A Practical Oxone®–Mediated, High-Throughput, Solution-Phase Synthesis of Benzimidazoles from 1,2-Phenylenediamines and Aldehydes and its Application to Preparative Scale Synthesis

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Abstract: Addition of oxone® to a mixture of a 1,2-phenylenediamine and an aldehyde in wet DMF at room temperature results in rapid formation of benzimidazoles under very mild conditions. The reaction is applicable to a wide range of substrates including aliphatic, aromatic and heteroaromatic aldehydes, and is not significantly affected by steric or electronic effects. In most cases, crude products are isolated in good to excellent yields (59–95%) and homogeneities (86–99%) by simple precipitation or extraction from the reaction mixture and do not require additional purification. Limitations to the scope of this methodology were encountered in cases where aldehydes were sensitive to oxone® under the acidic reaction conditions. The features of this methodology make it particularly well suited for the high-throughput, solution-phase synthesis of benzimidazole libraries. The low cost and simplicity of this procedure makes it equally attractive for preparative-scale syntheses where safety and environmental issues are of greater concern.

Key words: benzimidazoles, heterocycles, aldehydes, amines, oxone, combinatorial chemistry

Interest in benzimidazole-containing structures stems from their widespread occurrence in molecules that display a plethora of useful biological properties. Substituted benzimidazole derivatives have found commercial application in veterinarian medicine as anthelmintic agents and in such diverse human therapeutic areas as antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistaminics to name just a few.[1] In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly qualify them as 'privileged sub-structures' for drug design.[2]

The advent of high-throughput screening technologies has impacted significantly on the methodologies that are used for the synthesis of medicinal compounds. The implementation in the laboratory of high-throughput synthetic techniques to increase the number of molecules generated by chemists is now a prerequisite to competitive advantage in the field. The parallel synthesis of benzimidazole libraries is a good example of this trend and several publications describing methodologies for this application, both in solution phase and on solid supports, have appeared in the literature.[3]

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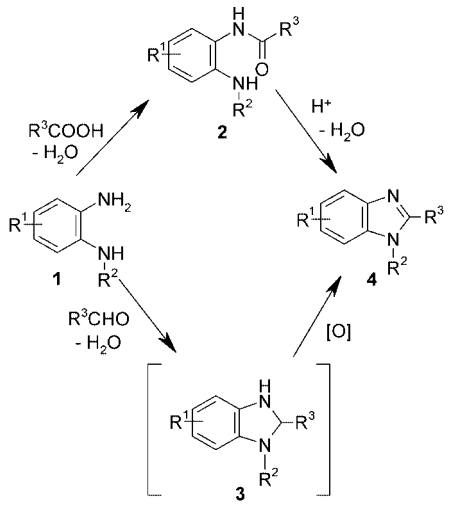
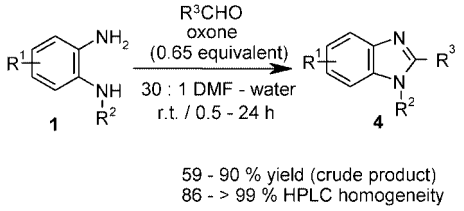
While many strategies are available for benzimidazole synthesis,[4] the most popular approaches generally involve condensation–dehydration of 1,2-phenylenediamines **1** with carboxylic acids (or equivalents), or condensation with aldehydes under oxidative conditions (Scheme 1). The use of carboxylic acids or equivalents (nitriles, amidates, orthoesters) is usually performed under strongly acidic[3a,b] or harsh dehydrating conditions that often require high temperatures[3d,5c] or the use of agents such as phosphorus anhydrides.[5] The reaction can also be performed stepwise via intermediate amides **2**. While extensive structural diversity is available commercially in the case of carboxylic acids, availability of nitriles, amidates and ortho esters is much more limited. In the case of aldehydes, good structural diversity is also accessible from commercial sources. In this case, the reaction proceeds through a benzimidazoline **3**, which requires an oxidative step for conversion to the corresponding benzimidazole **4** as shown in Scheme 1. While this oxidation can proceed spontaneously by disproportionation, this can lead to the occurrence of side-products.[3g,6] Other oxidative methods require the use of nitrobenzene or DMF at elevated temperatures,[7] metal ions,[5a,8] organic oxidants such as quinones,[9] tetracyanoethylene,[10] and benzofuroxan,[11] or inorganic sulfites under heating.[6b,12] Iodine can also be used for the oxidative step but can lead to side reaction when performed in the presence of aromatic rings prone to electrophilic attack.[13] While many published methods are effective, several are not conveniently performed in a high-throughput fashion. The main limitations arise from the use of high temperatures (often >150 °C), long reaction times, toxic solvents, and the use of strongly acidic conditions that may be detrimental to some sensitive substrates. The use of metal ions (e.g. Fe, Cu), in addition to environmental concerns, often requires de-complexation of the metal from the product benzimidazole with the help of obnoxious reagents such as H_2S.[5a,8] The use of organic oxidants, while practical for solid-phase chemistry, usually requires an additional separation–purification step to remove reduced by-products which limits their usefulness when performed in solution.

In setting out to develop a new methodology to prepare poly-substituted benzimidazole libraries, several criteria were defined in advance: applicability to high-throughput synthesis in solution phase, short reaction times, mild conditions, broad scope, clean reactions requiring minimal or



Scheme 1

no purification, ease of isolation and environmental friendliness. After screening a set of potential oxidizing agents, we discovered that oxone®[14] effects a clean conversion of 1,2-phenylenediamines **1** and aldehydes to the desired benzimidazoles **4** as shown in Scheme 2.



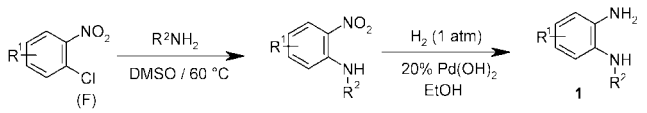
Scheme 2

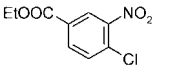
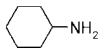
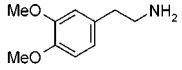
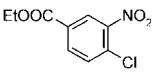
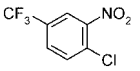
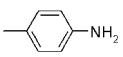
The transformation proceeded under very mild conditions and satisfied all of our previously set criteria. In particular, crude products were isolated in good to excellent yields (59–95%) by simple filtration of a precipitate or extraction with an organic solvent. The homogeneity (as determined by reversed-phase HPLC) of the crude products was generally > 86% which is satisfactory for direct biological testing or further structural elaboration. In several instances, isolated crude products gave satisfactory CHN elemental analyses. This paper describes the scope and limitations we encountered in the development of this methodology.

1,2-Phenylenediamine starting materials **1** were obtained either from commercial sources or prepared in two steps from 2-chloro- or 2-fluoronitroarenes via an S_NAr reaction followed by reduction of the nitro group by catalytic hydrogenolysis[15] as shown in Table 1.

Phenylenediamine **5** and 2-pyridinecarboxaldehyde were used as substrates for the initial optimization of the reaction conditions (Table 2, entry 1). In selecting an appropriate solvent for the transformation, several factors were taken into consideration: inertness towards oxidizing agents, adequate solubilizing capacity for a diverse set of

Table 1 1,2-Phenylenediamine Starting Materials **1**

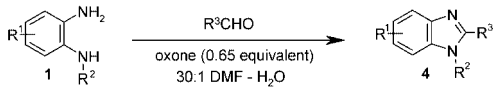


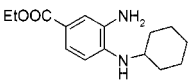
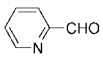
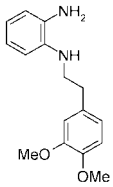
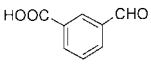
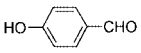
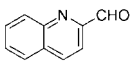
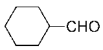
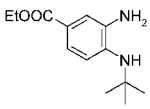
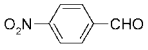
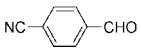
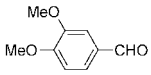
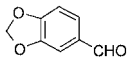
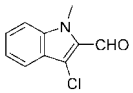
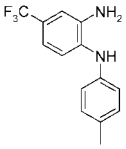
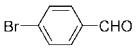
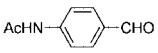
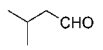
Starting material	R^2NH_2	Yield (%)	Yield (%)	
		98	99	**5**
		100	98	**6**
		99	70	**7**
		98	95	**8**

substrates, ease of recovery of products and ability to promote a reaction between organic substrates and an inorganic reagent (oxone®: 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[14] We found that 'wet' DMF (DMF–H_2O, 30:1) satisfied all of the above criteria: diamine **5** and 2-pyridinecarboxaldehyde (1.1 equiv) were dissolved in a 30:1 mixture of DMF–H_2O (ca. 1.5 mL on a mmol scale) and oxone® (0.65 equiv; the reagent provides two moles of oxidizing agent) was added. After stirring the light suspension for 30 minutes at room temperature, HPLC analysis indicated complete conversion to the desired benzimidazole (Table 2, entry 1). The reaction mixture, which still had the appearance of a very light suspension, was diluted with 20 volumes of water, causing precipitation of the product, which was collected by filtration, washed with water and dried. The yield of crude product was 85% and it had >99% homogeneity as shown by reversed-phase HPLC. Encouraged by this initial result, we set out to examine the scope and limitations of this procedure.

As can be seen from the results in Table 2, the methodology is applicable to a wide range of substrates. In all cases, crude benzimidazoles of >86% homogeneity, as determined by RP-HPLC, were isolated by simple filtration of a precipitate resulting from dilution of the reaction mixture with aqueous K_2CO_3. When the product remained in solution or as an oil, it was isolated by extraction with EtOAc. Crude products were recovered in 59–95% yield. Phenylenediamines containing electron-rich alkylaryl (**6**), hindered tertiary alkyl (**7**) or aromatic *N*-substituents (**8**) performed equally well. The diversity laid out in our selection of aldehydes (Table 2) further reinforces the scope of this methodology. Aromatic as well as heteroaromatic aldehydes can be used. Some nitrogen and sulfur containing heterocycles (entries 1, 4 and 14) were not affected by the oxidizing power of oxone®, and electron-rich aldehydes (entries 9 and 10) were also well tolerated. Functionalities such as carboxylic acid (entry 2) and phenolic hydroxyl groups (entry 3) do not require protection. Interestingly, the literature describes very limited examples of benzimidazole syntheses from aliphatic aldehydes.[3c,12a] As can be

Table 2 Preparation of Benzimidazoles



Entry	Starting material	R^3CHO	Reaction time (h)	Yield[a] (crude) (%)	Homogeneity[b] (crude) (%)
1			1	85	>99
2			0.5	66	98
3	**6**		1	84	>99
4	**6**		1	73	>99
5	**6**		2	80	96
6	**6**		0.5	83	>99
7			2.5	79	99
8	**7**		18	89	97
9	**7**		19	70	92
10	**7**		5	95	86
11	**7**		22	59	97
12			1.5	89	97
13	**8**		20	86	96
14	**8**		1.5	88	96
15	**8**		1.5	68	94

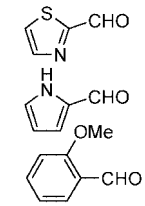
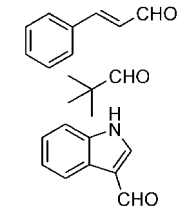
[a] Yield of crude material obtained after dilution of reaction mixture with 20 volumes of aq $K_2CO_3$and collection of the precipitate by filtration or extraction with EtOAc.
[b] Reversed-phase HPLC homogeneity of the crude products.

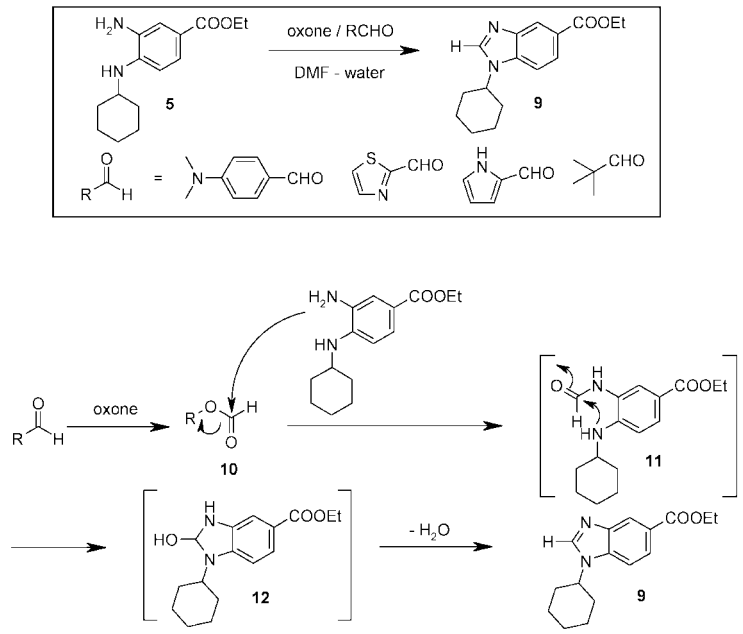
seen from entries 5, 6 and 15 in Table 2, aliphatic aldehydes are good substrates for the oxone®-mediated procedure.

In general, reactions are complete in less than 2 hours, extending to overnight in the case of hindered substrates (entries 9 and 11) or less electrophilic aldehydes (entries 9, 10 and 13). The longer reaction time required in the case of 4-cyanobenzaldehyde (entry 8) is quite surprising when compared to another electron-deficient substrate, 4-nitrobenzaldehyde (entry 7), which reacted much faster, however, both the yield and purity of the isolated product remained very high.

Nevertheless, some limitations were encountered in the development of this methodology and they are summarized in Table 3. In most cases, unsuccessful reactions could be traced to the aldehyde component and its incompatibility towards oxone®. For example α,β-unsaturated aldehydes (in entries 1 and 2 of Table 3) and indole 3-carboxaldehyde gave complex reaction mixtures. In the case of hindered aldehydes (e.g. pivalaldehyde), 4-(dimethylamino)benzaldehyde and some heterocyclic aldehydes (e.g. 2-thiazolylcarboxaldehyde, 2-pyrrolecarboxaldehyde) an unusual side reaction led to the formation of 2*H*-benzimidazoles such as **9** (entry 1 in Table 3 and Scheme 3). The occurrence of benzimidazole **9** can be rationalized from initial oxone®-promoted Bayer–Villiger oxidation of the aldehyde to give the corresponding formate ester **10**. This in turn formylates the phenylenediamine to produce intermediate formamide **11** and the reduced aldehyde (in some cases, the presence of the alcohol–phenol was confirmed by mass spectral analysis of the reaction mixture).[14c,16] Under the acidic conditions of the reaction, formamide **11** undergoes rapid ring closure to 2-hydroxybenzamidine **12** followed by dehydration to benzimidazole **9**. This process is comparable to the well-known formation of 2*H*-benzimidazoles from 1,2-phenylenediamines and orthoformates.[3a,b,17]

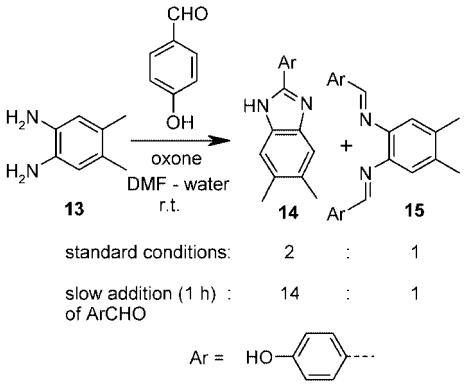
Table 3 Limitations of this Methodology

Entry	Diamine	Aldehydes	Comments
1	**5** or **7**		Aldehydes unstable to oxone Side reaction: (2*H*-benzimidazole)
2	**8**		Complex reaction mixture Indole: self-condensation



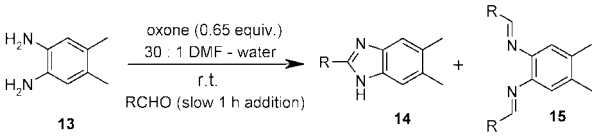
Scheme 3

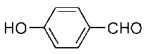
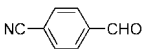
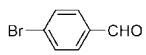
Extension of this methodology to the preparation of *N*-H-benzimidazoles required some minor adjustments to the general operating procedure. As shown in Scheme 4, when 4-hydroxybenzaldehyde and 4,5-dimethyl-1,2-phenylenediamine **13** were reacted with oxone® under standard conditions, a 2:1 mixture of the desired benzimidazole **14** and diimine **15** was obtained.[18] To minimize formation of diimine **15**, the aldehyde was added slowly over 1 h (as a solution in DMF using a syringe pump) to a mixture of phenylenediamine and oxone®. The observed ratio of desired benzimidazole **14** to diimine **15** improved to 14:1, providing a simple solution for the extension of the methodology to this class of products (Table 4). Table 4 illustrates that formation of the diimine side product **15** can be maintained under 10%. Despite the presence of this contaminant, the desired benzimidazole **14** was isolated in reasonable yield and purity using the standard isolation protocol (precipitation or extraction).



Scheme 4

Table 4 Extension of the Methodology to the Preparation of *N*-H-Benzimidazoles



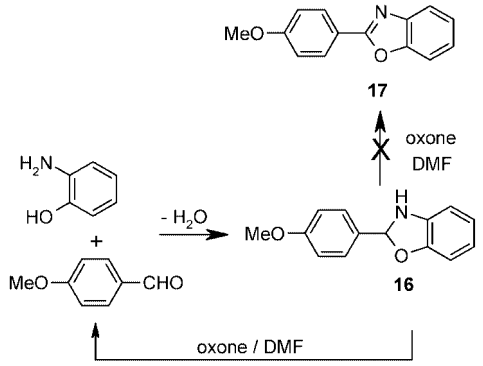
Entry	RCHO	HPLC ratio **14**:**15**	Reaction time[a] (h)	Yield **14** (crude)[b] (%)	% Homogeneity HPLC (crude)
1		14:1	3	82	87
2		9:1	0.5	85	90
3		15:1	0.25	55	>99

[a] Reaction time following addition of the aldehyde over 1 h using a syringe pump.
[b] Yield of crude material obtained after dilution of the reaction mixture with 20 volumes of water and collection of the precipitate by filtration or extraction with EtOAc.

The oxone®-mediated synthesis of benzimidazoles presented here also shows great potential as a method of choice for large-scale synthesis of these heterocycles under safe and environmentally sound conditions. To demonstrate this potential, the reaction shown in entry 1 of Table 2 was scaled-up to provide multi-gram quantities of the corresponding benzimidazole (72% yield, > 99% HPLC homogeneity, see Experimental section).[19]

Finally, as another potential extension of this methodology, we attempted to prepare benzoxazoles from *ortho*-aminophenols and aldehydes. Most methods capable of carrying out this transformation involve the use of metals.

However, a recent report describes a two-step process in which 2-aminophenols are first condensed with aldehydes to form a benzoxazoline intermediate **16** which undergoes oxidative conversion to a benzoxazole **17** with DDQ in an organic solvent.[20a] A redox system consisting of chromium(II) chloride and Mn^0 has also been reported to convert *ortho*-nitrophenols directly into benzoxazoles.[20b] As shown in Scheme 5, attempts to oxidize intermediate **16** with oxone® in wet DMF resulted in hydrolysis back to the starting materials and none of the desired benzoxazole **17** was formed. We suspect the acidic conditions associated with our procedure are not compatible with the hydrolytically sensitive aminal **16**. Running the reaction under basic conditions (in the presence of K_2CO_3) did not resolve the problem.



Scheme 5

In summary, we have developed an efficient methodology for the preparation of substituted benzimidazoles from 1,2-phenylenediamines and aldehydes, which makes use of a mild oxone®-mediated oxidative process. The methodology is applicable to a wide variety of aldehyde substrates (aliphatic, aromatic and heteroaromatic) and delivers crude products in good yield, excellent homogeneity and often analytically pure form, after simple isolation by precipitation or extraction. Reaction conditions are well adapted to the high-throughput, solution-phase synthesis of benzimidazole libraries. In addition, the methodology can be easily scaled-up to produce large amounts of product under safe and environmentally-friendly conditions.

Reagents and solvents (HPLC grade) were from commercial sources and were used as received. All reactions were carried out under open atmosphere with no precautions taken to exclude ambient moisture. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Avance-400 and are calibrated to the solvent chemical shift. Low-resolution mass spectra were obtained on a Micromass Platform LCZ model ZMD 4000 in electrospray mode. High-resolution mass spectra were obtained on a Micromass AutoSpec instrument in FAB ionization mode, using an NBA matrix. HPLC chromatograms were recorded on a Waters Alliance 2690 equipped with a Waters 2487 dual wavelength UV-absorbance detector set at 220/254 nm. Separations were performed on a YMC CombiScreen ODS-AQ 300 reversed-phase column (50 × 4.6 mm I.D., particle size S-5 M, 120 Å, 0 to 50% or 5 to 100% MeCN + 0.1% TFA in 0.1% TFA over 11 min). Mps are uncorrected and due to the amorphous nature of isolated solids, are reported only in cases where reasonably-well defined melting ranges were observed.

1,2-Phenylenediamines from 2-Chloronitroarenes or 2-Fluoronitroarenes and Amines; Ethyl 4-(*tert*-Butylamino)-3-nitrobenzoate and Ethyl 3-Amino-4-(*tert*-butylamino)benzoate (7); General Procedure

Ethyl 4-chloro-3-nitrobenzoate (5.00 g, 21.8 mmol) was dissolved in DMSO (20 mL) and *tert*-butylamine (9.2 mL, 87 mmol, 4 equiv) was added dropwise. The reaction mixture was stirred 6 h at 70 °C after which RP-HPLC analysis indicated completion of the reaction. H_2O (150 mL) was added and the resulting yellow precipitate was collected by filtration, washed with H_2O and dried under vacuum to give the desired nitroarene intermediate.

Yield: 5.75 g (98% yield); > 99% homogeneity by RP-HPLC; crystalline yellow solid; mp 124–125 °C.

^{1}H NMR (DMSO-d_6): δ = 8.58 (d, *J* = 2.2 Hz, 1 H), 8.49 (s, 1 H), 7.92 (dd, *J* = 9.2, 2.0 Hz, 1 H), 7.33 (d, *J* = 9.2 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.47 (s, 9 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 164.3, 146.7, 135.2, 131.1, 128.7, 116.3, 115.9, 60.6, 52.2, 28.9, 14.2.

HRMS (FAB+): *m*/*z* calcd for $C_{13}H_{18}N_2O_4$, 266.1267; found, 266.1270.

The nitroarene derivative from above (5.16 g, 19.4 mmol) was dissolved in MeOH (100 mL) and hydrogenated (1 atm H_2 gas) over 20% $Pd(OH)_2$ on charcoal (400 mg) for 24 h. The solution was filtered through a glass fiber filter and volatiles removed under reduced pressure to give a dark purple–blue oil that was purified by flash chromatography (silica gel; EtOAc–hexanes, 1:3→2:3) to give compound **7**.

Yield: 3.24 g (70% yield); >97% homogeneity by RP-HPLC; brown semi-solid.

^{1}H NMR (DMSO-d_6): δ = 7.20 (s, 1 H), 7.19 (dd, *J* = 9.0, 2.0 Hz, 1 H), 6.72 (d, *J* = 8.6 Hz, 1 H), 4.75 (br s, 2 H), 4.49 (br s, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 1.36 (s, 9 H), 1.26 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.3, 139.3, 135.2, 120.3, 116.9, 115.1, 111.3, 59.4, 50.6, 29.3, 14.4.

HRMS (FAB+): *m*/*z* calcd for $C_{13}H_{20}N_2O_2$, 236.1525; found 236.1530.

Ethyl 4-(Cyclohexylamino)-3-nitrobenzoate and Ethyl 3-Amino-4-(Cyclohexylamino)benzoate (5)

The nitroarene intermediate was obtained from ethyl 4-chloro-3-nitrobenzoate and cyclohexylamine (2.1 equiv).

Yield: 98%; 1.48 mole scale; >97% homogeneity by RP-HPLC; crystalline yellow solid; mp 82.5–83.5 °C.

^{1}H NMR (DMSO-d_6): δ = 8.61 (d, *J* = 2.0 Hz, 1 H), 8.28 (d, *J* = 7.8 Hz, 1 H), 7.95 (dd, *J* = 9.3, 2.0 Hz, 1 H), 7.22 (d, *J* = 9.1 Hz, 1 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 3.72 (m, 1 H), 2.00–1.92 (m, 2 H), 1.75–1.65 (m, 2 H), 1.65–1.56 (m, 1H), 1.48–1.38 (m, 4 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.30–1.22 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 164.3, 146.5, 135.7, 130.2, 128.5, 116.0, 115.1, 60.6, 50.6, 31.7, 24.9, 24.0, 14.2.

MS (ES^+): *m*/*z* = 293 (MH^+). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 62.02; 6.99; N, 9.67.

Hydrogenolysis of the nitro group following the model procedure gave compound **5** as an amorphous dark purple solid that was used without further purification.

Yield: 99%; >98% homogeneity by RP-HPLC; mp 98–105 °C.

^{1}H NMR (DMSO-d_6): δ = 7.18 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.16 (m, 1 H), 6.45 (d, *J* = 8.3 Hz, 1 H), 4.89 (br d, *J* = 6.6 Hz, 1 H), 4.79 (br s, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 1.95 (br d, *J* = 10.3 Hz, 2 H), 1.73 (br dt, *J* = 13.2, 3.4 Hz, 2 H), 1.62 (br dt, *J* = 12.7, 3.4 Hz, 1 H), 1.42–1.28 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.22–1.10 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.3, 139.4, 133.8, 120.7, 116.4, 114.5, 108.1, 59.3, 50.6, 39.5, 32.5, 25.5, 24.6, 14.4.

HRMS (FAB+): *m*/*z* calcd for $C_{15}H_{22}N_2O_2$, 262.1681; found, 262.1683.

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 69.02; 8.57; N, 10.33.

_N_-[2-(3,4-Dimethoxyphenyl)ethyl]-2-nitroaniline and _N_-[2-(3,4-Dimethoxyphenyl)ethyl]benzene-1,2-diamine (6)

From 2-fluoronitrobenzene and 3,4-dimethoxyphenethylamine (1.1 equiv) and diisopropylethylamine (1.4 equiv as an acid scavenger), the nitroarene intermediate was obtained after 16 h at 70 °C.

Yield: quantitative; >98% homogeneity; crystalline orange solid; mp 134–134.5 °C.

^{1}H NMR (DMSO-d_6): δ = 8.08 (br t, *J* = 6.2 Hz, 1 H), 8.04 (dd, *J* = 8.6, 1.4 Hz, 1 H), 7.56–7.50 (m, 1 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 1.6 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.80 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.70–6.64 (m, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.56 (q, *J* = 5.9 Hz, 2 H), 2.88 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 148.7, 147.4, 145.1, 136.7, 131.2, 130.9, 126.2, 120.7, 115.3, 114.6, 112.7, 112.0, 55.5, 55.4, 43.9, 34.0.

MS (ES$^+$): *m*/*z* = 267 (MH$^+$).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.37; 6.04; N, 9.28.

Hydrogenolysis of the nitro group following the model procedure gave compound **6** that was used without further purification.

Yield: 98%; 96% homogeneity by RP-HPLC; dark purple semi-solid.

^{1}H NMR (DMSO-d_6): δ = 6.90–6.85 (m, 2 H), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.58–6.46 (m, 3 H), 6.42 (dt, *J* = 7.1, 1.6 Hz, 1 H), 4.41 (br m, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.21 (t, *J* = 7.2 Hz, 2 H), 2.81 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 148.7, 147.2, 135.8, 135.1, 132.5, 120.5, 117.7, 116.9, 114.2, 112.7, 112.0, 110.0, 55.6, 55.4, 45.3, 34.5.

HRMS (FAB+): *m*/*z* calcd for $C_{16}H_{20}N_2O_2$, 272.1525; found, 272.1527.

_N_-(4-Methylphenyl)-2-nitro-4-(trifluoromethyl)aniline and _N_^{1}-(4-Methylphenyl)-4-(trifluoromethyl)benzene-1,2-diamine (8)

From 4-fluoro-3-nitrobenzotrifluoride and *para*-toluidine (1.05 equiv) and diisopropylethylamine (1.05 equiv as an acid scavenger), the nitroarene intermediate was obtained after 16 h at 70 °C.

Yield: 98%; >99% homogeneity by RP-HPLC; crystalline orange solid; mp 113.5–114 °C.

^{1}H NMR (DMSO-d_6): δ = 8.35 (br d, *J* = 1.0 Hz, 1 H), 7.72 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H, part of AB), 7.24 (d, *J* = 8.4 Hz, 2 H, part of AB), 7.13 (t, *J* = 4.5 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 145.2, 135.9, 135.3, 131.7, 131.6, 131.5, 130.2, 125.4, 124.0, 123.9, 117.4, 116.8 (q), 20.6.

MS (ES$^-$): *m*/*z* = 295 (M – H).

Anal. Calcd for $C_{14}H_{11}F_3N_2O_2$: C, 56.76; H, 3.74; N, 9.46. Found: C, 57.11; 3.57; N, 9.44.

Hydrogenolysis of the nitro group following the model procedure gave compound **8**, which was used without further purification.

Yield: 95%; 96% homogeneity by RP-HPLC; dark semi-solid.

^{1}H NMR (DMSO-d_6): δ = 7.10–7.03 (m, 3 H), 6.99 (br s, *J* = 1.6 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 2 H, part of AB), 6.80 (br d, *J* = 8.0 Hz, 1 H), 5.14 (br s, 1 H), 2.23 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 140.7, 139.3, 133.3, 129.5, 129.0, 121.3 (q), 118.0, 116.6, 113.2, 113.1, 110.7, 20.3.

HRMS (FAB+): *m*/*z* calcd for $C_{14}H_{13}F_3N_2$, 266.1031; found, 266.1041.

Oxone®-Mediated Preparation of Benzimidazoles from 1,2-Phenylenediamines and Aldehydes; Ethyl 1-Cyclohexyl-2-pyridin-2-yl-1*H*-benzimidazole-5-carboxylate (Entry 1, Table 2); General Procedure

Diamine **5** (0.500 g, 1.91 mmol, 1 equiv) was dissolved in DMF (3 mL) and distilled H_2O (0.1 mL) was added. 2-Pyridinecarboxaldehyde (0.20 mL, 2.1 mmol, 1.1 equiv) was added followed by oxone® (0.762 g, 1.24 mmol, 0.65 equiv). The mixture was stirred for 1 h at r.t. after which HPLC analysis indicated complete reaction. The reaction mixture was added dropwise with vigorous stirring into a mixture of K_2CO_3 (1 M; 2.5 mL) and H_2O (60 mL). In cases where the product precipitated as a free flowing solid, it was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated (as in this example) the product was extracted into EtOAc (40 mL), the organic phase was washed with H_2O, brine and dried ($MgSO_4$). Evaporation of the solvent gave a reddish brown solid that was dried under vacuum (0.567 g, 85% yield, > 99% homogeneity). The material was identical to that prepared on a larger scale (see below).

Preparative Scale Synthesis of Ethyl 1-Cyclohexyl-2-pyridin-2-yl-1*H*-benzimidazole-5-carboxylate (Entry 1, Table 2)

The procedure described above on 1 mmol scale was scaled up to prepare multi-gram quantities of benzimidazoles. The following procedure is representative. Diamine **5** (26.70 g, 101.7 mmol) was dissolved in DMF (160 mL) and H_2O (5.3 mL) was added. 2-Pyridinecarboxaldehyde (10.65 mL, 112 mmol) was added dropwise followed by oxone® (40.67 g, 66 mmol) in one portion. HPLC analysis indicated complete reaction after stirring for 30 min at r.t.. The reaction mixture was added slowly with vigorous stirring to H_2O (1 L) and K_2CO_3 (1 M; 110 mL) was added in small portions (caution: foaming). The precipitated solid was extracted into EtOAc (500 mL) and the extract washed successively with H_2O (2 ×) and brine. After drying ($MgSO_4$), the solvent was evaporated under reduced pressure to give a black residue. Trituration (hexane–*tert*-butyl methyl ether 9:1; 200 mL), filtration and drying under vacuum gave the desired benzimidazole product.

Yield: 25.80 g (72% yield); >99% homogeneity; grayish brown solid; mp 130–132 °C.

^{1}H NMR (DMSO-d_6): δ = 8.78 (br d, *J* = 4.1 Hz, 1 H), 8.31 (d, *J* = 1.2 Hz, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.05 (dd, *J* = 7.6, 1.6 Hz, 1 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 7.89 (dd, *J* = 8.6, 1.4 Hz, 1 H), 7.58 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1 H), 5.34 (tt, *J* = 12.4, 3.6 Hz, 1 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 2.28 (m, 2 H), 1.97 (m, 2 H), 1.87 (m, 2 H), 1.68 (m, 1 H), 1.47–1.30 (m, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.1, 152.3, 149.8, 149.0, 142.4, 137.7, 137.5, 125.6, 124.6, 123.7, 123.4, 121.4, 113.5, 60.5, 56.7, 30.5, 25.6, 24.5, 14.2.

MS(ES$^-$): *m*/*z* = 350 (M – H).

Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.02; H, 6.68; N, 11.88. Found: C, 71.75; 6.57; N, 11.76.

3-{1-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-benzimidazol-2-yl}benzoic Acid (Entry 2, Table 2)
From diamine **6** and 3-carboxybenzaldehyde, the product was isolated by extraction.

Yield: 66% yield; 98% homogeneity; amorphous light-beige solid; mp 167–172 °C.

^{1}H NMR (DMSO-d_6): δ = 13.17 (br s, 1 H), 8.03 (m, 2 H), 7.76 (t, *J* = 7.8 Hz, 2 H), 7.69 (d, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 6.31 (d, *J* = 1.2 Hz, 1 H), 6.25 (dd, *J* = 8.0, 1.4 Hz, 1 H), 4.53 (t, *J* = 6.3 Hz, 2 H), 3.65 (s, 3 H), 3.46 (s, 3 H), 2.90 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 166.8, 152.5, 148.5, 147.6, 142.6, 135.4, 133.1, 131.0, 130.6, 130.0, 129.8, 129.7, 128.7, 122.6, 122.1, 120.4, 119.2, 112.0, 111.5, 111.3, 55.3, 55.0, 45.9, 34.4.

HRMS (FAB+): *m*/*z* calcd for $C_{24}H_{33}N_2O_4$, 403.1658; found, 403.1662.

4-{1-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-benzimidazol-2-yl}-phenol (Entry 3, Table 2).
From diamine **6** and 4-hydroxybenzaldehyde, the product was isolated by precipitation.

Yield: 84% yield; > 99% homogeneity; amorphous dark-beige solid; mp 238–242 °C.

^{1}H NMR (DMSO-d_6): δ = 9.87 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 7.25 (t, *J* = 7.0 Hz, 1 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 2 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 4.44 (t, *J* = 6.8 Hz, 2 H), 3.67 (s, 3 H), 3.56 (s, 3 H), 2.90 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 158.5, 153.6, 148.6, 147.5, 142.5, 135.4, 130.5, 130.1, 121.9, 121.7, 121.0, 120.4, 118.7, 115.2, 112.2, 111.8, 110,8, 55.5, 55.1, 45.7, 34.4.

MS (ES$^+$): *m*/*z* = 375 (MH$^+$).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.55; 6.07; N, 7.40.

2-{1-[2-(3,4-Dimethoxyphenyl)ethyl]-1*H*-benzimidazol-2-yl}-quinoline (Entry 4, Table 2)
From diamine **6** and quinoline-2-carboxaldehyde, the product was isolated by precipitation.

Yield: 73% yield; > 99% homogeneity; as an amorphous dark-beige solid; mp 132–133 °C.

^{1}H NMR (DMSO-d_6): δ = 8.46 (d, *J* = 8.6 Hz, 1 H), 8.29 (d, *J* = 8.6 Hz, 1 H), 8.14 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.87 (t, *J* = 7.2 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.4 Hz, 1 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.59 (br s, 1 H), 6.55 (br d, *J* = 8.0 Hz, 1 H), 5.24 (t, *J* = 6.8 Hz, 2 H), 3.65 (s, 3 H), 3.47 (s, 3 H), 3.07 (t, *J* = 6.6 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 150.1, 149.3, 148.5, 147.4, 146.5, 142.1, 136.8, 136.4, 130.5, 130.2, 128.9, 128.0, 127.5, 127.3, 123.5, 122.5, 121.5, 120.6, 119.7, 112.4, 111.8, 111.1, 55.5, 54.9, 46.4, 35.4.

HRMS (FAB+): *m*/*z* calcd for $C_{26}H_{23}N_3O_2$, 409.1790; found, 409.1797.

Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 75.82; 5.70; N, 10.13.

2-Cyclohexyl-1-[2-(3,4-dimethoxyphenyl)ethyl]-1*H*-benzimidazole (Entry 5, Table 2)
From diamine **6** and cyclohexanecarboxaldehyde, the product was isolated by extraction.

Yield: 80%; 96% homogeneity; dark oil that solidified on standing.

^{1}H NMR (DMSO-d_6): δ = 7.55 (d, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 7.0 Hz, 1 H), 7.22–7.11 (m, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.51 (br s, 1 H), 6.47 (dd, *J* = 8.0, 1.6 Hz, 1 H), 4.39 (t, *J* = 6.3 Hz, 2 H), 3.67 (s, 3 H), 3.58 (s, 3 H), 2.94 (t, *J* = 6.1 Hz, 2 H), 2.36–2.29 (m, 1 H), 1.75–1.60 (m, 3 H), 1.55–1.40 (m, 4 H), 1.24–1.17 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.0, 148.7, 147.6, 142.3, 134.3, 130.7, 121.4, 121.2, 120.8, 118.4, 112.5, 111.9, 110.2, 55.6, 55.2, 44.5, 35.0, 34.7, 31.5, 25.7, 25.5.

HRMS (FAB+): *m*/*z* calcd for $C_{23}H_{29}N_2O_2$, 365.2229; found, 365.2244.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-isopropyl-1*H*-benzimidazole (Entry 6, Table 2)
From diamine **6** and isobutyraldehyde, the product was isolated by extraction.

Yield: 83%; >99% homogeneity; as a dark oil.

^{1}H NMR (DMSO-d_6): δ = 7.59 (d, *J* = 8.1 Hz, 1 H), 7.56 (d, *J* = 8.3 Hz, 1 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 8.3 Hz, 1 H), 6.55 (br d, *J* = 6.4 Hz, 1 H), 6.53 (br s, 1 H), 4.41 (t, *J* = 6.6 Hz, 2 H), 3.68 (s, 3 H), 3.58 (s, 3 H), 2.95 (t, *J* = 6.6 Hz, 2 H), 2.91 (m, 1 H), 1.13 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (DMSO-d_6): δ = 159.8, 158.7, 147.6, 134.2, 130.4, 122.0, 121.8, 120.9, 118.0, 112.6, 112.0, 110.7, 55.6, 55.3, 44.6, 34.6, 25.5, 21.5.

HRMS (FAB+): *m*/*z* calcd for $C_{20}H_{25}N_2O_2$, 325.1916; found, 325.1928.

Ethyl 1-*tert*-Butyl-2-(4-nitrophenyl)-1*H*-benzimidazole-5-carboxylate (Entry 7, Table 2)
From diamine **7** and 4-nitrobenzaldehyde, the product was isolated by precipitation.

Yield: 79%; 99% homogeneity; amorphous light-gray solid; mp 135–140 °C.

^{1}H NMR (DMSO-d_6): δ = 8.32 (d, *J* = 8.6 Hz, 2 H), 8.24 (s, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 1.58 (s, 9 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.0, 153.1, 147.8, 142.6, 141.8, 138.0, 131.3, 123.6, 123.0, 122.8, 121.0, 115.3, 60.6, 59.6, 30.7, 14.2.

HRMS (FAB+): *m*/*z* calcd for $C_{20}H_{22}N_3O_4$, 368.1610; found, 368.1608.

Ethyl 1-*tert*-Butyl-2-(4-cyanophenyl)-1*H*-benzimidazole-5-carboxylate (Entry 8, Table 2)
From diamine **7** and 4-cyanobenzaldehyde, the product was isolated by precipitation.

Yield: 89%; 97% homogeneity; amorphous beige solid; mp 287–292 °C.

^{1}H NMR (DMSO-d_6): δ = 8.23 (s, 1 H), 8.06 (d, *J* = 8.8 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 2 H), 7.91 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 1.56 (s, 9 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.0, 153.5, 142.6, 140.1, 138.0, 131.7, 130.8, 123.6, 123.0, 121.0, 118.5, 115.3, 112.0, 60.6, 59.6, 30.7, 14.3.

MS (ES$^+$): *m*/*z* = 348 (MH$^+$).

Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.76; 5.85; N, 12.07.

Ethyl 1-*tert*-Butyl-2-(3,4-dimethoxyphenyl)-1*H*-benzimidazole-5-carboxylate (Entry 9, Table 2)
From diamine **7** and 3,4-dimethoxybenzaldehyde, the product was isolated by precipitation.

Yield: 70%; 92% homogeneity; amorphous brown solid; mp 74–80 °C.

^{1}H NMR (DMSO-d_6): δ = 8.19 (s, 1 H), 8.00 (d, *J* = 8.8 Hz, 1 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.14 (s, 1 H), 7.04 (m, 2 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 1.58 (s, 9 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.2, 155.3, 149.4, 147.8, 142.4, 138.0, 127.3, 123.2, 122.5, 122.4, 120.7, 115.1, 113.5, 110.7, 60.5, 59.4, 55.7, 55.5, 30.6, 14.3.

HRMS (FAB+): *m*/*z* calcd for $C_{22}H_{27}N_2O_4$, 383.1971; found, 383.1968.

Ethyl 2-(1,3-Benzodioxol-5-yl)-1-*tert*-butyl-1*H*-benzimidazole-5-carboxylate (Entry 10, Table 2)
From diamine **7** and piperonal, the product was isolated by precipitation.

Yield: 95%; 86% homogeneity; brown semi-solid.

^{1}H NMR (DMSO-d_6): δ = 8.19 (m, 1 H), 7.99 (d, *J* = 8.8 Hz, 1 H), 7.86 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.15 (s, 1 H), 7.00 (s, 2 H), 6.12 (br s, 2 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 1.58 (s, 9 H), 1.35 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.1, 154.8, 147.9, 146.6, 142.4, 137.9, 128.5, 123.8, 123.2, 122.6, 120.7, 115.0, 110.3, 107.6, 101.4, 60.5, 59.4, 30.6, 14.2.

HRMS (FAB+): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$, 367.1658; found, 367.1659.

Ethyl 1-*tert*-Butyl-2-(3-chloro-1-methyl-1*H*-indol-2-yl)-1*H*-benzimidazole-5-carboxylate (Entry 11, Table 2)
From diamine **7** and 3-chloro-1-methyl-2-indolecarboxaldehyde, the product was isolated by precipitation.

Yield: 59% yield; 97% homogeneity; amorphous dark-beige solid; mp 182–185 °C.

^{1}H NMR (DMSO-d_6): δ = 8.34 (s, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 3.61 (s, 3 H), 1.60 (s, 9 H), 1.36 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 165.9, 143.1, 142.8, 137.7, 135.2, 128.8, 124.0, 123.9, 123.6, 123.5, 121.7, 121.0, 117.8, 115.5, 111.0, 105.4, 60.7, 59.8, 31.3, 29.2, 14.2.

HRMS (FAB+): *m*/*z* calcd for $C_{23}H_{25}ClN_3O_2$, 410.1635; found, 410.1628.

2-(4-Bromophenyl)-1-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-benzimidazole (Entry 12, Table 2)
From diamine **8** and 4-bromobenzaldehyde, the product was isolated by precipitation.

Yield: 89% yield; 97% homogeneity; amorphous light-beige solid; mp 134–138 °C.

^{1}H NMR (DMSO-d_6): δ = 8.17 (s, 1 H), 7.66–7.58 (m, 3 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.44–7.35 (m, 5 H), 2.42 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 153.2, 141.9, 139.4, 139.0, 133.0, 131.5, 131.1, 130.7, 128.4, 127.2, 123.8, 123.5, 120.1, 116.8, 116.7, 111.7, 20.7.

MS (ES$^+$): *m*/*z* = 431, 433 (MH$^+$).

Anal. Calcd for $C_{21}H_{14}BrF_3N_2$: C, 58.49; H, 3.27; N, 6.50. Found: C, 58.43; 3.02; N, 6.30.

***N*-{4-[1-(4-Methylphenyl)-5-(trifluoromethyl)-1*H*-benzimidazol-2-yl]phenyl}acetamide (Entry 13, Table 2)**
From diamine **8** and 4-acetamidobenzaldehyde, the product was isolated by precipitation.

Yield: 86% yield; 96% homogeneity; beige-pink amorphous solid; broad, undefined melting range.

^{1}H NMR (DMSO-d_6): δ = 10.13 (s, 1 H), 8.13 (s, H), 7.61–7.55 (m, 3 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.36 (s, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 2.42 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 168.7, 154.0, 141.8, 140.8, 139.4, 138.9, 133.3, 130.6, 129.9, 127.3, 123.3, 123.2, 119.7, 118.4, 116.4, 116.3, 111.5, 24.1, 20.8.

HRMS (FAB+): *m*/*z* calcd for $C_{23}H_{19}F_3N_3O$, 410.1480; found, 410.1481.

1-(4-Methylphenyl)-2-(2-thienyl)-5-(trifluoromethyl)-1*H*-benzimidazole (Entry 14, Table 2)
From diamine **8** and 2-thiophenecarboxaldehyde, the product was isolated by precipitation.

Yield: 88% yield; 96% homogeneity; amorphous light-beige solid; mp 139–145 °C.

^{1}H NMR (DMSO-d_6): δ = 8.12 (s, 1 H), 7.61 (dd, *J* = 5.1, 2.9 Hz, 1 H), 7.55 (d, *J* = 8.6 Hz, 1 H), 7.51–7.46 (m, 3 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.29–7.23 (m, 2 H), 2.47 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 150.3, 141.8, 139.6, 139.4, 133.0, 130.9, 130.2, 127.9, 127.7, 127.6, 127.1, 119.8, 119.7, 116.4, 116.3, 111.4, 20.9.

HRMS (FAB+): *m*/*z* calcd for $C_{19}H_{14}F_3N_2S$, 359.0830; found, 359.0843.

2-Isobutyl-1-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-benzimidazole (Entry 15, Table 2)
From diamine **8** and isovaleraldehyde, the product was isolated by extraction.

Yield: 68% yield; 94% homogeneity; amorphous light-beige solid; mp 103–107 °C.

^{1}H NMR (DMSO-d_6): δ = 8.03 (s, 1 H), 7.53–7.40 (m, 5 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 2.65 (d, *J* = 7.2 Hz, 2 H), 2.45 (s, 3 H), 2.09 (m, 1 H), 0.86 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (DMSO-d_6): δ = 156.8, 141.8, 139.1, 138.5, 132.3, 130.7, 127.2, 119.1, 119.0, 116.0, 115.9, 110.9, 35.9, 26.9, 22.3, 20.8.

MS (ES+): *m*/*z* = 333 (MH$^+$).

Anal. Calcd for $C_{19}H_{19}F_3N_2$: C, 68.66; H, 5.76; N, 8.43. Found: C, 68.96; 5.69; N, 8.10.

Ethyl 1-Cyclohexyl-1*H*-benzimidazole-5-carboxylate (9)
The reaction of diamine **5** with thiazole-2-carboxaldehyde gave compound **9** as the main product (81% according to RP-HPLC) which was isolated as the trifluoroacetic acid salt by preparative RP-HPLC.

Yield: 77% yield; > 99% homogeneity.

^{1}H NMR (DMSO-d_6): δ = 9.21 (s, 1 H), 8.33 (s, 1 H), 8.06–8.01 (m, 2 H), 4.60 (tt, *J* = 11.7, 3.8 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 2.17–2.08 (br m, 2 H), 1.95–1.80 (m, 4 H), 1.73 (br d, *J* = 9.3 Hz, 1 H), 1.52 (br q, *J* = 13.2 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.29 (qt, *J* = 13.0. 4.8, 1 H).

^{13}C NMR (DMSO-d_6): δ = 165.6, 143.1, 136.7, 135.0, 125.8, 124.7, 118.7, 112.6, 61.0, 55.8, 32.2, 24.9, 24.7, 14.2.

HRMS (FAB+): *m*/*z* calcd for $C_{16}H_{20}N_2O_2$, 272.1525; found, 272.1529.

_N_-Unsubstituted Benzimidazoles; 4-(5,6-Dimethyl-1*H*-benzimidazol-2-yl)phenol (Entry 1, Table 4); General Procedure

The following procedure is representative. 4,5-Dimethyl-1,2-phenylenediamine (**13**) (0.226 g, 1.66 mmol) was dissolved in DMF (2 mL) and H_2O (0.05 mL) was added, followed by oxone® (0.663 g, 1.08 mmol, 0.65 equiv). A solution of 4-hydroxybenzaldehyde (0.213 g, 1.75 mmol, 1.05 equiv) in DMF (1 mL) was added dropwise over 1 h (syringe pump) to the stirred reaction mixture. After completion, stirring was continued for an additional 3 h at which point RP-HPLC analysis indicated completion of the reaction. The reaction mixture was added dropwise with stirring to H_2O (60 mL) and the pH was adjusted to 7 by addition of solid K_2CO_3. The resulting amorphous orange-beige precipitate was collected by filtration, washed with H_2O and dried.

Yield: 0.323 g (82%); 87% homogeneity by RP-HPLC; mp >300 °C.

^{1}H NMR (DMSO-d_6): δ = 10.15 (br s, 1 H), 7.98 (d, *J* = 8.6 Hz, 2 H), 7.37 (s, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 2.33 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 159.9, 150.0, 135.2, 131.7, 128.6, 118.7, 115.9, 114.2, 20.0.

HRMS (FAB+): *m*/*z* calcd for $C_{15}H_{15}N_2O$, 239.1184; found, 239.1178.

4-(5,6-Dimethyl-1*H*-benzimidazol-2-yl)benzonitrile (Entry 2, Table 4)

From 4,5-dimethyl-1,2-phenylenediamine (**13**) and 4-cyanobenzaldehyde, the product was isolated by precipitation.

Yield: 85%; 90% homogeneity; amorphous cream-colored solid; mp 216–225 °C (decomp).

^{1}H NMR (DMSO-d_6): δ = 8.29 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.4 Hz, 2 H), 7.43 (s, 2 H), 2.34 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 148.2, 137.4, 133.8, 132.9, 132.0, 126.8, 118.6, 115.2, 111.7, 20.0.

HRMS (FAB+): *m*/*z* calcd for $C_{16}H_{14}N_3$, 248.1188; found, 248.1196.

2-(4-Bromophenyl)-5,6-dimethyl-1*H*-benzimidazole (Entry 3, Table 4)

From 4,5-dimethyl-1,2-phenylenediamine **13** and 4-bromobenzaldehyde, the product was isolated by precipitation.

Yield: 55% yield; >99% homogeneity; amorphous beige-orange solid; mp >300 °C.

^{1}H NMR (DMSO-d_6): δ = 8.09 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.55 (s, 2 H), 2.39 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 147.6, 134.4, 132.5, 129.1, 125.7, 124.6, 114.1, 19.9 (one resonance overlap).

HRMS (FAB+): calcd for $C_{15}H_{14}BrN_2$: 301.0340. Found: 301.0333.

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