2O_2$, 225.1598; found, 225.1594.

*Ethyl 2-Heptyl-1,5-dimethyl-1H-imidazole-4-carboxylate (**3k**).* Light yellow oil, 144 mg, 54% yield. Silica gel TLC R_f = 0.21 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.36 (q, J = 7.1 Hz, 2H), 3.46 (s, 3H), 2.76−2.64 (m, 2H), 2.51 (s, 3H), 1.76−1.63 (m, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.36−1.23 (m, 7H), 0.88 (t, J = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 148.4, 136.1, 127.3, 60.1, 31.7, 30.3, 29.5, 29.0, 28.1, 27.6, 22.6, 14.6, 14.1, 10.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{27}N_2O_2$, 267.2068; found, 267.2069.

*Ethyl 2-Cyclopropyl-1,5-dimethyl-1H-imidazole-4-carboxylate (**3l**).* Light yellow oil, 150 mg, 72% yield. Silica gel TLC R_f = 0.06 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.34 (q, J = 7.1 Hz, 2H), 3.58 (s, 3H), 2.51 (s, 3H), 1.78−1.70 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.08−1.00 (m, 2H), 0.98−0.90 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.1, 148.9, 136.3, 126.9, 60.1, 30.0, 14.5, 10.3, 7.5, 6.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_2$, 209.1285; found, 209.1281.

*Ethyl 2-Cyclohexyl-1,5-dimethyl-1H-imidazole-4-carboxylate (**3m**).* Light yellow solid, 175 mg, 70% yield, mp 85−86 °C. Silica gel TLC R_f = 0.23 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.36 (q, J = 7.1 Hz, 2H), 3.47 (s, 3H), 2.63 (tt, J = 12.1, 3.4 Hz, 1H), 2.51 (s, 3H), 1.92−1.83 (m, 4H), 1.81−1.68 (m, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.34−1.29 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 151.9, 135.8, 127.4, 60.1, 36.4, 31.0, 30.0, 26.3, 25.6, 14.6, 10.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2$, 251.1755; found, 251.1756.

*Ethyl 1,2-Diisopropyl-5-methyl-1H-imidazole-4-carboxylate (**3n**).* Light yellow oil, 130 mg, 55% yield. Silica gel TLC R_f = 0.36 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 4.53 (hept, J = 7.1 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.06 (hept, J = 6.9 Hz, 1H), 2.62 (s, 3H), 1.52 (d, J = 7.1 Hz, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.36 (d, J = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.4, 60.1, 47.2, 27.2, 21.8, 14.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{23}N_2O_2$, 239.1755; found, 239.1754.

*Ethyl 1-Benzyl-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**3o**).* Light yellow oil, 203 mg, 63% yield. Silica gel TLC R_f = 0.22 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.51 (d, J = 6.7 Hz, 2H), 7.41−7.29 (m, 6H), 6.97 (d, J = 7.3 Hz, 2H), 5.19 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.1, 148.1, 137.1, 136.0, 130.0, 129.4, 129.2, 128.5, 127.9, 125.6, 60.4, 48.1, 14.6, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_2$, 321.1598; found, 321.1596.

*Ethyl 1-Benzyl-2-isopropyl-5-methyl-1H-imidazole-4-carboxylate (**3p**).* Light yellow oil, 202 mg, 71% yield. Silica gel TLC R_f = 0.39 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.34−7.27 (m, 3H), 6.90 (d, J = 6.8 Hz, 2H), 5.10 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.92 (hept, J = 6.9 Hz, 1H), 2.42 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.29 (d, J = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.2, 153.3, 135.9, 135.7, 129.1, 127.9, 125.5, 60.3, 46.5, 26.6, 21.6, 14.6, 10.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$, 287.1755; found, 287.1755.

*Ethyl 1-Cyclohexyl-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**3q**).* White solid, 116 mg, 37% yield, mp 103−105 °C. Silica gel TLC R_f = 0.50 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.48−7.40 (m, 5H), 4.38 (q, J = 7.1 Hz, 2H), 4.08 (tt, J = 12.1, 4.0 Hz, 1H), 2.75 (s, 3H), 1.98−1.80 (m, 6H), 1.70−1.63 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.24−1.10 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.3, 147.8, 136.3, 131.4, 129.9, 129.2, 128.3, 60.2, 57.8, 32.0, 26.1, 25.1, 14.6, 12.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_2$, 313.1911; found, 313.1911.

*Ethyl 1-(4-Fluorophenyl)-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**3r**).* Beige solid, 135 mg, 42% yield, mp 134−136 °C. Silica gel TLC R_f = 0.87 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.35 (d, J = 7.2 Hz, 2H), 7.27−7.18 (m, 3H), 7.17 (d, J = 6.4 Hz, 4H), 4.44 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 164.0, 162.6 (d, J = 250.8 Hz), 146.9, 138.1, 132.4, 129.8, 129.7, 129.5, 129.2, 128.8, 128.2, 116.96 (d, J = 23.0 Hz), 60.5, 14.6, 11.1. ^{19}F NMR (471 MHz, chloroform-d): δ −113.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}FN_2O_2$, 325.1347; found, 325.1344.

*tert-Butyl 1,5-Dimethyl-2-phenyl-1H-imidazole-4-carboxylate (**4a**).* White solid, 183 mg, 67% yield, mp 224−225 °C. Silica gel TLC R_f = 0.25 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.62−7.52 (m, 2H), 7.47−7.38 (m, 3H), 3.57 (s, 3H), 2.58 (s, 3H), 1.60 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 163.4, 147.3, 136.1, 130.3, 129.9, 129.2, 129.0, 128.5, 80.6, 32.0, 28.5, 10.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_2$, 273.1598; found, 273.1599.

*1-Methyl-2,4,5-triphenyl-1H-imidazole (**4b**).* White solid, 222 mg, 72% yield, mp 146−148 °C. Silica gel TLC R_f = 0.78 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.75 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.52−7.39 (m, 8H), 7.21 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 3.51 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 147.9, 137.7, 134.6, 131.2, 131.0, 130.9, 130.5, 129.1, 129.1, 128.8, 128.6, 128.1, 127.0, 126.3, 33.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}N_2$, 311.1543; found, 311.1542.

*5-(4-Methoxyphenyl)-1-methyl-2,4-diphenyl-1H-imidazole (**4c**).* White solid, 239 mg, 70% yield, mp 157−158 °C. Silica gel TLC R_f = 0.69 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-d): δ 7.74 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.22 (t, J = 7.6 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 3.88 (s, 3H), 3.49 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 159.8, 147.6, 137.5, 134.8, 132.2, 131.1, 130.3, 129.1, 128.7, 128.6, 128.1, 126.8, 126.2, 123.3, 114.5, 55.3, 33.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{21}N_2O$, 341.1649; found, 341.1648.

*5-(4-Fluorophenyl)-1-methyl-2,4-diphenyl-1H-imidazole (**4d**).* White solid, 255 mg, 78% yield, mp 168−170 °C. Silica gel TLC R_f = 0.77 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, DMSO-d_6): δ 7.79 (d, J = 7.5 Hz, 2H), 7.59−7.48 (m, 5H), 7.44 (d, J = 7.7 Hz, 2H), 7.39 (t, J = 8.6 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 3.48 (s, 3H), 3.35 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 162.7 (d, J = 246.1 Hz), 147.4, 137.1, 135.1, 133.5 (d, J = 8.3 Hz), 131.1, 129.9, 129.2, 129.0, 128.6, 127.6, 126.7, 116.6 (d, J = 21.3 Hz), 33.5. ^{19}F NMR (471 MHz, chloroform-d): δ −115.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}FN_2$, 329.1449; found, 329.1447.

*5-(4-Chlorophenyl)-1-methyl-2,4-diphenyl-1H-imidazole (**4e**).* White solid, 272 mg, 79% yield, mp 187−188 °C. Silica gel TLC R_f = 0.81 (hexane/EtOAc = 2/1); ^1H NMR (500 MHz, chloroform-d): δ 7.73 (d, J = 7.4 Hz, 2H), 7.55−7.47 (m, 4H), 7.47−7.41 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.3 Hz,

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1H), 3.51 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 148.3, 138.2, 134.7, 134.4, 132.2, 130.8, 129.7, 129.4, 129.1, 128.9, 128.6, 128.2, 127.1, 126.6, 33.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{18}ClN_2$, 345.1154 and 347.1124; found, 345.1155 and 347.1126.

5-Benzyl-1-methyl-2,4-diphenyl-1H-imidazole (**4f**). White solid, 146 mg, 45% yield, mp 160−161 °C. Silica gel TLC R_f = 0.69 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.71−7.64 (m, 4H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.35 (q, *J* = 7.8 Hz, 4H), 7.29−7.22 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 4.28 (s, 2H), 3.46 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 147.7, 139.4, 138.3, 135.0, 130.9, 129.1, 128.9, 128.7, 128.5, 128.5, 127.9, 127.3, 126.7, 126.7, 32.1, 30.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{21}N_2$, 325.1700; found, 325.1698.

tert-Butyl 2-Isopropyl-1,5-dimethyl-1H-imidazole-4-carboxylate (**5a**). White solid, 116 mg, 49% yield, mp 99−101 °C. Silica gel TLC R_f = 0.26 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 3.45 (s, 3H), 2.98 (hept, *J* = 6.9 Hz, 1H), 2.44 (s, 3H), 1.58 (s, 9H), 1.34 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 163.3, 152.4, 134.3, 128.6, 80.1, 30.0, 28.4, 26.6, 20.9, 10.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{23}N_2O_2$, 239.1755; found, 239.1753.

2-Isopropyl-1-methyl-4,5-diphenyl-1H-imidazole (**5b**). White solid, 188 mg, 68% yield, mp 92−93 °C. Silica gel TLC R_f = 0.70 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.48−7.36 (m, 5H), 7.32 (d, *J* = 6.1 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 3.39 (s, 3H), 3.09 (hept, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 152.8, 136.2, 135.1, 131.5, 130.9, 128.9, 128.6, 128.2, 128.0, 126.9, 125.9, 30.7, 26.7, 21.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2$, 277.1700; found, 277.1701.

2-Isopropyl-5-(4-methoxyphenyl)-1-methyl-4-phenyl-1H-imidazole (**5c**). White solid, 204 mg, 67% yield, mp 156−158 °C. Silica gel TLC R_f = 0.60 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.47 (d, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 3.37 (s, 3H), 3.08 (p, *J* = 6.9 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 159.6, 152.5, 136.0, 135.2, 132.2, 128.3, 128.0, 126.8, 125.8, 123.7, 114.4, 55.3, 30.6, 26.7, 21.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2O$, 307.1805; found, 307.1806.

5-(4-Fluorophenyl)-2-isopropyl-1-methyl-4-phenyl-1H-imidazole (**5d**). White solid, 216 mg, 73% yield, mp 138−139 °C. Silica gel TLC R_f = 0.29 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.43 (d, *J* = 7.0 Hz, 2H), 7.34−7.27 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 3H), 7.16−7.09 (m, 2H), 3.38 (s, 3H), 3.09 (p, *J* = 6.9 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 162.70 (d, *J* = 248.1 Hz), 152.9, 136.5, 134.9, 132.8 (d, *J* = 8.2 Hz), 128.1, 127.5 (d, *J* = 3.1 Hz), 127.4, 126.9, 126.0, 116.1 (d, *J* = 21.8 Hz), 30.7, 26.7, 21.4. ^{19}F NMR (471 MHz, chloroform-*d*): δ −116.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}FN_2$, 295.1606; found, 295.1606.

5-(4-Chlorophenyl)-2-isopropyl-1-methyl-4-phenyl-1H-imidazole (**5e**). White solid, 224 mg, 72% yield, mp 132−133 °C. Silica gel TLC R_f = 0.36 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.47−7.38 (m, 4H), 7.26 (d, *J* = 3.9 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 3.39 (s, 3H), 3.08 (p, *J* = 6.9 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 153.2, 136.8, 134.8, 134.3, 132.2, 129.9, 129.2, 128.2, 127.2, 127.0, 126.2, 30.8, 26.7, 21.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}ClN_2$, 311.1310 and 313.1281; found, 311.1311 and 313.1283.

5-Benzyl-2-isopropyl-1-methyl-4-phenyl-1H-imidazole (**5f**). White solid, 166 mg, 57% yield, mp 104−106 °C. Silica gel TLC R_f = 0.58 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.35−7.28 (m, 4H), 7.25−7.17 (m, 2H), 7.14 (d, *J* = 7.4 Hz, 2H), 4.16 (s, 2H), 3.32 (s, 3H), 3.03 (p, *J* = 6.9 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 152.7, 138.7, 137.8, 135.5, 128.8, 128.4, 127.8, 127.2, 126.5, 126.3, 124.7, 30.2, 30.1, 26.5, 21.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2$, 291.1856; found, 291.1857.

2-(4-Methoxyphenyl)-1-methyl-4,5-diphenyl-1H-imidazole (**6a**). White solid, 234 mg, 69% yield, mp 169−171 °C. Silica gel TLC R_f = 0.65 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.50−7.39 (m, 5H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 3.48 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 160.0, 147.9, 137.5, 134.7, 130.9, 130.5, 130.1, 129.0, 128.5, 128.1, 126.9, 126.3, 123.4, 114.0, 55.4, 33.1. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{21}N_2O$, 341.1649; found, 341.1651.

1-Methyl-2-(5-methylfuran-2-yl)-4,5-diphenyl-1H-imidazole (**6b**). White solid, 186 mg, 59% yield, mp 137−139 °C. Silica gel TLC R_f = 0.44 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.52−7.48 (m, 2H), 7.47−7.43 (m, 3H), 7.37−7.34 (m, 2H), 7.21−7.16 (m, 2H), 7.15−7.10 (m, 1H), 6.77 (d, *J* = 3.3 Hz, 1H), 6.14−6.11 (m, 1H), 3.60 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 153.1, 143.7, 139.7, 137.9, 134.3, 131.0, 130.7, 130.0, 129.1, 128.7, 128.0, 127.1, 126.4, 111.1, 107.6, 32.7, 13.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O$, 315.1492; found, 315.1493.

1,2-Dimethyl-4,5-diphenyl-1H-imidazole (**6c**). White solid, 172 mg, 69% yield, mp 109−110 °C. Silica gel TLC R_f = 0.17 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.47−7.40 (m, 5H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 3.37 (s, 3H), 2.50 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 144.7, 136.2, 134.7, 131.4, 130.9, 128.9, 128.9, 128.4, 128.1, 126.7, 126.1, 31.1, 13.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{17}N_2$, 249.1387; found, 249.1389.

2-(tert-Butyl)-1-methyl-4,5-diphenyl-1H-imidazole (**6d**). Light beige solid, 146 mg, 50% yield, mp 123−124 °C. Silica gel TLC R_f = 0.62 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.48−7.40 (m, 5H), 7.34−7.30 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.51 (s, 3H), 1.54 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 153.9, 135.1, 135.0, 131.7, 131.2, 130.2, 128.9, 128.4, 128.0, 126.7, 125.8, 33.6, 33.2, 29.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_2$, 291.1856; found, 291.1858.

2-Cyclopropyl-1-methyl-4,5-diphenyl-1H-imidazole (**6e**). White solid, 160 mg, 58% yield, mp 110−111 °C. Silica gel TLC R_f = 0.24 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.46−7.38 (m, 5H), 7.34−7.30 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.49 (s, 3H), 1.91−1.80 (m, 1H), 1.20−1.10 (m, 2H), 1.04−0.95 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 149.2, 135.9, 134.9, 131.4, 130.9, 128.9, 128.9, 128.3, 128.0, 126.8, 125.9, 30.8, 7.6, 6.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_2$, 275.1543; found, 275.1545.

2-Cyclohexyl-1-methyl-4,5-diphenyl-1H-imidazole (**6f**). White solid, 249 mg, 79% yield, mp 119−120 °C. Silica gel TLC R_f = 0.58 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.48−7.36 (m, 5H), 7.35−7.29 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.39 (s, 3H), 2.71 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.04−1.97 (m, 2H), 1.95−1.87 (m, 2H), 1.87−1.73 (m, 3H), 1.47−1.33 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 152.2, 136.4, 135.2, 131.6, 130.9, 128.9, 128.4, 128.2, 128.0, 126.9, 125.9, 36.6, 31.6, 30.7, 26.5, 25.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{25}N_2$, 317.2013; found, 317.2014.

1,2-Diisopropyl-4,5-diphenyl-1H-imidazole (**6g**). White solid, 72 mg, 24% yield, mp 171−172 °C. Silica gel TLC R_f = 0.51 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.44−7.41 (m, 3H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.37−7.30 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 4.30 (p, *J* = 7.1 Hz, 1H), 3.18 (p, *J* = 6.8 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.39 (d, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*): δ 152.6, 136.5, 135.2, 132.7, 131.8, 128.8, 128.4, 127.9, 127.4, 126.7, 125.7, 47.1, 27.8, 22.8, 22.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{25}N_2$, 305.2013; found, 305.2014.

1-Cyclohexyl-2,4,5-triphenyl-1H-imidazole (**6h**). White solid, 121 mg, 32% yield, mp 165−166 °C. Silica gel TLC R_f = 0.81 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, chloroform-*d*): δ 7.66−7.60 (m, 2H), 7.51−7.39 (m, 10H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.97 (tt, *J* = 12.3, 3.5 Hz, 1H), 1.85 (d, *J* = 12.4 Hz, 2H), 1.68−1.49 (m, 4H), 1.45 (d, *J* = 13.5 Hz, 1H), 1.04 (qt, *J* = 13.0, 3.6

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Hz, 2H), 0.73 (qt, J = 13.2, 3.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 147.7, 137.8, 134.7, 132.6, 132.5, 132.2, 130.1, 129.1, 128.9, 128.8, 128.7, 128.4, 127.9, 126.7, 126.0, 58.4, 33.6, 26.2, 25.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}N_2$, 379.2169; found, 379.2168.

*1-Benzyl-2-isopropyl-4,5-diphenyl-1H-imidazole (**6i**).* White solid, 293 mg, 83% yield, mp 120−121 °C. Silica gel TLC R_f = 0.58 (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, chloroform-d): δ 7.50 (d, J = 7.1 Hz, 2H), 7.35−7.24 (m, 5H), 7.24−7.16 (m, 5H), 7.11 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 7.3 Hz, 2H), 4.99 (s, 2H), 2.90 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d): δ 153.3, 137.6, 131.3, 131.1, 128.8, 128.8, 128.4, 128.3, 128.1, 127.4, 126.9, 126.0, 125.7, 46.7, 26.7, 22.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}N_2$, 353.2013; found, 353.2016.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03288.

Detailed optimization of the reaction conditions and copies of ^1H, $^{13}C\{^1H\}$, and 2D NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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