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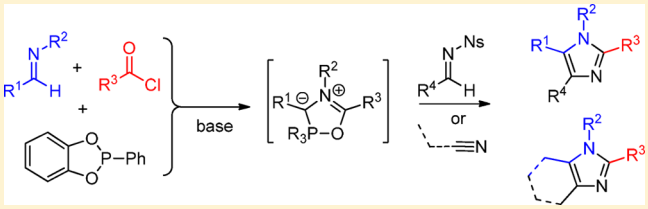
Multicomponent Synthesis of Substituted and Fused-Ring Imidazoles via Phospha-münchnone Cycloaddition

Sara Aly, Mikhail Romashko, and Bruce A. Arndtsen*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada

Supporting Information

ABSTRACT: A new, one-pot synthesis of imidazoles from imines, acid chlorides, and *N*-nosyl imines or tethered nitriles is reported. The reaction is mediated by the phosphonite PPh(catechyl) and proceeds via regioselective cycloaddition with an in situ-generated phospha-münchnone 1,3-dipole. This provides an efficient route to construct both highly substituted and polycyclic imidazoles directly from available substrates, without metal catalysts, and with access to product diversity.



INTRODUCTION

Imidazoles are among the most common heterocyclic motifs found in biologically relevant compounds, with examples including natural products,[1] commercial drugs,[2] and other pharmaceutically relevant compounds.[3] These heterocycles are also the core of ionic liquids,[4] metal-coordinating ligands,[5] N-heterocyclic carbene precursors,[6] and various advanced materials.[7] In light of this utility, there have been a broad range of methods developed to construct imidazoles. However, the assembly of highly substituted variants remains a challenge. Strategies toward these products often involve cyclocondensation reactions, TOSMIC cyclization, or substitution reactions on preformed imidazoles, such as via cross-coupling, electrophilic substitution, or even C−H activation reactions.[8,9] While effective, these can require the multistep synthesis of the starting materials for cyclization, or iterative substitution chemistry.

One of the more convergent approaches to imidazole synthesis is via 1,3-dipolar cycloaddition reactions. For example, the dipolar cycloaddition of 1,3-oxazolium-5-oxides (münchnones) developed by Huisgen[10] with *N*-tosyl-substituted imines can provide a useful approach to tetrasubstituted imidazoles. This transformation was first reported by Ferraccioli and co-workers[11] and has since been employed in the assembly of a number of substituted derivatives.[12] Nevertheless, münchnones are typically prepared via the dehydration of presynthesized α-amido acid derivatives,[10] which can themselves require a multistep synthesis. *N*-Tosyl-substituted imines are also sensitive substrates, and their cycloaddition leads to the formation of stoichiometric sulfinic acid waste. Some solutions to these issues have been described. Münchnones can be more easily prepared via the palladium-catalyzed coupling of imines, acid chlorides, and CO and employed in cycloaddition reactions.[13] This includes our report of coupling the catalytic formation with *N*-tosyl imine cycloaddition to assemble imidazoles.[14] With regard to the dipolarophile, early studies with münchnones demonstrated that the more atom economical cycloaddition of nitriles to münchnones can be performed.[15] Unfortunately, most nitriles are not sufficiently electron-deficient to participate in münchnone cycloaddition, with only the very electron-poor ethyl cyanoformate (EtO_2CCN) reacting in good yield.

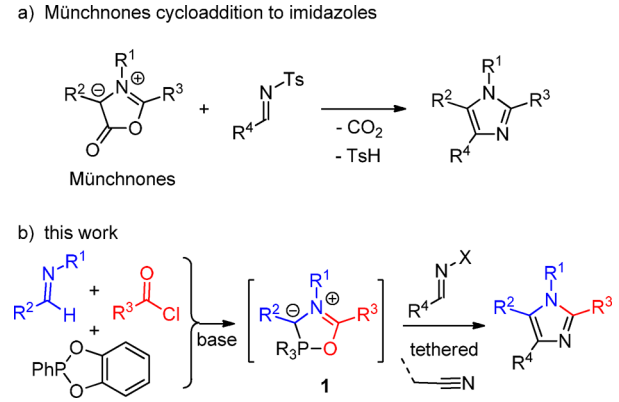


Figure 1. Münchnones and phospha-münchnones in imidazole synthesis.

In considering an alternative approach to imidazole synthesis, we have recently reported a new variant of münchnones, phospha-münchnone **1** (Figure 1).[16] These dipoles are easily generated from imines, acid chlorides, and PhP(catechyl) and participate in cycloaddition reactions with alkynes in a fashion analogous to münchnones. In addition to its one-pot synthesis, an important feature of **1** is its high cycloaddition reactivity toward electron-poor dipolarophiles.[17] In light of these features, we became interested in whether these dipoles could provide a more effective platform for cycloaddition with electron-deficient nitrogen-containing dipolarophiles to generate imidazoles. We describe herein that the in situ formation and cycloaddition of phospha-münchnones can allow the modular assembly of imidazoles from simple imines and acid chlorides without the need for metal

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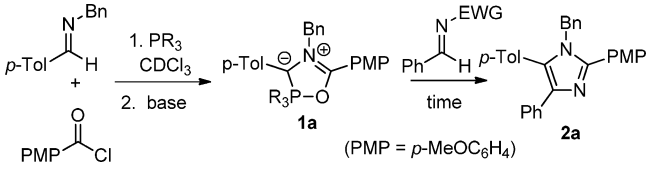
catalysis. This reaction can also be extended to tethered-nitrile dipolarophiles, providing a novel route to polycyclic imidazole products.

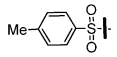
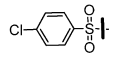
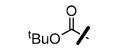
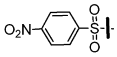
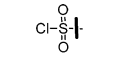
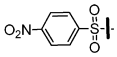
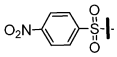
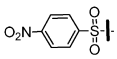
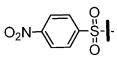
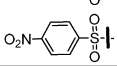
RESULTS AND DISCUSSION

Cycloaddition with Imines. Our initial work probed the reaction of phospha-münchnone **1a** with electron-deficient imines (Table 1). The in situ formation of **1a** followed by the addition of *N*-tosyl imine leads to the complete consumption of the dipole over the course of 2 h but forms imidazole **2a** in only low yield (20%, entry 1). ^{1}H and ^{31}P NMR analysis of the reaction mixture shows that the dipole has decomposed to a number of unidentifiable side products, together with the near quantitative formation of phosphine oxide.[18] To improve the efficiency of this reaction, both the imine dipolarophile and phosphine were modified. First, as phospha-münchnones react most rapidly with electron-poor dipolarophiles, we probed the potential of other N-substituted imines to increase the reaction yield. The use of an *N*-*p*-chloroarylsulfonyl imine leads to results similar to that observed with *N*-tosyl imines (entry 2), while the more electron-rich *N*-Boc-substituted imine does not react with **1a** (entry 3). However, the use of the highly electron-deficient *N*-nosyl imine leads to the formation of **2a** in useful overall yield (65%, entry 4).

Previous studies have demonstrated that the structure adopted by **1** and its cycloaddition reactivity with alkynes are strongly influenced by the phosphorus reagent employed (Figure 2).[16] We see similar influences on the reaction with *N*-nosyl imines (entries 6–10). More electron-rich trialkylphosphines, which adopt an acyclic Wittig-type structure **1′**, do not allow cycloaddition (entry 6). However, several phosphites can mediate imidazole formation in moderate yields, including simple triphenyl phosphite (entry 8) and in situ-generated Horner–Wadsworth–Emmons reagents (entries 9 and 10). Nevertheless, cycloaddition is most rapid and efficient with PhP(catechyl) (entry 4). The latter presumably reflects the favored generation of the dipole brought about by the strained catechyl unit in the 5-coordinate phosphorus of **1a**.

Table 1. Cycloaddition of Phospha-Münchnones with Electron-Deficient Imines[a]



Entry	PR_3	EWG	Base	Time	% **2a**
1	PPh(catechyl)		DBU	2h	20
2	PPh(catechyl)		DBU	2h[b]	25
3	PPh(catechyl)		DBU	2h	-
4	PPh(catechyl)		DBU	2h	65
5	PPh(catechyl)		DBU	2h	10
6	$P(Cy)_3$		LiHMDS[c]	18h	-
7	$P(OCH_2CF_3)_3$		DBU	3h	18
8[d]	$P(OPh)_3$		LiHMDS[c]	18h	40
9[d,e]	(catechyl)POTMS		LiHMDS[c]	4h	47
10[e]	$P(OEt)_3$		LiHMDS[c]	18h	19

[a]Imine (42 mg, 0.2 mmol), acid chloride (38 mg, 0.22 mmol), 0.5 mL $CDCl_3$, 30 min rt; then PhP(catechyl) (48 mg, 0.22 mmol) 30 min rt; DBU (91 mg, 0.6 mmol); imine (87 mg, 0.3 mmol), rt. [b]50 °C. [c]Added at −78 °C. [d]PR_3 added with 0.2 mmol of TMSOTf. [e]0.2 mmol of TMSCl.

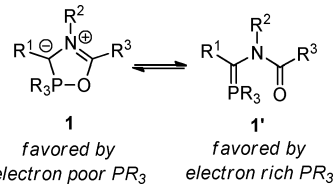
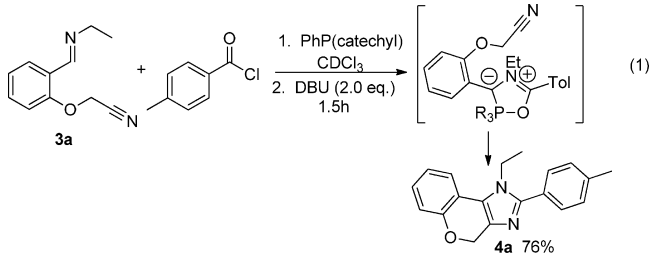


Figure 2. Phosphine-dependent isomers of phospha-münchnone **1**.

With the optimized conditions, we explored the generality of the reaction. A useful feature of the phosphorus-based 1,3-dipole **1** is its modular formation from PhP(catechyl), imines, and acid chlorides. Thus, it is straightforward to tune any of the three dipole substituents. As shown in Table 2, the reaction proceeds with various *C*-aryl- and *C*-heteroaryl-substituted imines (**2c**), as well as those with *N*-alkyl, *N*-benzyl, or *N*-aryl substituents (**2i**). Similarly, a variety of acid chlorides can be employed. These include not only substituted aroyl chloride but also heteroaryl (**2d**, **2g**) and alkyl acid chlorides (**2h**). The *N*-nosyl-substituted imine can also be modulated with a range of aryl and heteroaryl substituents. However, aliphatic *N*-nosyl imines do not undergo cycloaddition but instead lead to decomposition of the dipole. Overall, this provides straightforward access to polysubstituted imidazoles where any of the four substituents can be systematically modified in a one-pot reaction.

Cycloaddition with Nitriles. An atom-economical alternative to the use of *N*-nosyl imines in cycloaddition would be the reaction of nitriles with phospha-münchnones **1**. Nitriles are readily available and would obviate the need to synthesize *N*-tosyl imines, and their cycloaddition leads to no waste from the C═N fragment. Unfortunately, nitriles are also poor cycloaddition substrates. For example, the formation of phospha-münchnone **1a** in acetonitrile solvent leads to no detectable formation of imidazole even upon prolonged reaction.

However, since the phospha-münchnone is generated from imines and acid chlorides, we postulated that it should be straightforward to incorporate simple, unactivated nitriles into **1** from nitrile-tethered imines for a more entropically favorable intramolecular cycloaddition. The nitrile-tethered imine **3a** can be generated from salicylaldehyde and bromoacetonitrile, followed by condensation with ethylamine.[19] As was hoped, the formation of phospha-münchnone from **3a** leads to a spontaneous cycloaddition to generate polycyclic imidazole **4a** in 76% yield.



(1)

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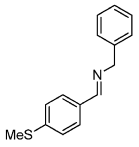
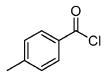
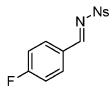
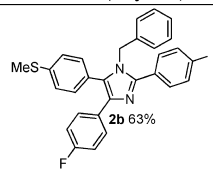
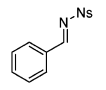
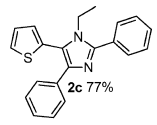
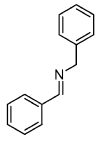
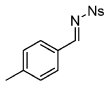
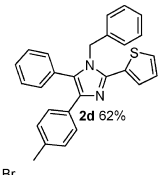
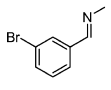
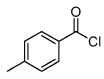
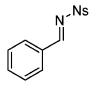
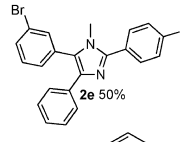
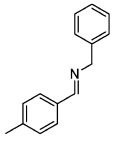
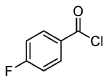
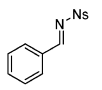
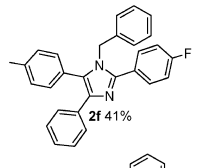
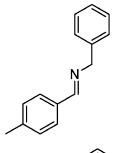
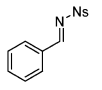
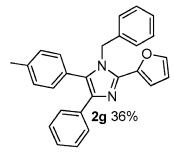
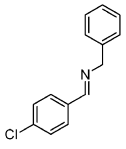
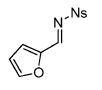
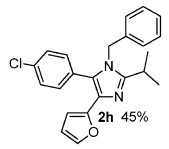
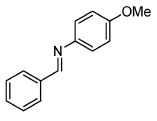
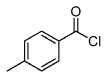
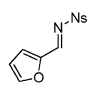
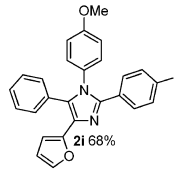
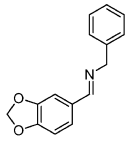
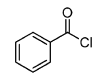
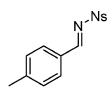
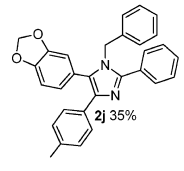
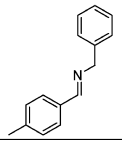
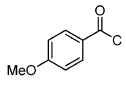
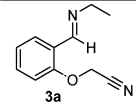
Table 2. Synthesis of Diversely Substituted Imidazoles[a]

Imine	Acid Chloride	Imine	Product (% yield)
			 **2b** 63%
			 **2c** 77%
			 **2d** 62%
			 **2e** 50%
			 **2f** 41%
			 **2g** 36%
			 **2h** 45%
			 **2i** 68%
			 **2j** 35%
			-

[a]Conditions of Table 1, entry 4.

Similar to the results in Table 2, the generation of polycyclic imidazoles via nitrile cycloaddition is easily generalized. A number of imines can be used in this imidazole synthesis (Table 3), including those with electron-rich or electron-poor aryl (entries 5 and 6), naphthyl (entry 7), and pyrrole (entries 8 and 9) units. The nitrile tether can also be varied, with oxygen- or nitrogen-

Table 3. Scope of Polycyclic Imidazole Synthesis via Phospha-münchnones[a]

Entry	Substrate	Acid Chloride	Product (% yield)
1	 **3a**		**4b** 68%
2	**3a**		**4c** 74%
3	**3a**		**4d** 47%
4	**3a**		**4e** 51%
5	**3b**		**4f** 79%
6	**3c**		**4g** 77%
7	**3d**		**4h** 82%
8[b]	**3e**		**4i** 63%
9[b]	**3f**		**4j** 59%

[a]Imine (0.2 mmol), acid chloride (0.22 mmol), 0.5 mL of $CDCl_3$, 30 min rt; then PhP(catechyl) (0.22 mmol) 30 min rt; DBU (0.4 mmol). [b]CD_3CN.

tethered nitriles generating imidazole in good yields (entries 1, 8). Similarly, modulating the tether length can afford 6,6-, 6,5-, and even 5,5-fused ring imidazole products (entries 7–9). Various aryl-, heteroaryl- (entries 2, 5), and even alkyl- (entry 6) substituted acid chlorides lead to imidazoles in high yields.

This cycloaddition chemistry can be expanded beyond acid chlorides. Chloroformates and chlorothioformates are established to react with imines to form iminium salts. The use of the latter in this reaction provides efficient access to 2-thioalkyl (entry 4) and 2-phenoxy- (entry 3) substituted products in moderate to good yield. It is notable that each of these cycloadditions involves unactivated, alkyl-substituted nitriles in cycloaddition. This contrasts with the previous use of electron-poor nitriles in reaction with münchnones[15,20] and presumably reflects the favored intramolecular cycloaddition as well as the high reactivity of the phospha-münchnone.

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CONCLUSIONS

Phospha-münchnones have been found to participate in 1,3-dipolar cycloaddition reaction with electron-deficient imines and tethered-nitriles to generate imidazoles. The latter represents, to our knowledge, the first general use of nitriles in cycloadditions with münchnone derivatives and forms polycyclic imidazoles in good yield. These reactions are modular, easily generalized, and allow access to highly substituted or polycyclic imidazoles in one pot from available substrates where all the substituents can be independently varied with high regiocontrol. Experiments directed toward exploiting this transformation in directed imidazole synthesis are in progress.

EXPERIMENTAL SECTION

General Procedures. All reactions were performed under nitrogen. All reagents were purchased from commercial sources and used as received. PCy_3 was dried by heating at 120 °C under high vacuum. Liquid $P(OCH_2CF_3)_3$ and $P(OPh)_3$ were dried over 4 Å molecular sieves. PhP(catechyl),[16a] (catechyl)POTMS,[16b] aldehyde precursors to imines,[19] and imines[21] were prepared as described in the literature. The nitrile-tethered imines **3** were prepared and characterized as described in Supporting Information. Deuterated $CDCl_3$ was distilled from CaH_2 under nitrogen. ^1H and ^{13}C NMR spectra were recorded on 300 and 400 MHz instruments. HRMS were obtained with electron impact (EI) ionization (TOF mass analyzer).

Typical Synthesis of Tetrasubstituted Imidazoles 2. In a glovebox, imine *p*-tolyl(H)C═NBn (41.9 mg, 0.20 mmol) and *p*-$MeOC_6H_4COCl$ (37.5 mg, 0.22 mmol) were mixed in $CDCl_3$ (0.5 mL) and allowed to stand at room temperature for 30 min. PhP(catechyl) (47.5 mg, 0.22 mmol) was added, and after 30 min DBU (91.0 mg, 0.60 mmol) was added as a solution in $CDCl_3$, followed by the addition of *N*-nosyl-substituted imine Ph(H)C═NNs (87.1 mg, 0.30 mmol). The reaction was complete within 3 h. The crude solution was concentrated in vacuo and purified by column chromatography on a 4 g column of silica gel 60 using a ethyl acetate:hexanes gradient (0−40%) on an automated chromatography system, giving pure **2a** as an off-white solid (56.0 mg, 65%).

*1-Benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(p-tolyl)-1H-imidazole (**2a**).* Isolated yield: 65% (56 mg). Off-white solid. mp 127−129 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, J = 9.3 Hz, 4H), 7.26−7.23 (m, 5H), 7.17−7.04 (m, 5H), 6.90 (d, J = 6.6 Hz, 2H), 6.83 (d, J = 6.3 Hz, 2H), 5.07 (s, 2H), 3.81 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 147.7, 138.5, 137.7, 130.9, 130.4, 129.8, 129.5, 128.6, 128.0, 127.8, 127.3, 126.7, 126.3, 125.9, 114.0, 55.3, 48.1, 21.4. HRMS (ESI^+) for $C_{30}H_{27}N_2O^+$; calculated: 431.2118,found: 431.2117.

*1-Benzyl-4-(4-fluorophenyl)-5-(4-(methylthio)phenyl)-2-(p-tolyl)-1H-imidazole (**2b**).* Isolated yield: 63% (59 mg). Yellow solid. mp 102−104 °C. ^1H NMR (400 MHz, $CDCl_3$ 7.61−7.47 (m, 4H), 7.29−7.12 (m, 7H), 7.08 (d, J = 8.3 Hz, 2H), 6.90 (t, J = 8.8 Hz, 2H), 6.85−6.78 (m, 2H), 5.08 (s, 2H), 2.48 (s, 3H), 2.36 (s, 3H). HRMS (ESI+) for $C_{30}H_{26}N_2FS^+$; calculated: 465.1795, found: 465.1780.

*1-Ethyl-2,4-diphenyl-5-(thiophen-2-yl)-1H-imidazole (**2c**).* Isolated yield: 77% (51 mg). Yellow solid. mp 102−104 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.9, 1.5 Hz, 2H), 7.65−7.57 (m, 2H), 7.54 (dd, J = 4.8, 1.5 Hz, 1H), 7.53−7.42 (m, 3H), 7.26−7.22 (m, 2H), 7.19−7.14 (m, 3H), 3.99 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 131.4, 130.4, 129.1, 129.1, 128.6, 128.5, 128.1, 127.7, 126.8, 126.6, 126.3, 124.4, 121.1, 39.8, 16.6. HRMS (ESI+) for $C_{21}H_{19}N_2S^+$; calculated: 331.1264, found: 331.1255.

*1-Benzyl-5-phenyl-2-(thiophen-2-yl)-4-(p-tolyl)-1H-imidazole (**2d**).* Isolated yield: 62% (50 mg). Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.2 Hz, 2H), 7.39−7.15 (m, 10H), 7.12 (d, J = 2.8 Hz, 1H), 7.07−6.89 (m, 4H), 5.19 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 138.3, 137.3, 136.1, 131.3, 131.0, 130.7, 130.1, 128.81, 128.79, 128.69, 127.4, 127.4, 126.8, 126.8, 126.3, 126.1, 125.8, 124.4, 48.2, 21.2. HRMS (ESI+) for $C_{27}H_{23}N_2S^+$; calculated: 407.1576, found: 407.1587.

*5-(3-Bromophenyl)-1-methyl-4-phenyl-2-(p-tolyl)-1H-imidazole (**2e**).* Isolated yield: 50% (40 mg). White solid. mp 181−183 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.50 (m, 6H), 7.36−7.27 (m, 4H), 7.27−7.13 (m, 3H), 3.50 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 138.9, 138.2, 134.3, 133.5, 131.6, 130.5, 129.7, 129.3, 128.9, 128.6, 128.2, 127.8, 127.0, 126.5, 124.4, 122.9, 33.2, 21.4. HRMS (ESI^+) for $C_{23}H_{20}N_2Br^+$; calculated: 403.0804, found: 403.0801.

*1-Benzyl-2-(4-fluorophenyl)-4-phenyl-5-(p-tolyl)-1H-imidazole (**2f**).* Isolated yield: 41% (34 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (m, 4H), 7.23−7.20 (m, 5H), 7.14−7.04 (m, 7H), 6.82 (d, J = 6.9 Hz, 2H), 5.06 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 131.0, 130.8, 130.2, 129.6, 128.7, 128.1, 127.5, 126.8, 126.5, 125.8, 115.8, 115.5, 48.1, 21.4. HRMS (ESI+) for $C_{29}H_{24}N_2F^+$; calculated: 419.1918, found: 419.1910.

*1-Benzyl-2-(furan-2-yl)-4-phenyl-5-(p-tolyl)-1H-imidazole (**2g**).* Isolated yield: 36% (28 mg). Orange oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.3 Hz, 2H), 7.46 (d, J = 1.0 Hz, 1H), 7.28−7.18 (m, 6H), 7.15 (dd, J = 7.4, 4.8 Hz, 3H), 7.09 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 6.8 Hz, 2H), 6.72 (s, 1H), 6.43 (dd, J = 3.4, 1.8 Hz, 1H), 5.25 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.83 137.3, 130.9, 130.4, 129.6, 128.6, 128.0, 127.3, 126.9, 126.5, 125.9, 111.5, 48.3, 21.4. HRMS (ESI+) for $C_{27}H_{23}ON_2^+$; calculated: 391.1805, found: 391.1796.

*1-Benzyl-5-(4-chlorophenyl)-4-(furan-2-yl)-2-isopropyl-1H-imidazole (**2h**).* Isolated yield: 45% (34 mg). Yellow-orange solid. mp 129−131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 2.7 Hz, 2H), 7.30−7.24 (m, 5H), 7.17 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 7.0 Hz, 2H), 6.28 (s, 1H), 6.06 (d, J = 3.0 Hz, 1H), 4.97 (s, 2H), 1.34 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 149.5, 141.1, 136.9, 134.7, 132.2, 130.2, 128.9, 128.9, 128.7, 127.6, 126.8, 125.5, 110.7, 105.1, 46.7, 26.6, 21.8. HRMS (ESI+) for $C_{23}H_{22}ON_2Cl^+$; calculated: 377.1415, found: 377.1411.

*4-(Furan-2-yl)-1-(4-methoxyphenyl)-5-phenyl-2-(p-tolyl)-1H-imidazole (**2i**).* Isolated yield: 68% (55 mg). White solid. mp 177−179 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 0.9 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.29−7.24 (m, 3H), 7.20 (dt, J = 7.5, 3.7 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.96−6.91 (m, 2H), 6.78−6.72 (m, 2H), 6.33 (dd, J = 3.3, 1.8 Hz, 1H), 6.27 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 149.4, 147.5, 141.3, 138.2, 131.0, 130.6, 129.9, 129.7, 129.3, 128.8, 128.7, 128.0, 128.0, 127.4, 114.2, 110.8, 105.7, 55.3, 21.3. HRMS (ESI+) for $C_{27}H_{23}O_2N_2^+$; calculated: 407.1754, found: 407.1743.

*5-(Benzo[d][1,3]dioxol-5-yl)-1-benzyl-2-phenyl-4-(p-tolyl)-1H-imidazole (**2j**).* Isolated yield: 35% (31 mg). Yellow solid. mp 172−174 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64−7.63 (m, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.41−7.36 (m, 3H), 7.28−7.15 (m, 3H), 7.05 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 7.7 Hz, 2H), 6.75 (d, J = 7.9 Hz, 1H), 6.72−6.67 (m, 1H), 6.64 (d, J = 1.4 Hz, 1H), 5.97 (s, 2H), 5.10 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.8, 147.7, 138.1, 137.6, 135.9, 131.5, 131.0, 129.07, 129.02, 128.8, 128.59, 128.56, 127.3, 126.6, 126.0, 125.1, 124.4, 111.3, 108.7, 101.2, 48.2, 21.2. HRMS (ESI^+) for $C_{30}H_{25}N_2O_2^+$; calculated: 445.1911, found: 445.1897.

Synthesis of Nitrile-Tethered Imines 3. In analogy to a previous report,[19] 2-(2-formylphenoxy)acetonitrile was prepared from salicylaldehyde (500 mg, 4.09 mmol) in DMF (15 mL). To this solution was added K_2CO_3 (848 mg, 6.15 mmol), and the solution was stirred at rt for 15 min. Bromoacetonitrile (589 mg, 4.92 mmol) was added and stirred at rt for 18 h. Reaction mixture was filtered, diluted with EtOAc (100 mL), washed with water (3 × 100 mL) and brine (2 × 10 mL), and dried over Na_2SO_4. The solvent was evaporated, and the crude residue was purified by column chromatography with a solvent gradient of EtOAc/hexanes 0−40% to give the final product, 2-(2-formylphenoxy)acetonitrile, as a pale yellow solid (84%). To a solution of 2-(2-formylphenoxy)-acetonitrile (500 mg, 3.1 mmol) in dichloromethane (15 mL) were added $MgSO_4$ and ethylamine (2.0 M in THF, 1.7 mL, 3.41 mmol). The heterogeneous mixture was stirred at room temperature for 18 h. The reaction mixture was filtered, and the solvent and excess amine were evaporated in vacuo to provide imine **3a** as a dark orange oil in 95% yield (556 mg). All other imines **3b−f** were formed in near quantitative yield (at 1−3 mmol scale) and used in the cyclization without any further purification.

*(E)-2-(2-((Ethylimino)methyl)phenoxy)acetonitrile (**3a**).* Isolated yield: 95% (556 mg). Orange oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.65

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(s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 6.9 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 4.84 (s, 2H), 3.66 (q, J = 6.2 Hz, 2H), 1.30 (t, J = 7.3 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 131.7, 128.1, 125.9, 123.4, 114.9, 112.4, 56.2, 54.0, 16.3. HRMS (ESI$^+$) for $C_{11}H_{13}N_2O^+$; calculated: 189.1022, found: 189.1023.

(E)-2-(4-Bromo-2-((ethylimino)methyl)phenoxy)acetonitrile ***(3b)***. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.13 (d, J = 2.5 Hz, 1H), 7.52 (dd, J = 8.8, 2.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 4.82 (s, 2H), 3.66 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.8, 134.2, 130.9, 127.7, 116.5, 114.2, 56.2, 54.2, 16.2. HRMS (ESI$^+$) for $C_{11}H_{12}N_2OBr^+$; calculated: 267.0128, found: 267.0116.

(E)-2-((1-((Ethylimino)methyl)naphthalen-2-yl)oxy)acetonitrile ***(3c)***. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09−8.81 (m, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.57 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.45 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.35−7.20 (m, 1H), 4.92 (s, 1H), 3.81 (qd, J = 7.3, 1.4 Hz, 1H), 1.43 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 154.2, 132.3, 132.0, 130.6, 128.22, 128.19, 125.7, 125.3, 120.8, 114.3, 77.4, 77.0, 76.6, 57.4, 55.7, 16.6. HRMS (ESI$^+$) for $C_{15}H_{15}N_2O^+$; calculated: 239.1179, found: 239.1175.

(E)-2-(2-((Ethylimino)methyl)-6-methoxyphenoxy)acetonitrile ***(3d)***. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.57 (dd, J = 7.9, 1.4 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.99 (dd, J = 8.2, 1.4 Hz, 1H), 4.87 (s, 2H), 3.90 (s, 3H), 3.69 (qd, J = 7.3, 1.3 Hz, 2H), 1.31 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.8, 130.5, 125.7, 119.2, 115.5, 114.0, 57.7, 56.2, 55.9, 16.2. HRMS (ESI$^+$) for $C_{12}H_{15}N_2O_2^+$; calculated: 219.1128, found: 219.1122.

(E)-2-(2-((Ethylimino)methyl)-1H-pyrrol-1-yl)acetonitrile ***(3e)***. Red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.82 (s, 1H), 6.45 (dd, J = 3.8, 1.6 Hz, 1H), 6.23 (dd, J = 3.7, 2.9 Hz, 1H), 5.57 (s, 2H), 3.53 (q, J = 7.3 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CD_3CN) δ 151.6, 127.2, 125.0, 117.3, 109.6, 55.5, 36.7, 16.0. HRMS (ESI$^+$) for $C_9H_{12}N_3^+$; calculated: 162.1031, found: 162.1026

(E)-3-(2-((Ethylimino)methyl)-1H-pyrrol-1-yl)propanenitrile ***(3f)***. Red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 6.87−6.72 (m, 1H), 6.47 (d, J = 2.0 Hz, 1H), 6.17 (dd, J = 3.7, 2.8 Hz, 1H), 4.59 (t, J = 6.6 Hz, 2H), 3.51 (q, J = 7.3 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 1.23 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 128.9, 127.4, 117.9, 108.7, 56.1, 44.8, 19.8, 16.7 HRMS (ESI$^+$) for $C_{10}H_{14}N_3^+$; calculated: 176.1182, found: 176.1187.

Synthesis of Polycyclic Imidazoles 4. In a glovebox, imine **3a** (37.8 mg, 0.20 mmol) and *p*-toluoyl chloride (33.9 mg, 0.22 mmol) were mixed in $CDCl_3$ (0.5 mL) and allowed to stand at room temperature for 30 min. PhP(catechyl) (47.5 mg, 0.22 mmol) was added, and after 30 min DBU (91 mg, 0.6 mmol) was added as a solution in $CDCl_3$. The reaction was complete within 5 min. The crude solution was concentrated in vacuo and purified by column chromatography on a 4 g column of silica gel 60 using a ethyl acetate:hexanes gradient (0−40%) on an automated chromatography system, giving pure **4a** as a pale yellow powder (44.3 mg, 76%).

1-Ethyl-2-(p-tolyl)-1,4-dihydrochromeno[3,4-d]imidazole ***(4a)***. Isolated yield: 76% (44 mg). Yellow solid. mp 147−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 8.0 Hz, 2H), 6.30 (d, J = 7.9 Hz, 1H), 6.22 (d, J = 7.9 Hz, 2H), 6.12−6.00 (m, 1H), 5.94−5.90 (m, 2H), 4.30 (s, 2H), 3.22 (q, J = 7.2 Hz, 2H), 1.36 (s, 3H), 0.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 149.5, 139.1, 134.2, 129.4, 129.0, 127.5, 127.4, 122.2, 121.7, 119.7, 117.9, 117.4, 66.4, 40.7, 21.4, 16.4. HRMS (ESI+) for $C_{19}H_{19}ON_2^+$; calculated: 291.1492, found: 291.1490.

1-Ethyl-2-(4-fluorophenyl)-1,4-dihydrochromeno[3,4-d]imidazole ***(4b)***. Isolated yield: 68% (40 mg). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.52 (m, 2H), 7.46−7.32 (m, 1H), 7.26−7.13 (m, 3H), 7.05−6.95 (m, 2H), 6.80−6.65 (m, 3H), 5.33 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 161.6, 153.0, 148.2, 144.7, 134.1, 131.1, 131.0, 127.8, 126.4, 122.5, 121.8, 120.1, 119.8, 117.7, 117.5, 116.0, 115.7, 115.0, 66.1, 40.8, 16.3. HRMS (ESI+) for $C_{18}H_{16}ON_2F^+$; calculated: 295.1241, found: 295.1232.

1-Ethyl-2-(furan-2-yl)-1,4-dihydrochromeno[3,4-d]imidazole ***(4c)***. Isolated yield: 74% (40 mg). Orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.8, 0.8 Hz, 1H), 7.41−7.33 (m, 1H), 7.19−7.08 (m, 1H), 7.03−6.94 (m, 2H), 6.89 (dd, J = 3.5, 0.8 Hz, 1H), 6.54 (dd, J = 3.5, 1.8 Hz, 1H), 5.31 (s, 2H), 4.49 (q, J = 7.2 Hz, 2H), 1.59 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 145.3, 142.9, 140.0, 134.4, 127.8, 122.6, 121.9, 119.8, 117.6, 115.0, 111.7, 110.2, 66.1, 41.2, 16.2. HRMS (ESI+) for $C_{16}H_{15}O_2N_2^+$; calculated: 267.1133, found: 267.1120.

1-Ethyl-2-(ethylthio)-1,4-dihydrochromeno[3,4-d]imidazole ***(4d)***. Isolated yield: 47% (25 mg). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.19 (m, 1H), 7.17−7.04 (m, 1H), 6.99−6.92 (m, 2H), 5.29 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.11 (q, J = 7.4 Hz, 2H), 1.47−1.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 143.2, 134.7, 127.5, 122.8, 121.8, 119.4, 117.6, 117.4, 66.3, 40.7, 29.0, 15.8, 15.1. HRMS (ESI+) for $C_{14}H_{17}ON_2S^+$; calculated: 261.1056, found: 261.1048.

1-Ethyl-2-phenoxy-1,4-dihydrochromeno[3,4-d]imidazole ***(4e)***. Isolated yield: 51% (30 mg). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H), 7.29−7.14 (m, 4H), 7.14−7.04 (m, 1H), 6.99−6.93 (m, 2H), 5.24 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 152.5, 151.2, 129.8, 128.8, 127.0, 124.7, 121.7, 118.7, 118.7, 118.0, 117.7, 117.2, 66.1, 38.9, 15.7. HRMS (ESI$^+$) for $C_{18}H_{17}N_2O_2^+$; calculated: 293.1285, found: 293.1283.

8-Bromo-1-ethyl-2-(thiophen-2-yl)-1,4-dihydrochromeno[3,4-d]-imidazole ***(4f)***. Isolated yield: 79% (57 mg). Orange solid. mp 95−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 5.4 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.42−7.38 (m, 1H), 7.22 (dd, J = 8.6, 2.2 Hz, 1H), 7.19−7.13 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.35 (s, 2H), 4.42 (q, J = 7.3 Hz, 2H), 1.61 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 143.7, 135.2, 132.0, 130.2, 127.7, 127.4, 126.3, 122.1, 121.9, 119.4, 119.1, 114.1, 66.3, 40.9, 16.1. HRMS (ESI+) for $C_{16}H_{14}ON_2BrS^+$; calculated: 361.0004, found: 361.0002.

1-Ethyl-2-isopropyl-6-methoxy-1,4-dihydrochromeno[3,4-d]-imidazole ***(4g)***. Isolated yield: 77% (42 mg). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96−6.89 (m, 2H), 6.82−6.66 (m, 1H), 5.35 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.01 (dq, J = 13.6, 6.8 Hz, 1H), 1.42 (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 149.0, 141.3, 132.9, 121.5, 120.6, 118.9, 111.9, 110.3, 66.9, 56.0, 39.2, 25.9, 22.1, 16.4. HRMS (ESI+) for $C_{16}H_{21}O_2N_2^+$; calculated: 273.1598, found: 273.1589.

1-Ethyl-2-(4-methoxyphenyl)-1,4-dihydrobenzo[5,6]chromeno-[3,4-d]imidazole ***(4h)***. Isolated yield: 82% (59 mg). Orange solid. mp 213−215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 8.1 Hz, 3H), 7.53 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 5.24 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 0.66 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 152.6, 152.2, 135.7, 130.1, 130.1, 128.6, 128.3, 127.7, 126.1, 125.1, 124.7, 124.0, 123.6, 118.7, 114.2, 112.7, 66.6, 55.4, 43.5, 15.2. HRMS (ESI+) for $C_{23}H_{21}O_2N_2^+$; calculated: 357.1597, found: 357.1589.

1-Ethyl-2-(p-tolyl)-1,4-dihydroimidazo[4,5-a]pyrrolizine ***(4i)***. Isolated yield: 63% (33 mg). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 2.0 Hz, 1H), 6.30−6.21 (m, 1H), 6.01 (d, J = 3.1 Hz, 1H), 4.74 (s, 2H), 4.19 (q, J = 7.3 Hz, 2H), 2.41 (s, 3H), 1.54 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 144.8, 138.5, 130.3, 129.3, 129.2, 128.4, 127.9, 117.9, 110.4, 95.6, 47.0, 41.6, 21.3, 15.8. HRMS (ESI$^+$) for $C_{17}H_{18}N_3^+$; calculated: 264.1495, found: 264.1495.

1-Ethyl-2-(p-tolyl)-4,5-dihydro-1H-imidazo[4,5-g]indolizine ***(4j)***. Isolated yield: 59% (33 mg). Dark orange solid. mp 87−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.86−6.64 (m, 1H), 6.29−6.16 (m, 2H), 4.29−4.11 (m, 4H), 3.15 (t, J = 7.0 Hz, 2H), 2.42 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 145.0, 138.7, 129.3, 128.9, 123.3, 121.1, 119.9, 115.0, 108.1, 101.3, 45.7, 40.4, 24.2, 21.3, 15.9. HRMS (ESI+) for $C_{18}H_{20}N_3^+$; calculated: 278.1657, found: 278.1641.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: bruce.arndtsen@mcgill.ca.

Notes

The authors declare no competing financial interest.

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