Mild and General One-Pot Reduction and Cyclization of Aromatic and Heteroaromatic 2-Nitroamines to Bicyclic 2*H*-Imidazoles

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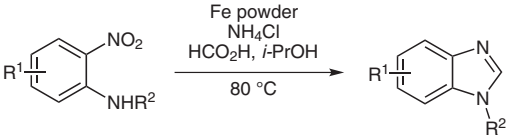
Abstract: A one-pot procedure for the conversion of aromatic and heteroaromatic 2-nitroamines into bicyclic 2*H*-benzimidazoles is described. The procedure employs formic acid, iron powder, and an additive such as NH_4Cl to reduce the nitro group and effect the imidazole cyclization with high-yielding conversions generally within one to two hours. The compatibility with a wide range of functionality demonstrates the general utility of this procedure.

Key words: cyclization, heterocycles, imidazole, iron, reduction

Fused bicyclic imidazoles (benzimidazoles and their aza equivalents) are a common feature in biologically active molecules.[1] Being closely related in structure to purines, which are recognized by an enormous variety of proteins, benzimidazoles are an important chemotype in current pharmaceutical research.[2] 2-Nitroanilines can be a useful synthetic starting point, and converted into the corresponding benzimidazoles through a two-step procedure consisting of reduction of the nitro group followed by Phillips cyclization of the *ortho*-dianiline with a methylene source.[3] Trialkylorthoformates, formamidine acetate, and formic acid are among methylene sources commonly used to culminate the production of 2*H*-benzimidazoles.[3] In order to carry out this two-step transformation in one pot, reductants such as palladium or tin are often combined with similar methylene sources.[4] However, palladium and other transition metals have the disadvantage of high cost as well as incompatibility with common functionality, and tin reductants are disfavored due to their toxicity.

In the course of our research, we had the need to transform heterocyclic 2-nitroamines into the corresponding fused bicyclic 2-*H*-imidazoles, and an efficient one-pot transformation was desired. As an inexpensive and nontoxic metal with minimal cross-reactivity, iron is an ideal reductant for this purpose. One-pot nitro reduction and benzimidazole formation mediated by iron is well precedented for benzimidazoles having a carbon substituent at the imidazole 2-position, particularly when the amine is already acylated.[5] Iron/acetic acid is a known combination resulting in 2-methylbenzimidazoles,[6] but iron used in conjunction with formic acid as the bicyclic imidazole C-2 carbon source is poorly explored. Several non-heterocyclic examples are present in the literature, but these typically require the presence of aqueous hydrochloric acid or supplemental triethylorthoformate and acetic acid.[7] We wished to optimize the reaction conditions to be as mild as possible (avoiding the use of strong mineral acids), and to explore the scope of this transformation with regard to functional-group tolerance both on benzene and heteroaromatic cores (Scheme 1).

Using 2-nitroaniline as a test substrate, we found that iron and formic acid alone were not sufficient to effect reduction of the nitro group. However, we found NH_4Cl, which has broader functional-group compatibility, to be a suitable alternative to aqueous HCl. After exploring molar ratios of both iron powder and NH_4Cl, the presence and type of co-solvent, time, and temperature of the reaction, the optimal conditions were established. For the majority of substrates, these were determined to be 10 equivalents iron powder, 10 equivalents NH_4Cl, and a 1:1 mixture of formic acid–isopropanol as solvent. For conversions requiring a higher reaction temperature, 1-butanol could be substituted for isopropanol.[8] Under these conditions, most reactions completed within one to two hours at 80 °C.[9] While a 10 equivalent excess of both iron powder and NH_4Cl provided optimal reaction times, 2–5 equivalents of each are sufficient to complete the transformation although reaction times extend to 24 hours. Similarly, a lower reaction temperature (60 °C) is sufficient but extends the reaction time by several fold.



Scheme 1 One-pot conversion: *o*-nitroanilines into 2*H*-benzimidazoles

Using these optimized reaction conditions, we examined the scope of this reaction with 2-nitroanilines substituted with varying functionality (Table 1). Most products could be obtained at >95% purity after filtration and a simple aqueous extraction, with no chromatography required; unless otherwise noted, product yields given in Tables 1– 3 are determined after aqueous workup.

The reaction proceeds equally well when the aniline is either unsubstituted or is a secondary alkyl- or aryl-substituted aniline (substrates **1**–**3**), although the secondary

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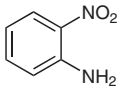
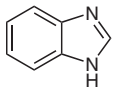
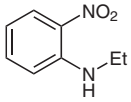
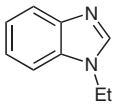
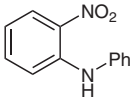
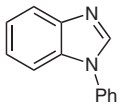
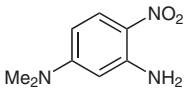
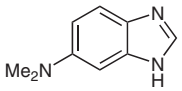
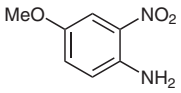
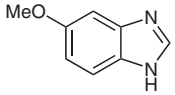
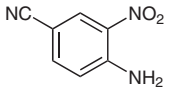
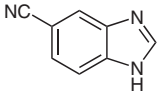
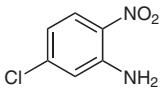
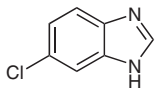
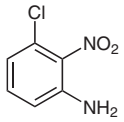
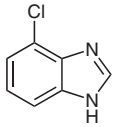
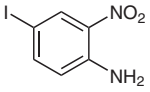
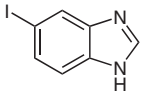
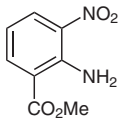
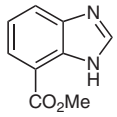
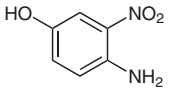
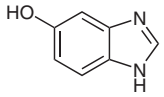
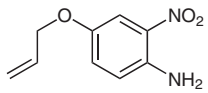
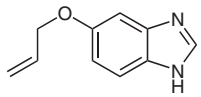
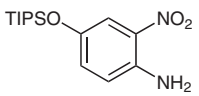
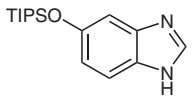
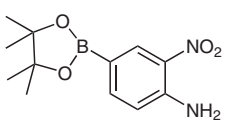
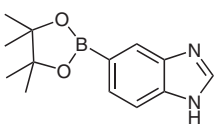
Table 1 Reaction Scope with Aniline Substrates[a]

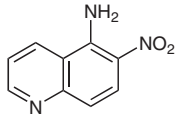
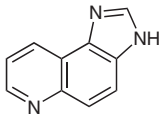
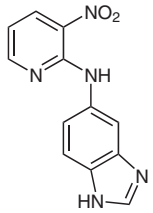
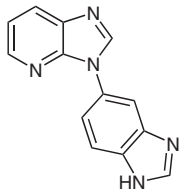
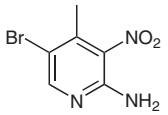
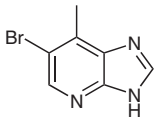
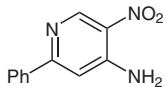
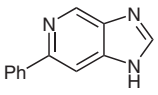
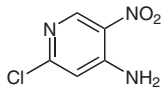
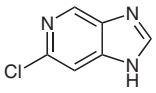
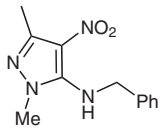
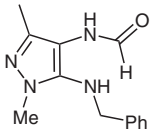
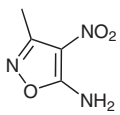
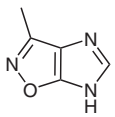
Substrate		Time (h)	Product[b]		Isolated yield (%)
1		1	**1**		97
2		2	**2**		93
3		2	**3**		94
4		1	**4**		89
5		1	**5**		98
6		1	**6**		84
7		2[c]	**7**		99
8		1.5	**8**		94
9		1	**9**		90
10		1	**10**		94
11		1	**11**		87
12		1	**12**		73[d]
13		3	**13**		52[d]
14		1.5	**14**		73[d]

[a] Reaction conditions: substrate (1.0 mmol), Fe powder (10.0 mmol), NH_4Cl (10.0 mmol), 2-PrOH (5.0 mL), formic acid (5.0 mL), 80 °C.
[b] All products were characterized by LC-MS and ^1H NMR.[10]
[c] Reaction at 90 °C.
[d] Isolated via silica gel chromatography.

anilines require a slightly longer reaction time. The phenyl ring may be substituted with either electron-donating (substrates **4** and **5**) or electron-withdrawing substituents (substrates **6**–**10**) while still resulting in excellent yields. Halogens in various positions are well tolerated under these conditions (substrates **7**–**9**), which is particularly useful since halogen-containing substrates are often incompatible with palladium-catalyzed nitro group reductions. Both the phenol and allyloxy-containing substrates also resulted in good conversion into product (substrates **11** and **12**). Surprisingly, a TIPS-protected phenol provided the corresponding TIPS-containing product (substrate **13**), albeit in moderate yield. This substrate required a slightly longer reaction time of three hours to go to completion, by which point some desilylated phenol was observed. Even a boronate pinacol ester was compatible with these reaction conditions, providing the cyclized product in good yield (substrate **14**).

We next turned our attention to heterocyclic substrates, which are of great interest in our medicinal chemistry programs (Table 2). We found that the one-pot transformation was highly efficient for a variety of heterocyclic substrates, although some limitations were observed. The quinoline substrate proceeded uneventfully, with no change in reaction conditions required to provide the product in excellent yield (substrate **15**). The more complex benzimidazole-containing pyridyl substrate **16** required a reaction time of 2.5 hours, but provided the cyclized product in excellent yield. Pyridine substrate **17** required an even longer 22 hours at 80 °C to complete the cyclization, and while the conversion was good (79% by crude HPLC), the exceedingly poor solubility of the product in any combination of dichloromethane and methanol or isopropanol reduced the isolated yield significantly. Interestingly, the pyridine regioisomers **18** and **19**, 5-nitropyridin-4-amines, required a substantially higher

Table 2 Reaction Scope with Heterocyclic Substrates

Substrate		Conditions[a]	Time (h)	Product[b]		Isolated yield (%)
15		A	1	**15**		95
16		B	2.5	**16**		98[c]
17		A	22	**17**		36[c] (79[d])
18		C	120	**18**		74
19		C	24	**19**		23[e]
20		A	1	**20**		100[d]
21		A	2	**21**		0

[a] Reaction conditions: Fe powder (10 equiv), NH_4Cl (10 equiv) with (A) substrate (1.0 mmol), 2-PrOH (5.0 mL), formic acid (5.0 mL), 80 °C; (B) substrate (0.32 mmol), 2-PrOH (4.0 mL), formic acid (4.0 mL), 80 °C; (C) substrate (1.0 mmol), 1-BuOH (5.0 mL), formic acid (5.0 mL), 120 °C.

[b] All products were characterized by LC-MS and ^1H NMR.[10]

[c] Isolated via silica gel chromatography.

[d] Crude yield as determined by HPLC.

[e] Isolated via reversed-phase HPLC.

temperature and longer reaction time than the 3-nitropyridin-2-amines **16** and **17**. Substrate **18** proved to be extraordinarily recalcitrant to cyclization: reduction and monoformylation was observed after 24 hours at 120 °C, with complete cyclization to the product occurring after 5 days. However, despite extended heating at high temperature, no side products were observed, and the product was isolated in good yield. 2-Halo-pyridine substrates such as **19** exposed some limitations to this method, with the extended heating at high temperatures resulting in the formation of degradation side products and comparatively poor product yields (23% yield for compound **19** after nontrivial preparatory HPLC separation).

Five-membered heterocyclic rings proved to be challenging substrates. Under standard reaction conditions, pyrazole substrate **20** was rapidly converted into the reduced and monoformylated intermediate product **20** as shown in Table 2, but this intermediate did not cyclize to yield the desired 5,5-bicyclic system even after prolonged heating at 120 °C. This is perhaps unsurprising, since the only literature reports for cyclizing acylated 4,5-diaminopyrazoles require either phosphoryl trichloride or thionyl chloride to first form the highly activated imidoyl chloride.[11] 3-Methyl-4-nitroisoxazol-5-amine **21** was also subjected to the standard reaction conditions, but only decomposition of the starting material was observed.[12]

In an attempt to determine the role played by the NH_4Cl additive, we examined the performance of other salts as additives in the conversion of 2-nitro-*N*-phenylaniline into 1-phenyl-1*H*-benzo[*d*]imidazole (Table 3). NH_4Cl could be replaced by LiCl or NaCl with no decrease in yield. NaI resulted in a slower reduction, with 88% product isolated after two hours with the mass balance identified as the unreduced nitro starting material. When no additive is used, the nitro reduction is exceedingly sluggish, with only 33% conversion after two hours (the remaining material was identified as unreacted 2-nitro-*N*-phenylaniline). Considering that iron powder is oxidized to $FeCl_2$ and $FeCl_3$ in the presence of hydrochloric acid, we wanted to determine if the halide (X) salt additives are merely promoting the formation of FeX_2 in the reaction mixture, with FeX_2 as the active reductant. However, when the reaction was attempted using $FeCl_2$ instead of iron powder with no additional salt additives, absolutely no reduction was observed, suggesting that Fe(0) is the active reducing agent.

The ability of chloride salts to promote metal-based reactions has been observed by others. Notably, the work of Knochel et. al. provides the observation that LiCl allows the direct insertion of zinc into aryl-iodide bonds, provides a 'spectacular rate increase' for Br–Mg exchange, and forms a solubilized iron(II) base for the ferration of arenes.[13] Knochel and co-workers propose that LiCl solubilizes organometallic complexes, thereby constantly cleaning the metal surface and allowing further reactions to take place.[14] We suggest that the halide salts are serving a similar function here, accelerating the transfer of iron into solution and renewing the available source of Fe(0). It is remarkable that while LiCl works quite well, the inexpensive and easier-to-handle NH_4Cl and NaCl salts perform equally well.

Table 3 Comparison of Additives in the Conversion of 2-Nitro-*N*-phenylaniline into 1-Phenyl-1*H*-benzo[*d*]imidazole[a]

Additive	Isolated yield (%)
NH_4Cl	94
LiCl	97
NaCl	96
NaI	88
none	33

[a] Reaction conditions: 2-nitro-*N*-phenylaniline (1.0 mmol), Fe powder (10.0 mmol), additive (10.0 mmol), 2-PrOH (5.0 mL), formic acid (5.0 mL), 80 °C, 2 h.

In conclusion, we have optimized a simple one-pot conversion of aromatic *ortho*-nitroamines into cyclized C2–H bicyclic imidazoles using inexpensive and easily handled reagents. This reaction is tolerant of a wide range of functionality and may be applied to heterocyclic substrates. We are optimistic that the flexibility in choice of co-solvent and additive will allow this method to be useful in a wide range of organic syntheses.

Representative Experimental Procedure

1*H*-Benzo[*d*]imidazole[15] (1)

A 40 mL glass vial was charged with *o*-nitroaniline (0.138 g, 1.00 mmol), iron powder 325 mesh (0.558 g, 10.0 mmol), NH_4Cl (0.535 g, 10.0 mmol), and a magnetic stir bar. 2-PrOH (5.0 mL) and formic acid (5.0 mL) were added, and the reaction vial was sealed with a Teflon-lined cap. The reaction mixture was stirred at 80 °C for 1 h at which time LC-MS analysis indicated that conversion into the product was complete. The reaction mixture was diluted with 2-PrOH (10 mL) and filtered to remove insoluble materials. The filtrate was concentrated to dryness, and the resulting residue partitioned between CH_2Cl_2 (20 mL) and (5 mL) sat. aq $NaHCO_3$. The aqueous layer was extracted with additional CH_2Cl_2 (5×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield the pure product as a light yellow solid (0.114 g, 97%). ESI-MS: $m/z = 119.4$ $[M + H]^+$. ^1H NMR (400 MHz, DMSO): $\delta = 12.42$ (s, 1 H), 8.20 (s, 1 H), 7.58 (m, 2 H), 7.18 (dd, $J = 6.0, 3.1$ Hz, 2 H).

References and Notes

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232.

(2) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *Tetrahedron Lett.* **2001**, *42*, 8751.

(3) (a) Phillips, M. A. *J. Chem. Soc.* **1928**, 2393. (b) Wright, J. B. *Chem. Rev.* **1951**, *48*, 397. (c) Subasinghe, N. L.; Travins, J. M.; Ali, F.; Huang, H.; Ballentine, S. K.; Marugan, J. J.; Khalil, E.; Hufnagel, H. R.; Bone, R. F.; Desjarlais, R. L.; Crysler, C. S.; Ninan, N.; Cummings,

M. D.; Molloy, C. J.; Tomczuk, B. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2200. (d) Minetti, P.; Tinti, M. O.; Carminati, P.; Castorina, M.; Di Cesare, M. A.; Serio, S. D.; Gallo, G.; Ghirardi, O.; Giorgi, F.; Giorgi, L.; Piersanti, G.; Bartoccini, F.; Tarzia, G. *J. Med. Chem.* **2005**, *48*, 6887. (e) Suzuki, N.; Tanaka, Y.; Dohmori, R. *Chem. Pharm. Bull.* **1980**, *28*, 235. (f) Seley, K. L.; O'Daniel, P. I.; Salim, S. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 2133. (g) Maron, D.; Kontorowitsch, M.; Bloch, J.-J. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1352. (h) van Galen, P. J. M.; Nissen, P.; van Wijngaarden, I.; Ijzerman, A. P.; Soudijn, W. *J. Med. Chem.* **1991**, *34*, 1202. (i) Palmer, B. D.; Smaill, J. B.; Boyd, M.; Boschelli, D. H.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Kraker, A. J.; Panek, R. L.; Lu, G. H.; Dahring, T. K.; Winters, R. T.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 5457.

(4) (a) Boydston, A. J.; Pecinovsky, C. S.; Chao, S. T.; Bielawski, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 14550. (b) Wallace, E. M.; Lyssikatos, J. P.; Marlow, A. L.; Hurley, T. B. US 2003/216460 A1, **2003**. (c) Huisgen, R. *Justus Liebigs Ann. Chem.* **1948**, *559*, 101. (d) Cholody, W. M.; Hernandez, L.; Hassner, L.; Scudiero, D. A.; Djurickovic, D. B.; Michejda, C. J. *J. Med. Chem.* **1995**, *38*, 3043. (e) VanVliet, D. S.; Gillespie, P.; Scicinski, J. J. *Tetrahedron Lett.* **2005**, *46*, 6741. (f) Chen, J. J.; Thakur, K. D.; Clark, M. P.; Laughlin, S. K.; George, K. M.; Bookland, R. G.; Davis, J. R.; Cabrera, E. J.; Easwaran, V.; De, B.; Zhang, Y. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5633. (g) Boydston, A. J.; Khramov, D. M.; Bielawski, C. W. *Tetrahedron Lett.* **2006**, *47*, 5123. (h) Boydston, A. J.; Vu, P. D.; Dykhno, O. L.; Chang, V.; Wyatt, A. R.; Stockett, A. S.; Ritschdorff, E. T.; Shear, J. B.; Bielawski, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 3143.

(5) (a) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W.; Michejda, C. J. *J. Med Chem.* **1997**, *40*, 4199. (b) Nozary, H.; Piguet, C.; Tissot, P.; Bernardinelli, G.; Bunzli, J.-C. G.; Deschenaux, R.; Guillon, D. *J. Am. Chem. Soc.* **1998**, *120*, 12274. (c) Suami, T.; Day, A. *J. Org. Chem.* **1959**, *24*, 1340. (d) Piguet, C.; Bocquet, B. *Helv. Chim. Acta* **1994**, *77*, 931. (e) McKenzie, B. M.; Miller, A. K.; Wojtecki, R. J.; Johnson, J. C.; Burke, K. A.; Tzeng, K. A.; Mather, P. T.; Rowan, S. J. *Tetrahedron* **2008**, *64*, 8488.

(6) (a) Radl, S.; Hradil, P. *Coll. Czech. Chem. Commun.* **1991**, *56*, 2420. (b) Efremov, I. V.; Rogers, B. N.; Duplantier, A. J.; Zhang, L.; Zhang, Q.; Maklad, N. S. US 2008/0312271 A1, **2008**.

(7) (a) Wu, W.-L.; Burnett, D. A.; Spring, R.; Greenlee, W. J.; Smith, M.; Favreau, L.; Fawzi, A.; Zhang, H.; Lachowicz, J. E. *J. Med. Chem.* **2005**, *48*, 680. (b) Burnett, D. A.; Wu, W.-L. US 2008/312218 A1, **2008**. (c) Bounaud, P.-Y.; Smith, C. R.; Jefferson, E. A. WO 2008/51808 A2, **2008**. (d) Foster, R.; Ing, H. R.; Rogers, E. F. *J. Chem. Soc.* **1957**, 1671. (e) Bolger, J.; Castelhano, A. L.; Crew, A. P.; Dong, H.-Q.; Honda, A.; Laufer, R.; Li, A.-H.; Mulvihill, K.; Qui, L.; Sambrook-Smith, C. P.; Sun, Y.; Wynne, G. M.; Zhang, T. WO 2005/21531A1, **2005**. (f) Crew, A. P.; Cox, M.; Laufer, R.; Pegg, N. A.; Smith, S.; Peter, C.; Sun, Y.; Wilkes, R. D.; Williams, J. US 2006/116402 A1, **2006**.

(8) The role of the alcohol co-solvent in this reaction is to increase solubilization of the substrate and may be omitted for substrates with good solubility in neat formic acid (unpublished observation).

(9) If the reaction is followed by LC-MS at shorter time intervals, the progression from starting material to bisaniline to N-formylated aniline to cyclized product can typically be observed.

(10) **Analytical Data for Compounds 2–19**

1-Ethyl-1*H*-benzo[*d*]imidazole[16] (2)
ESI-MS: *m/z* = 147.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 8.23 (s, 1 H), 7.62 (dd, *J* = 18.0, 7.9 Hz, 2 H), 7.22 (dt, *J* = 15.0, 7.2 Hz, 2 H), 4.28 (q, *J* = 7.3 Hz, 2 H), 1.41 (t, *J* = 7.3 Hz, 3 H).

1-Phenyl-1*H*-benzo[*d*]imidazole[17] (3)
ESI-MS: *m/z* = 195.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 8.56 (s, 1 H), 7.78 (dd, *J* = 6.5, 2.3 Hz, 1 H), 7.69 (dd, *J* = 8.4, 1.1 Hz, 2 H), 7.67–7.60 (m, 3 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.38–7.28 (m, 2 H).

***N*,*N*-Dimethyl-1*H*-benzo[*d*]imidazol-6-amine (4)**
ESI-MS: *m/z* = 162.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.0 (br s, 1 H), 7.96 (s, 1 H), 7.40 (br s, 1 H), 6.78 (d, *J* = 7.9 Hz, 2 H), 2.88 (s, 6 H).

5-Ethoxy-1*H*-benzo[*d*]imidazole[18] (5)
ESI-MS: *m/z* = 163.0 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO, reported as a mixture of tautomers): δ = 12.25 (br s, 0.4 H), 12.20 (br s, 0.6 H), 8.10 (br s, 0.4 H), 8.04 (br s, 0.6 H), 7.49 (br d, *J* = 8.8 Hz, 0.6 H), 7.38 (br d, *J* = 8.2 Hz, 0.4 H), 7.14 (br s, 0.4 H), 6.98 (br s, 0.6 H), 6.83–6.77 (m, 1 H), 4.03 (q, *J* = 6.9 Hz, 2 H), 1.34 (t, *J* = 6.9 Hz, 3 H).

1*H*-Benzo[*d*]imidazole-5-carbonitrile[19] (6)
ESI-MS: *m/z* = 144.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.96 (s, 1 H), 8.47 (s, 1 H), 8.16 (s, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H).

5-Chloro-1*H*-benzo[*d*]imidazole[20] (7)
ESI-MS: *m/z* = 152.9 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.60 (s, 1 H), 8.27 (s, 1 H), 7.62 (m, 2 H), 7.22 (d, *J* = 7.7 Hz, 1 H).

4-Chloro-1*H*-benzo[*d*]imidazole[21] (8)
ESI-MS: *m/z* = 153.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 8.31 (s, 1 H), 7.55 (d, *J* = 7.9 Hz, 1 H), 7.30–7.05 (m, 2 H).

5-Iodo-1*H*-benzo[*d*]imidazole[22] (9)
ESI-MS: *m/z* = 244.9 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.52 (br s, 1 H), 8.19 (s, 1 H), 7.95 (s, 1 H), 7.47 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H).

Methyl 1*H*-Benzo[*d*]imidazole-7-carboxylate[23] (10)
ESI-MS: *m/z* = 177.3 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.56 (s, 1 H), 8.31 (s, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 3.95 (s, 3 H).

1*H*-Benzo[*d*]imidazol-5-ol[24] (11)
ESI-MS: *m/z* = 135.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.21 (br s, 1 H), 9.08 (s, 1 H), 8.03 (s, 1 H), 7.37 (d, *J* = 8.6 Hz, 1 H), 6.87 (s, 1 H), 6.68 (d, *J* = 8.5 Hz, 1 H).

5-(Allyloxy)-1*H*-benzo[*d*]imidazole (12)
ESI-MS: *m/z* = 175.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.25 (s, 1 H), 8.08 (s, 1 H), 7.45 (s, 1 H), 7.08 (s, 1 H), 6.83 (dd, *J* = 8.7, 2.0 Hz, 1 H), 6.07 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1 H), 5.41 (ddd, *J* = 17.3, 3.4, 1.6 Hz, 1 H), 5.26 (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.61–4.54 (m, 2 H).

5-(Triisopropylsilyloxy)-1*H*-benzo[*d*]imidazole (13)
ESI-MS: *m/z* = 291.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.17 (s, 1 H), 8.09 (s, 1 H), 7.43 (s, 1 H), 6.99 (s, 1 H), 6.76 (d, *J* = 8.9 Hz, 1 H), 1.25 (dd, *J* = 14.9, 7.2 Hz, 3 H), 1.07 (d, *J* = 7.4 Hz, 18 H).

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole (14)
ESI-MS: *m/z* = 245.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.48 (s, 1 H), 8.24 (s, 1 H), 7.90 (s, 1 H), 7.57 (s, 1 H), 7.50 (d, 1 H), 1.31 (s, 12 H).

3*H*-Imidazo[4,5-*f*]quinoline[25] (15)
ESI-MS: *m/z* = 169.9 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 13.51 (br s, 0.5 H), 12.94 (br s, 0.5 H), 8.86–

8.85 (m, 1 H), 8.78 (br s, 1 H), 8.38 (br s, 1 H), 7.97 (br d, J = 7.8 Hz, 1 H), 7.81 (d, J = 8.9 Hz, 1 H), 7.61 (dd, J = 8.3, 4.3 Hz, 1 H).

3-{1*H*-Benzo[*d*]imidazol-5-yl}-3*H*-imidazo[4,5-*b*]pyridine (16)

ESI-MS: m/z = 250.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 12.72 (s, 1 H), 8.83 (s, 1 H), 8.36 (s, 1 H), 8.28 (s, 1 H), 8.13 (s, 1 H), 8.02 (s, 1 H), 7.85–7.60 (m, 2 H), 2.46 (s, 3 H).

6-Bromo-7-methyl-3*H*-imidazo[4,5-*b*]pyridine[26] (17)

ESI-MS: m/z = 211.9 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 8.42 (s, 1 H), 8.40 (s, 1 H), 2.60 (s, 3 H).

6-Phenyl-1*H*-imidazo[4,5-*c*]pyridine (18)

ESI-MS: m/z = 196.3 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 9.00 (s, 1 H), 8.40 (s, 1 H), 8.16–8.06 (m, 3 H), 7.53–7.43 (m, 2 H), 7.43–7.34 (m, 1 H).

6-Chloro-1*H*-imidazo[4,5-*c*]pyridine[27] (19)

ESI-MS: m/z = 153.8 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO): δ = 8.74 (s, 1 H), 8.45 (s, 1 H), 7.67 (s, 1 H).

(11) (a) Bongartz, J.-P.; Andre, M.; Meerpoel, L.; Boeckx, G. M.; Van Lommen, G.; Buyck, C.; Obrecht, D.; Ermert, P.; Luther, A. WO 2008/148840 A1, **2008**. (b) Popil'nichenko, S. V.; Brovarets, B. S.; Drach, B. S. *Russ. J. Org. Chem.* **2004**, *40*, 219.

(12) (a) $FeCl_2$ has been reported to reductively cleave isoxazoles: Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*, 10911. (b) Nitro-isoxazoles have been reported to undergo acid-catalyzed thermal isomerization and hydrolysis: Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925.

(13) (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (c) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

(14) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

(15) Wundt, E. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 826.

(16) v. Auwers, K.; Maws, W. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 2415.

(17) Fischer, O.; Rigaud, M. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 4204.

(18) Sekikawa, I. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 252.

(19) Van Vliet, D. S.; Gillespie, P.; Scicinski, J. J. *Tetrahedron Lett.* **2005**, *46*, 6741.

(20) Fischer, O. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 557.

(21) Rabiger, D. J.; Joullie, M. M. *J. Chem. Soc.* **1964**, 915.

(22) Rabiger, D. J.; Joullie, M. M. *J. Org. Chem.* **1961**, *26*, 1649.

(23) Howell, J. R.; Rasmussen, M. *Austr. J. Chem.* **1993**, *46*, 1177.

(24) Robinson, F. M.; Miller, I. M.; McPherson, J. F.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *77*, 5192.

(25) Weidenhagen, R.; Weeden, U. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 2347.

(26) Graboyes, H.; Day, A. R. *J. Am. Chem. Soc.* **1957**, *79*, 6421.

(27) Rousseau, R. J.; Robins, R. K. *J. Heterocycl. Chem.* **1965**, *2*, 196.