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A facile base-mediated synthesis of *N*-alkoxy-substituted benzimidazoles

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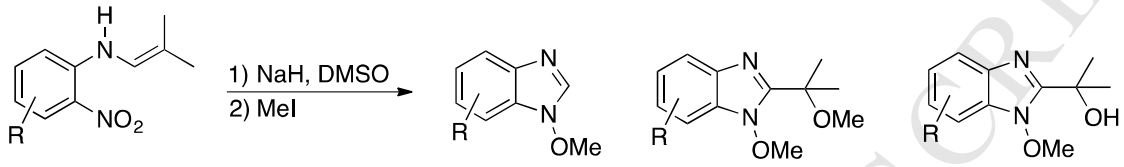


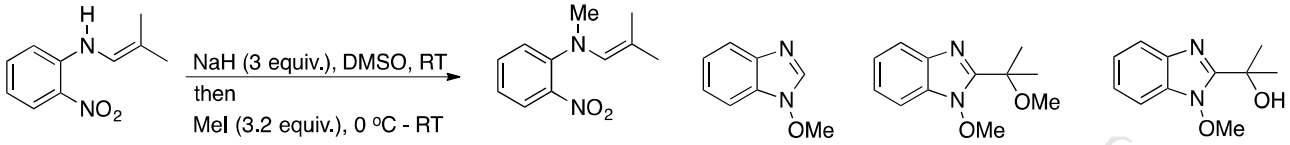
Abstract

Base mediated cyclization of enamines derived from condensation of 2-nitroanilines with α-branched aldehydes, in the presence of an electrophile, affords *N*-alkoxy-substituted benzimidazoles with or without an oxygenate side chain in the 2-position.

Introduction

In an attempt to *N*-methylate enamine **1**, the compound was dissolved in dimethylsulfoxide (DMSO) and 3 equivalents of sodium hydride was added at ambient temperature (Scheme 1). After mixing for 1 h, the resulting reaction mixture was cooled to 0 °C and 3.2 equivalents of methyl iodide was added. After slowly warming to ambient temperature over 2 h, the reaction mixture was worked up and purified by chromatography to give three different products. The expected methylated product **2** was not isolated instead, 1-methoxybenzimidazole (**3**), 1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (**4**), and 1-methoxy-2-(2-hydroxy-2-propyl)benzimidazole (**5**) were obtained in 5%, 57%, and 15% yield, respectively.

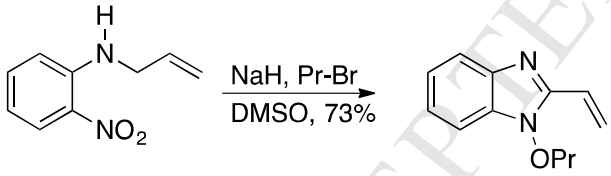
Scheme 1. Formation of benzimidazoles **3**-**5** from enamine **1**.



1 **2** (not observed) **3** (5%) **4** (57%) **5** (15%)

The transformation of **1** to benzimidazoles **3**-**5** is related to base-mediated cyclizations of *N*-phenacyl-2-nitroaniline[1] and *N*-benzyl-2-nitroanilines to give *N*-oxygenated benzimidazoles.[2] Gardiner and coworkers have developed and extensively utilized a more general methodology for the formation of 2-substituted 1-alkoxybenzimidazoles employing 2-nitroanilines and organic halides in the presence of a base (Scheme 2).[3,4] In addition to Gardiners' methodology, *N*-alkoxybenzimidazoles can be prepared from *N*-hydroxybenzimidazoles either via a Williamson type ethers synthesis[5] or by a Mitsunobu reaction with an alcohol.[6] Although relatively unusual, *N*-oxygenated benzimidazoles have been shown to exhibit anti-protoza[7] and anti-HIV activities.[3d]

Scheme 2. Cyclization of *N*-allyl-2-nitroaniline to give 2-ethenyl-*N*-propoxybenzimidazole.[3f]



The reaction of **1** to give **3**-**5** seen in Scheme 1 significantly differs from previously reported cyclizations in that either a loss of or oxygenation of the side chain is observed. To the best of our knowledge, no examples of *N*-alkoxy-2-(alkoxyalkyl)benzimidazoles or *N*-alkoxy-2-(hydroxyalkyl)benzimidazoles have been reported to date. Herein we present a study of the scope and limitation of the base mediated cyclization of enamines derived from 2-nitroanilines

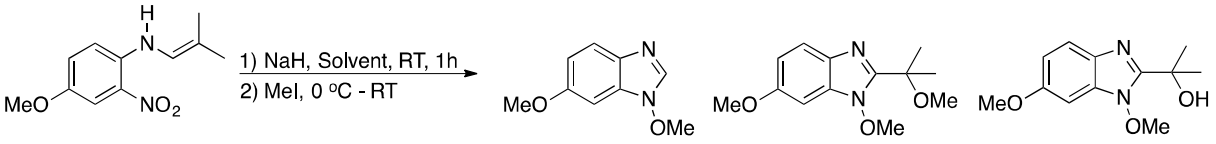
and α-branched aliphatic aldehydes to give *N*-oxygenated benzimidazoles. A plausible mechanism for the reaction is also discussed.

Results and discussion

An initial set of experiments were carried out in an attempt to establish, if possible, optimal reaction conditions for the selective formation of all three types of benzimidazole products (**3**-**5** in Scheme 1) by simply varying the amount of base and alkylating reagent used. Thus, the number of equivalents of sodium hydride and methyl iodide was systematically varied using enamine **6** (Table 1). This substrate was selected in place of **1** in order to facilitate product ratio determinations by ^{1}H NMR of the crude products since the methoxy group situated on the benzene ring offered an additional resonance for integration. Reaction of **6** with 1.05 equivalents of both NaH and MeI did not furnish any appreciable amount of either of the possible products **7**-**9** (Table 1, entry 1). A trace amount of 1,6-dimethoxybenzimidazole (**7**) was observed in the ^{1}H NMR spectrum of the crude reaction mixture. It should be noted that compound **7** was observed in the crude product or isolated as an inseparable mixture with 2-(2-hydroxy-2-propyl)-1,6-dimethoxybenzimidazole (**9**) in ≤ 7% yield in all entries in Table 1 when DMSO was used as the solvent (entries 1-9). Maintaining the amount of base at 1.05 equivalents and increasing the amount of MeI to 2.10 equivalents resulted in the formation of benzimidazole **9** in moderate yield in addition to a significant amount of unreacted enamine **6**. The yield of **9** was not further improved using 3.10 equivalents of MeI (entries 2-3). Gratifyingly, an almost exclusive formation of alcohol **9** was observed in a reaction wherein the amount of base was increased to 2.10

equivalents together with 1.05 equivalent of MeI (entry 4). From the results seen in entries 1-4, it appears that N-O methylation is faster compared to C-O methylation since selective formation of **9** can be achieved using 1.05 equivalents of MeI. Addition of 2.10 equivalents of both NaH and MeI resulted in the formation of the dialkylated product 1,6-dimethoxy-2-(2-methoxy-2-propyl)benzimidazole (**8**) at the expense of **9** however, further increasing the amount of MeI did not improve the yield of **8** or the overall yield of the reaction (entries 5-6). Finally, using 3.15 equivalents of both NaH and MeI resulted in a clean conversion of **6** to **8** with only trace amounts of the other two benzimidazoles observed in the ^{1}H NMR spectrum of the crude reaction mixture (entry 7). It is interesting to note that three equivalents of base was also found to be the optimum for the reaction forming 1-alkoxybenzimidazoles reported by Gardiner *et al* (Scheme 2).[3b] Further increase in the amount of base and alkylating reagent did not improve the yield of **8** (entry 9). In addition to DMSO, *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidinone (NMP), and acetonitrile (MeCN) were examined as potential solvents for the cyclization however, only a low yield of **8** was isolated in each case (entries 9-11). The formation of benzimidazole **7** was observed in each case in yields ranging from trace amounts in NMP, 29% in DMF, and 65% in acetonitrile.

Table 1. Product distribution dependence on the equivalents of NaH and MeI and solvent used.



6 **7** **8** **9**

Entry	Eq. NaH	Eq. MeI	Solvent	Alkoxybenzimidazoles[a]		
1[b]	1.05	1.05	DMSO	**7**[c]		
2[d]	1.05	2.10	DMSO	**7** (~1%)		**9** (~34%)
3[e]	1.05	3.17	DMSO	**7** (~3%)		**9** (~30%)
4	2.10	1.05	DMSO	**7** (~2%)	**8** (tr.)	**9** (~74%)
5	2.10	2.10	DMSO	**7** (~5%)	**8** (17%)	**9** (~56%)
6	2.10	3.16	DMSO	**7** (~7%)	**8** (18%)	**9** (~46%)
7	3.15	3.15	DMSO	**7**[c]	**8** (69%)	**9**[c]
8	3.75	3.33	DMSO	**7** (~5%)	**8** (64%)	**9** (~2%)
9	5.0	5.0	DMSO	**7**[c]	**8** (65%)	
10	3.74	3.20	DMF	**7** (21%)	**8** (8%)	
11	3.75	3.32	NMP	**7**[c]	**8** (29%)	
12	3.74	3.20	MeCN	**7** (65%)	**8** (13%)	

a) Isolated yields of pure products after chromatography unless stated as ~%. The ~% are yields calculated from the ^{1}H NMR spectrum of an inseparable mixture. b) The starting material was recovered in 48% yield. c) Trace amount of the compound was observed in the ^{1}H NMR of the crude reaction mixture. d) The starting material was recovered in 40% yield. e) The starting material was recovered in 35% yield.

The scope and limitation of the base-mediated cyclization to give *N*-oxygenated benzimidazoles was probed using fifteen different enamines and the results of these reactions are summarized in Table 2. In addition to ten previously reported enamines, five new enamines were prepared by condensation of the appropriately substituted 2-nitroaniline with an aldehyde in dichloromethane or benzene in the presence of molecular sieves. Enamines derived from condensation of 2-nitroanilines bearing a substituent in the 4- or 5-position and 3-methylpropanal were selected in order to evaluate the effects of electronic properties and the

relative position of the substituent on the benzene ring in a systematic fashion without a significant steric contribution (Table 2, entries 1-25). The enamines were subjected to two different reaction conditions selected from Table 1 varying only in the stoichiometry of the added reagents. experiments using 3.15 equivalents of both NaH and MeI to afford dimethylated benzimidazoles are referred to as Conditions A (See Table 1, entry 7) and reactions using 2.1 equivalents NaH and 1.05 equivalents of MeI to give mono-methylated benzimidazoles as the major product are referred to as Conditions B (See Table 1, entry 4). We initially considered acetonitrile and the ratio of reagents seen in entry 12 in Table 1 to be plausible conditions for the synthesis of 2H-*N*-alkoxybenzimidazoles. However, when applied to other enamines, complex mixtures of products in inferior yields were obtained using these conditions.

The reactions of enamines with sodium hydride followed by addition of methyl iodide under Conditions A are summarized in Table 2. As seen in the table, all substrates but the 4-nitro-substituted enamine **23** furnish *N*-methoxybenzimidazole(s) under these conditions. Enamines with a methoxy- (**6**), chloro- (**10**), bromo- (**12**), or fluoro- (**15**) group in the 4-position gave good to excellent yields (69-94%) of dimethylated benzimidazoles as the only product isolated after chromatography (Table 2, entries 1-8).

In each of the reactions, an immediate color change to deep purple was observed upon addition of a solution of the enamine to a suspension of NaH in DMSO. In most cases, the purple color rapidly changed to brown or orange-brown within two minutes. The brown color was indicative of a "resting" state of the reaction and no further transformations would occur until the addition of MeI. For example, addition of MeI either after 2 minutes or after 9 h of stirring at ambient temperature gave almost identical isolated yields of **8** (entries 2-3). This sequence of color

changes was observed for all substrates, although longer reaction times were required in some cases before the purple color would disappear.

Apart from the selective reactions observed for the first four substrates in Table 2, the experiments summarized in entries 9-29 gave either 2*H*-unsubstituted *N*-methoxybenzimidazoles, mixtures of *N*-methoxybenzimidazoles, or *N*-methylation of the starting material. For some substrates, different product patterns were obtained under Conditions A depending on the time elapsed prior to addition of MeI and the addition temperature. The parent enamine **1** and the 4-methyl- and 5-methyl-substituted analogs **17** and **32** produced mixtures of three benzimidazoles when the addition of MeI was made at 0 °C (entries 9, 11, and 24). In contrast, monoalkylated benzimidazoles (**5**, **20**, and **35**) were not observed when MeI was added at ambient temperature (entries 10, 12, and 25). The reason for this difference in product pattern is unclear.

Two substrates containing an electron-withdrawing group, a methyl ester (**21**) and a nitro group (**23**), in the 4-position of the aromatic ring were examined (Table 2, entries 13-16). Treatment of ester functionalized substrate **21** with NaH followed by addition of MeI, after 10 minutes at ambient temperature resulted in *N*-methylation of the starting material in 62% yield. No benzimidazole product was observed. However, allowing the substrate-base mixture to stir for 24 h prior to the addition of MeI furnished *N*-methoxybenzimidazole **22** in good isolated yield. No trace of a 2-substituted benzimidazole was observed by ^{1}H NMR of the crude reaction mixture. Treatment of **23** gave in a similar fashion the product derived from *N*-methylation of the starting material in 85% yield as the sole product upon addition of MeI after 1 h at 0 °C. In contrast to ester derivative **21**, extending the reaction time for the nitro analog **23** prior to

addition of MeI did neither produce a benzimidazole or any other product nor was the starting material recovered.

N-Methylation of the amino-group of the starting material was not limited to the electron-deficient substrates **21** and **23** but was also observed when an insufficient amount of time was given before the addition of MeI. For example, reaction of the 5-methoxy- and the 5-chloro-substituted enamines **24** and **26** gave *N*-methylation of the amino group of the aniline as the major or sole product (entries 17 and 19). However, extending the reaction time for the substrate-NaH-DMSO mixture of **24** and **26** eliminated the amino-group methylation and *N*-methoxybenzimidazoles were isolated (entries 18 and 20).

Two additional enamines **36** and **39**, obtained from condensation of 4-methoxy-2-nitroaniline with cyclohexane carbaldehyde and 4-bromo-2-nitroaniline with 2-phenylpropanal, respectively, were also examined (Table 2, entries 26-29). The methoxy-substituted enamine **36** behaved similar to **6**, affording the expected di-alkylated benzimidazole **37**. In addition, a minor amount of the mono-alkylated benzimidazole **38** was isolated upon addition of MeI at ambient temperature (entry 27). Finally, enamine **39** proved to be sensitive to the temperature for the addition of MeI. All three previously encountered type of *N*-oxygenated benzimidazoles **13**, **40**, and **41** were obtained each in low yield at 0 ^{o}C. In contrast, only **13** was obtained at ambient temperature in excellent yield.

Table 2. Base-mediated formation of benzimidazoles under Conditions A.

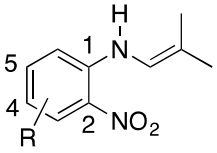
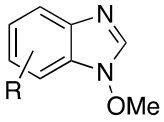
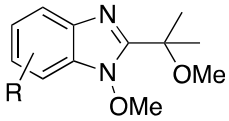
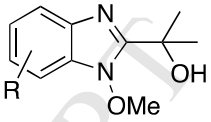
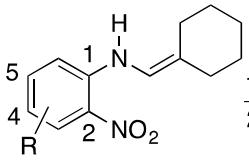
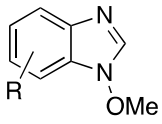
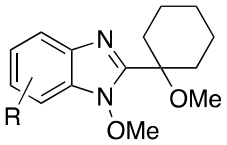
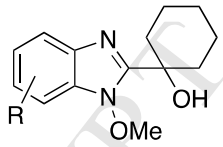
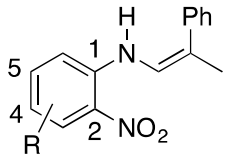
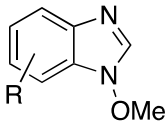
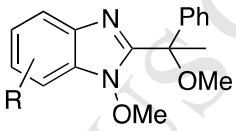
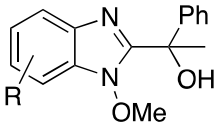
Entry	Enamine	Temp/time[a]	Alkoxybenzimidazoles[b]			Σ (%)[c]
		1) NaH, DMSO 2) MeI				
1	**6** (R=4-OMe)	1 h - 0 °C	**7**[d]	**8** (71%)		(71%)
2	**6**	2 min - RT	**7**[d]	**8** (71%)		(71%)
3	**6**	9 h - RT	**7**[d]	**8** (69%)		(69%)
4	**10** (R=4-Cl)	1 h - 0 °C		**11** (86%)		(86%)
5	**10**	1 h - RT		**11** (94%)		(94%)
6	**12** (R=4-Br)	1 h - 0 °C	**13**[d]	**14** (78%)		(78%)
7	**12**	4 min - RT	**13**[d]	**14** (93%)		(93%)
8	**15** (R=4-F)	1 h - RT		**16** (75%)		(75%)
9	**17** (R=4-Me)	1 h - 0 °C	**18** (28%)	**19** (52%)	**20** (5%)	(85%)
10	**17**	1 h - RT	**18** (27%)[e]	**19** (68%)		(95%)
11	**1** (R=H)	1 h - 0 °C	**3** (5%)	**4** (57%)	**5** (15%)	(77%)
12	**1**	1 h - RT	**3** (31%)	**4** (34%)		(65%)
13	**21** (R=4-CO_2Me)	10 min – RT[f]				(-)
14	**21**	24 h - RT	**22** (74%)			(74%)
15	**23** (R=4-NO_2)	1 h - 0 °C[g]				(-)
16	**23**	24 h – RT[h]				(-)
17	**24** (R=5-OMe)	1 h – RT[i]				(-)
18	**24**[j]	24 h - RT	**25** (51%)			(51%)
19	**26** (R=5-Cl)	6 min – RT[k]		**28** (9%)		(9%)
20	**26**	1 h - 0 °C	**27** (56%)	**28** (27%)		(83%)
21	**26**	1 h - RT	**27** (52%)	**28** (31%)		(83%)
22	**29** (R=5-Br)	10 min - RT	**30** (67%)	**31** (28%)		(95%)
23	**29**	1 h - RT	**30** (55%)	**31** (29%)		(84%)
24	**32** (R=5-Me)	1 h - 0 °C	**33** (21%)	**34** (22%)	**35** (20%)	(63%)
25	**32**	10 min - RT	**33** (31%)	**34** (26%)		(57%)

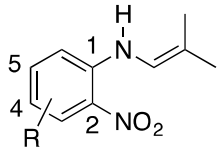
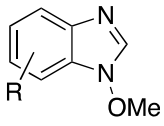
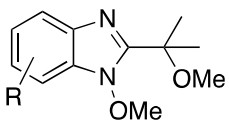
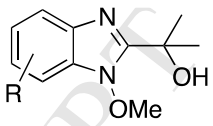
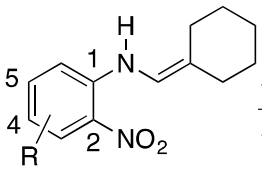
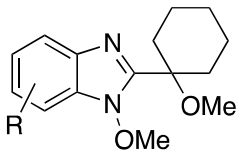
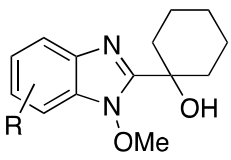
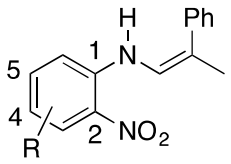
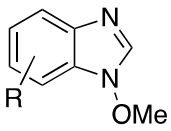
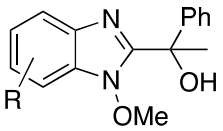
Table 2. Base mediated formation of benzimidazoles under Conditions A continued.

Entry	Enamine	Temp/time[a]	Alkoxybenzimidazoles[b]		Σ (%)[c]
		1) NaH, DMSO 2) MeI				
26	**36** (R=OMe)	1 h - 0 °C	**7**[d]	**37** (78%)		(78%)
27	**36**	2 min - RT	**7**[d]	**37** (84%)	**38** (11%)[l]	(95%)
		1) NaH, DMSO 2) MeI				
28	**39** (R=4-Br)	1 h - 0 °C	**13** (22%)	**40** (22%)	**41** (13%)	(57%)
29	**39**	38 min - RT	**13** (92%)			(92%)

a) 3.15 equivalents of NaH and MeI were used. The Time/Temp is the time elapsed before addition of MeI and the temperature of the reaction mixture for the addition. b) Isolated yields of pure products after chromatography unless stated as ~%. The ~% are yields calculated from the ^{1}H NMR spectrum of an inseparable mixture. c) Total yield of benzimidazole(s) isolated. d) Trace amount of the compound was observed in the ^{1}H NMR of the crude reaction mixture. e) Trace amount of **17** was observed in the ^{1}H NMR spectrum. f) 4-Carbomethoxy-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)-2-nitroaniline, the *N*-methylation product of **21**, was isolated in 62% yield. g) 2,4-Dinitro-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)aniline, the *N*-methylation product from **23**, was isolated in 85% yield. h) No product or unreacted **23** was observed. i) 5-Methoxy-2-nitro-*N*-methylaniline[8] was isolated in 55% yield. j) 5.0 Equivalents of NaH and 3.9 equivalents of MeI were used. k) 5-Chloro-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)-2-nitroaniline, the *N*-methylation product of **26**, was isolated in 52% yield. l) Trace amount of **7** was observed in the ^{1}H NMR spectrum.

The feasibility of a selective formation of mono-methylated benzimidazoles was evaluated next using Conditions B. All enamines, but the 4-nitro-substituted enamine **23**, were treated in sequence with NaH and MeI under Conditions B and the results are summarized in Table 3. In general, cyclizations under Conditions B were not as selective as the reaction of the 4-methoxy-substituted enamine **6** to give **9** (See Table 1, entry 4 and Table 3, entry 1). However, cyclization to produce a benzimidazole(s) occurred in all cases. For all enamines examined apart from the 4-carbomethoxy- and the 5-methoxy-substituted compounds **21** and **24**, all reactions furnished mono-methylated benzimidazoles in 45-74% yield as the major product in addition to minor amounts of either 2*H*-*N*-methoxybenzimidazoles (2-21%) or dimethylated benzimidazoles (15-22%). In contrast to the reactions performed under Conditions A, the position of and the electronic properties of the substituents on the aromatic ring had little effect on the product distribution. For enamines **21** and **24**, as was observed under Conditions A, extended reaction times were required prior to the addition of methyl iodide and only 2*H*-*N*-methoxybenzimidazoles were isolated (entries 7-10).

Table 3. Base mediated formation of *N*-alkoxybenzimidazoles under Conditions B.

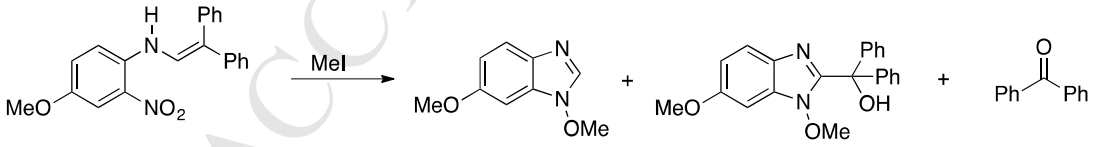
Entry[a]	Enamine	Alkoxybenzimidazoles[b]			Σ (%)[c]
					
1	**1** (R=H)			**5** (55%)[d]	(55%)
2	**6** (R=4-OMe)	**7** (~2%)		**9** (~74%)	(76%)
3	**10** (R=4-Cl)		**11** (20%)	**42** (59%)	(79%)
4	**12** (R=4-Br)		**14** (22%)	**43** (68%)	(90%)
5	**15** (R=4-F)		**16** (15%)	**44** (56%)	(72%)
6	**17** (R=4-Me)	**18** (~11%)		**20** (~45%)	(55%)
7	**21** (R=4-CO_2Me)[e]				(-)
8	**21**[f]	**22** (73%)			(73%)
9	**24** (R=5-OMe)[g]				(-)
10	**24**[f]	**25** (64%)			(64%)
11	**26** (R=5-Cl)		**28** (15%)	**45** (55%)	(70%)
12	**29** (R=5-Br)		**31** (16%)	**46** (63%)	(79%)
13	**32** (R=5-Me)			**35** (61%)	(61%)
					
14	**36** (R=OMe)		**37** (19%)	**38** (51%)	(70%)
					
15	**39** (R=4-Br)	**13** (22%)		**41** (52%)	(74%)

a) Conditions B: 2.1 equivalents of NaH and 1.05 equivalents of MeI. The mixture was stirred for 1 h at ambient temperature then cooled to 0 °C prior to addition of MeI unless otherwise stated. b) Isolated yields of pure products after chromatography unless stated as ~%. The ~% are yields calculated from the ^{1}H NMR spectrum of an inseparable mixture. c) Total yield of benzimidazole(s) isolated. d) Trace amount of **3** was observed in the ^{1}H NMR spectrum. e) A ~3:1 mixture of 4-carbomethoxy-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)-2-nitroaniline and **21** was

observed in the ^{1}H NMR of the crude reaction mixture. f) The base substrate mixture was stirred for 24 h before addition of MeI. g) No product or starting material was observed.

The formation of 2*H*-benzimidazoles, wherein only the α-carbon of the enamine was retained in the product, involves a carbon-carbon bond fission at some point during the reaction. For the majority of enamines examined, a three-carbon unit is lost probably in the form of acetone (see mechanistic discussion below). Neither acetone nor acetophenone or cyclohexanone, the anticipated by-products from enamines **36** and **39**, were recovered after chromatographic purification. This is probably due to evaporative loss upon removal of solvents. In order to isolate, characterize, and quantify any potential by-product derived from carbon-carbon bond cleavage to form 2*H*-benzimidazoles, enamine **47** derived from 2,2-diphenylethanal and 4-methoxy-2-nitroaniline was prepared. Treatment of **47** with NaH-MeI under Conditions A gave rise to two products, the mono alkylated benzimidazole **48** as the major product and a small amount of impure benzophenone (**49**) (Scheme 3). Gratifyingly, when the solvent and base system described by Gardiner *et al*[3b] was used (t-BuOH/t-BuOK), an almost quantitative yield of benzophenone (**49**) was isolated in addition to 2*H*-benzimidazole **7** in 78% yield.

Scheme 3 Synthesis of *N*-methoxybenzimidazole **48** and benzophenone (**49**).

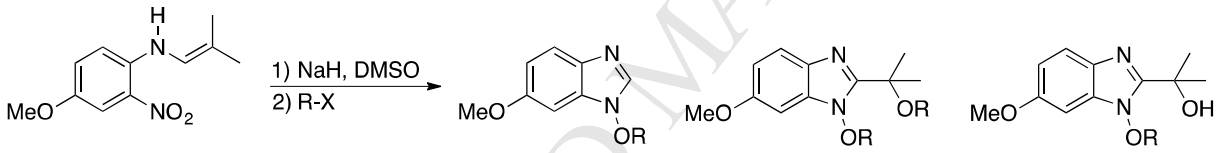


47 NaH in DMSO, RT, 2 h — **48** (89%) — **49** (≤9%)

47 *t*-BuOK in *t*-BuOH, RT, 24 h — **7** (78%) — **49** (97%)

In addition to methyl iodide, a small selection of electrophiles including benzyl bromide, allyl bromide, diiodomethane, propargyl bromide, and 3-bromo-1-butyne were examined using enamine **6** as the substrate (Table 4). Moderate yields (40-69%) of *N*-oxygenated benzimidazoles were isolated from these reactions. The reaction of **6** with a base and diiodomethane is interesting in that a ring is formed between the benzimidazole oxygen and the side chain (entry 5). Less reactive electrophiles such as alkyl bromides did not furnish any isolable amounts of products.

Table 4. Base mediated formation of *N*-oxygenated benzimidazoles from enamine **6**.

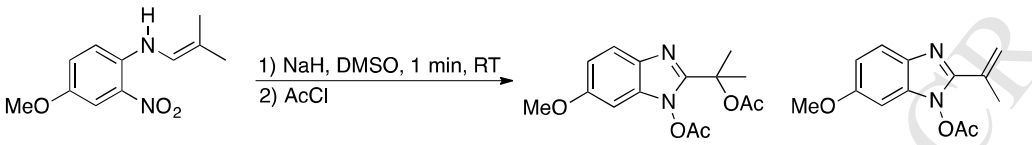


Entry	Temp/time[a]	Electrophile (R-X)	Alkoxybenzimidazoles[b]		Σ (%)[c]
1	1 h - 0 °C	Bn-Br		**50** (38%)	**51** (29%)	(67%)
2	2 min - RT	Bn-Br		**50** (19%)	**51** (50%)	(69%)
3	1 h - 0 °C	Allyl-Br	**52** (~5%)	**53** (14%)	**54** (~31%)	(50%)
4	1 min - RT	Allyl-Br		**53** (59%)		(59%)
5	2 min - RT	CH_2I_2		**55** (40%)		(40%)
6	1 min - RT	Propargyl-Br	**56** (6%)		**57** (47%)	(53%)
7	1 h - 0 °C	3-Bromo-1-butyne	**58** (9%)		**59** (41%)	(50%)
8	2 min - RT	3-Bromo-1-butyne			**59** (66%)	(66%)

a) Conditions A: 3.15 equivalents of NaH and R-X. The Time/Temp is the time before addition of R-X and the temperature for the addition. b) Isolated yields of pure products after chromatography unless stated as ~%. The ~% are yields calculated from the ^{1}H NMR spectrum of an inseparable mixture. c) Total yield of benzimidazole(s) isolated.

Finally, enamine **6** was treated with NaH in DMSO followed by addition of acetyl chloride. Two products were obtained in low isolated yields from this reaction, diacetoxybenzimidazole **60** and acetoxybenzimidazole **61** having an unsaturated substituent in the 2-position (Scheme 4). The latter product is probably formed by elimination of acetic acid from **60**.

Scheme 4. Reaction of **6** with acetyl chloride.



6 **60** (18%) **61** (6%)

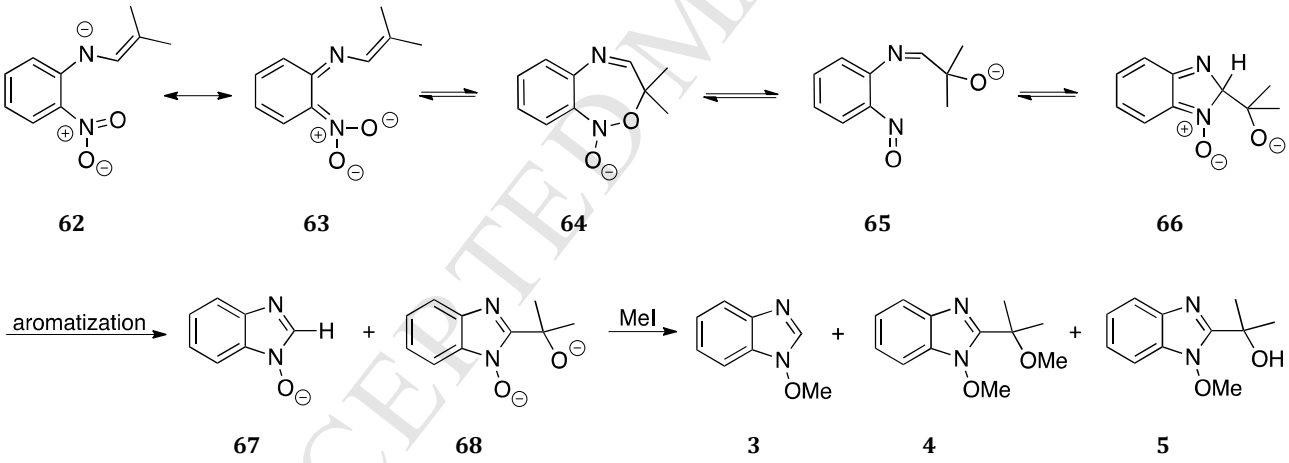
The base-mediated transformation to yield *N*-alkoxybenzimidazoles is limited to enamines derived from condensation of α-branched aldehydes and 4- or 5-substituted-2-nitroanilines. Attempts to prepare enamines from 2-nitroanilines and simple unbranched aliphatic aldehydes, for example propanal and hexanal, were unsuccessful affording complex mixtures of inseparable products. In addition, 3- and 6-substituted 2-nitrobenzeneamines did not form enamines with any aldehyde using the conditions presented herein, even under more forced reaction conditions. Only unreacted 2-nitroaniline starting materials were isolated from these reactions.

Mechanistic considerations

The overall transformation presented above to afford *N*-oxygenated benzimidazoles can mechanistically be rationalized as follows. Deprotonation of **1** would form an anion and two of several possible resonance forms, **62** and **63**, are depicted in Scheme 5. 1,7-Electrocyclization of **63** would furnish **64**, which may undergo ring opening to form the nitroso-imine **65**. 1,5-Electrocyclization of **65** to give **66** is plausible. While electrocyclization of imines derived from 2-nitrosoaniline and aldehydes are rare, the formation of 2-phenyl-1-hydroxybenzimidazole from

in situ reaction of 2-nitrosoaniline and benzaldehyde has been described.[9] Aromatization of intermediate **66** would furnish *N*-alkoxybenzimidazole **67** by loss of acetone or dialkoxybenzimidazole **68** via deprotonation. The timing of the alkylation is unclear since it is plausible that alkylation can occur both prior to and after aromatization. The proposed mechanism suggests that two equivalents of a base is required for the transformation of **1** to give **4** and **5**, one for the initial deprotonation to give **62**/**63** and one for deprotonation - aromatization of **66** to give **68**. Although 2.15 equivalents proved optimum for the formation of the mono-alkylated benzimidazoles, it is unclear why an additional equivalent of base was required to maximize the yield of dialkylated benzimidazoles.

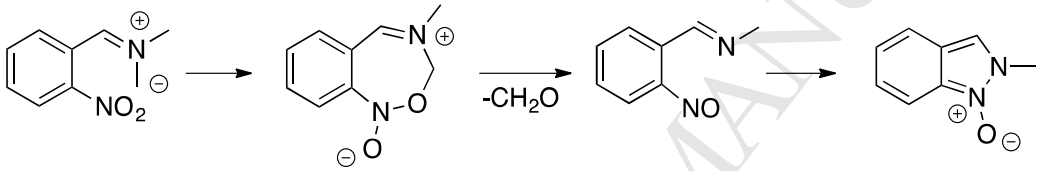
Scheme 5. Proposed mechanism for the formation of the *N*-oxygenated benzimidazoles **3**-**5**.



The mechanism outlined in Scheme 5 is supported by a limited number of related reactions reported in the literature. For example, Nyerges *et al* proposed a 1,7-electrocyclization of azomethine ylide (**69**), as a key mechanistic step toward indazole-*N*-oxide **72** (Scheme 6).[10,11] The authors suggested a ring-contraction of the cylization intermediate **70** with concurrent loss of formaldehyde to give the final product without any intermediates. However loss of

formaldehyde to give nitroso-imine **71** followed by a 1,5-electrocyclization as shown in Scheme 6 would also furnish **72**. The reactions in Schemes 3-6 are the result of an intramolecular oxidation-reduction wherein the alkyl-substituent on the amino group is oxidized to an alkoxide at the same time the nitro group is reduced to a nitroso group followed by further steps. We have reported a related palladium catalyzed reductive cyclization of 2-nitrostyrenes in the presence of a base to give 2-unsubstituted or 2-oxygenated indoles.[12] A similar mechanistic rational was proposed to explain the side-chain oxygenation.

Scheme 6 Proposed mechanism for the formation of indazole-*N*-oxides.



69 **70** **71** **72**

In summary, a synthetic route to *N*-alkoxybenzimidazoles via a base mediated cyclization of enamines ▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯α-branched aldehydes with 4- or 5-substituted 2-nitroaniline has been developed. Cyclization to afford *N*-alkoxybenzimidazoles in the presence of an alkyl halide was realized in moderate to excellent yield in all but one case.

Supporting Information

Supplementary information associated with this article including all experimental procedures and ^{1}H and ^{13}C NMR spectra of new compounds can be found in the online version, at http://dx.doixxxxxxxxx

Acknowledgements

We gratefully acknowledge the C. Eugene Bennett Department of Chemistry for support. The National Science Foundation-MRI program is also acknowledged for the funding of a 400 MHz NMR system (CHE-1228366). The authors would like to thank Mr. Mahdiar Khakinejad for HRMS analyses.

General Procedures. NMR spectra were determined in $CDCl_3$ at 600 or 400 MHz (^1H NMR) and at 150 or 100 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to $SiMe_4$ (0.0 ppm, ^1H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. The multiplicity of each resonance observed in the ^1H NMR spectra are reported as, s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.

Dichloromethane was purified/dried via two consecutive columns composed of activated alumina on a Glass Contours solvent purification system. Anhydrous dimethylsulfoxide, *N*-methylpyrrolidinone, and *N,N*-dimethylformamide were used as received. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Melting points are uncorrected.

4-Bromo-2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (12). Treatment of a solution of 4-bromo-2-nitrobenzenamine (1.04 g, 4.78 mmol) and 2-methylpropanal (414 mg, 5.74 mmol) in dichloromethane (DCM, 12 mL) at ambient temperature under a nitrogen atmosphere in the presence of 4 Å molecular sieves (3 g), as described for **24** (24 h), gave after work up and chromatography, (hexane/EtOAc, 95:5), **12** (726 mg, 2.68 mmol, 56%) as a violet solid. mp=119-120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J*=8.0 Hz, 1H), 8.29 (d, *J*=2.4 Hz, 1H), 7.47 (dd, *J*=9.2, 2.4 Hz, 1H), 6.93 (d, *J*=9.6 Hz, 1H), 6.20 (d, *J*=9.6 Hz, 1H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.8, 128.8, 119.9, 117.9, 116.0, 107.6, 22.5, 16.8; IR (ATR) 2912, 1564, 1340, 1165 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}BrN_2O_2$ ($M+H^+$) 271.0082, found 271.0078.

4-Fluoro-2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (15). Treatment of a solution of 4-fluoro-2-nitrobenzenamine (845 mg, 5.41 mmol) with 2-methylpropanal (390 mg, 5.41 mmol) in DCM (12 mL), in the presence of 5 Å molecular (12 g), at ambient temperature under a nitrogen atmosphere, as described for **24**, (24 h), gave after work up and chromatography (hexane/EtOAc, 97:3), **15** (788 mg, 3.75 mmol, 69%) as a reddish-brown solid. mp=79-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J*=7.6 Hz, 1H), 7.87 (dd, *J*=8.8, 2.8 Hz, 1H), 7.27-7.22 (ddd, *J*=9.6, 6.4, 2.4 Hz, 1H), 7.02 (dd, *J*=9.6, 4.8 Hz, 1H), 6.21 (d, with further fine splitting *J*=9.6 Hz, 1H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (d, $J^{C\text{-}F}$=239.0 Hz), 138.6 (d, $J^{C\text{-}F}$=1.0 Hz), 130.5 (d, $J^{C\text{-}F}$=8.0 Hz), 124.9 (d, $J^{C\text{-}F}$=24 Hz), 119.2, 118.2, 115.7 (d, $J^{C\text{-}F}$=8.0 Hz), 111.8 (d, $J^{C\text{-}F}$=26.0 Hz), 22.3, 16.7; IR (ATR) 1580, 1519, 1404, 1185, 1158, 1112 cm^{-1}; HRMS (ESI) $C_{10}H_{12}FN_2O_2$ ($M+H^+$) 211.0883, found 211.0897.

5-Methoxy-2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (24). To a solution of 5-methoxy-2-nitrobenzenamine (1.00 g, 5.95 mmol) and 2-methylpropanal (515 mg, 7.14 mmol) in dichloromethane (DCM, 12 mL) at ambient temperature under a nitrogen atmosphere was added 4 Å molecular sieves (3 g, activated by heating at 120 °C under vacuum overnight, then stored under nitrogen). The reaction mixture was allowed to sit without agitation or stirring for 48 h. The mixture was then filtered and the sieves were washed with DCM (20 mL). The filtrate was concentrated under reduced pressure and the resulting residue was purified by chromatography (hexane/EtOAc, 9:1) to give **24** (484 mg, 2.18 mmol, 37%) as a red solid. mp=83-84 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (d, *J*=7.2 Hz, 1H), 8.14 (d, *J*=9.6 Hz, 1H), 6.32 (d, *J*=3.0 Hz, 1H), 6.29 (dd, *J*=9.6, 2.4 Hz, 1H), 6.20 (dpent, *J*=9.6, 1.2 Hz, 1H), 3.88 (s, 3H), 1.83 (s, 3H), 1.80 (s, 3H); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 165.7, 143.5, 129.0, 126.0, 119.0, 118.0, 106.1, 95.0, 55.7, 22.5, 16.8; IR (ATR) 2923, 1616, 1585, 1497, 1239 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}N_2O_3Na$ ($M+Na^+$) 245.0902, found 245.0896.

5-Bromo-2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (29). Treatment of a solution of 5-bromo-2-nitrobenzenamine (455 mg, 2.10 mmol) with 2-methylpropanal (182 mg, 2.52 mmol) in benzene (6 mL), in the presence of 4 Å molecular sieves (4 g), at ambient temperature under a nitrogen atmosphere, as described for **24** (24 h), gave after work up and chromatography (hexane/EtOAc, 95:5), **29** (416 mg, 1.534 mmol, 73%) as a red solid. mp=94-95 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 9.56 (d, *J*=7.2 Hz, 1H), 8.03 (d, *J*=9.0 Hz, 1H), 7.20 (d, *J*=1.2 Hz, 1H), 6.81 (dd, *J*=9.0, 1.8 Hz, 1H), 6.18 (d with further fine splitting, *J*=9.6 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.8, 131.6, 130.7, 128.1, 120.7, 119.8, 117.8, 117.0, 22.5, 16.9; IR (ATR) 3495, 3381, 1616, 1560, 1489, 1218 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}BrN_2O_2$ ($M+H^+$) 271.0082, found 271.0078.

5-Methyl-2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (32). Treatment of a solution of 5-methyl-2-nitrobenzenamine (200 mg, 1.31 mmol) and 2-methylpropanal (114 mg, 1.58 mmol) in benzene (3 mL), in the presence of 4 Å molecular sieves (1 g) at ambient temperature under a nitrogen atmosphere, as described for **24** (24 h), gave after work up and chromatography (hexane/EtOAc, 95:5), **32** (106 mg, 0.514 mmol, 39%) as a red solid. mp=75-76 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 9.63 (d, *J*=7.8 Hz, 1H), 8.06 (d, *J*=9.0 Hz, 1H), 6.81 (s, 1H), 6.51 (dd, *J*=9.0, 1.2 Hz, 1H), 6.27 (d with further fine splitting, *J*=9.0 Hz, 1H), 2.35 (s, 3H), 1.82 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 141.4, 129.9, 126.8, 118.5, 118.4, 118.2, 113.8, 22.5, 22.1, 16.8; IR

(ATR) 1618, 1578, 1332, 1210, 1183 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2O_2$ ($M+H^+$) 207.1133, found 207.1128.

4-Bromo-2-nitro-*N*-(2-phenyl-1-propen-1-yl)benzenamine (39). Treatment of a solution of 4-bromo-2-nitrobenzenamine (430 mg, 1.98 mmol) with 2-phenylpropanal (239 mg, 1.78 mmol) in DCM (7 mL), in the presence of 5 Å molecular sieves (3.5 g), at ambient temperature under a nitrogen atmosphere, as described for **24** (24 h), gave after work up and chromatography (hexane/EtOAc, 95:5), **36** (446 mg, 1.34 mmol, 67%) as a violet solid. mp=106-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (d, *J*=10.4 Hz, 1H), 8.37 (d, *J*=2.4 Hz, 1H), 7.56 (dd, *J*=9.2, 2.4 Hz, 1H), 7.42-7.34 (m, 4H), 7.29-7.25 (m, 1H), 7.09 (d, *J*=9.2 Hz, 1H), 6.87 (dq, *J*=10.4, 1.2 Hz, 1H), 2.21 (d, *J*=1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 139.4, 138.9, 132.7, 129.0, 128.5, 126.8, 125.3, 120.6, 120.5, 116.0, 108.8, 14.7; IR (ATR) 1618, 1564, 1175, 1126, 749 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}BrN_2O_2$ ($M+H^+$) 333.0238, found 333.0234.

A detailed experimental procedure for the experiment in Entry 1 in Table 1 is shown below. All other entries in Tables 1-3 are slight variations of this procedure. Detailed experimental procedures for all entries discussed can be found in the Supporting Information file associated with this paper.

Table 2, Entry 1

1-Methoxybenzimidazole (3),[13] **1-Methoxy-2-(2-methoxy-2-propyl)benzimidazole (4), and 2-(2-Hydroxy-2-propyl)-1-methoxybenzimidazole (5).** A mixture of 2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamine (**1**)[14] (160 mg, 0.833 mmol) and sodium hydride[15] (NaH, 74.4 mg, 3.10

mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at ambient temperature under a nitrogen atmosphere. After stirring for 1 h, the mixture was cooled to 0 °C and methyl iodide (379 mg, 2.67 mmol) was added via a syringe. The reaction vessel was removed from the cold bath and stirred for 1 h. The resulting mixture was diluted with EtOAc (20 mL), washed with water (5x15 mL), dried ($MgSO_4$), and filtered. The solvents were removed from the filtrate under reduced pressure and the resulting residue was purified by chromatography (hexane/EtOAc, 7:3 then 3:7) to give, in order of elution **4** (105 mg, 0.477 mmol, 57%) as a colorless oil, **5** (25.3 mg, 0.123 mmol, 15%) as a white solid, and **3** (6.3 mg, 0.043 mmol, 5%) as a colorless oil.

Analytical data for all compounds:

1-Methoxybenzimidazole (3). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.78 (d, *J*=8.0 Hz, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.34 (td, *J*=7.2, 1.2 Hz, 1H), 7.29 (td, *J*=8.0, 1.2 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.4, 129.2, 123.6, 122.5, 120.9, 108.3, 67.2; IR (ATR) 1476, 1449, 1318, 1074, 962 cm^{-1}; HRMS (ESI) calcd for $C_8H_9N_2O$ ($M+H^+$) 149.0715, found 149.0710.

1-Methoxy-2-(2-methoxy-2-propyl)benzimidazole (4). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.0 Hz, 1H), 7.45 (d, *J*=8.0 Hz, 1H), 7.32 (td, *J*=7.2, 1.2 Hz, 1H), 7.26 (td, *J*=7.2, 1.2 Hz, 1H), 4.20 (s, 3H), 3.19 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 136.9, 131.4, 123.4, 122.2, 120.4, 108.3, 74.5, 65.2, 51.3, 24.8; IR (ATR) 1244, 1176, 1151, 1066, 969 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_2$ ($M+H^+$) 221.1290, found 221.1285.

1-Methoxy-2-(2-hydroxy-2-propyl)benzimidazole (5). White solid; mp=121-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*=7.6 Hz, 1H), 7.43 (d, *J*=8.4 Hz, 1H), 7.31 (td, *J*=7.2, 1.2 Hz, 1H), 7.26 (td, *J*=8.0, 1.6 Hz, 1H), 4.22 (s, 3H), 3.51 (br s, 1H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 136.9, 131.2, 123.3, 122.5, 120.4, 108.5, 69.8, 65.7, 28.8; IR (ATR) 3240, 1438, 1359, 1234, 1176, 1147 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2O_2$ ($M+H^+$) 207.1133, found 207.1118.

1,6-Dimethoxybenzimidazole (7). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.64 (d, *J*=9.6 Hz, 1H), 6.93-6.90 (m, 2H), 4.17 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 136.6, 133.9, 129.9, 121.6, 112.4, 91.3, 67.0, 55.8; IR (ATR) 1493, 1236, 1020, 815 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}N_2O_2$ ($M+H^+$) 179.0820, found 179.0814.

1,6-Dimethoxy-2-(2-methoxy-2-propyl)benzimidazole (8). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=9.6 Hz, 1H), 6.88 (dd, *J*=7.2, 2.4 Hz, 1H), 6.87 (s, 1H), 4.17 (s, 3H), 3.88 (s, 3H), 3.16 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 150.5, 132.1, 131.3, 121.1, 111.8, 91.4, 74.5, 65.0, 55.8, 51.3, 24.9; IR (ATR) 2929, 1738, 1215, 1063, 817 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_2O_3$ ($M+H^+$) 251.1395, found 251.1389.

2-(2-Hydroxy-2-propyl)-1,6-dimethoxybenzimidazole (9). Data from a 37:1 mixture of **9** and **7**: White solid; mp=119-120 °C, ^{1}H NMR δ 7.59 (d, *J*=8.6 Hz, 1H), 6.90 (dd, *J*=8.8, 2.5 Hz, 1H), 6.87 (d, *J*=2.2 Hz, 1H), 4.21 (s, 3H), 3.89 (s, 3H), 3.26 (br s, 1H), 1.76 (s, 6H); ^{13}C NMR δ 157.1, 153.4, 131.8, 131.4, 121.0, 111.8, 92.0, 69.8, 65.5, 55.9, 28.8; IR (neat) 3234, 1625, 1497, 1242, 1217, 1178, 1147, 1018, 956, 823 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_3$ ($M+H^+$) 237.1239, found 237.1229.

6-Chloro-1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (11). Orange solid; mp=66-67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J*=8.4 Hz, 1H), 7.41 (d, *J*=1.6 Hz, 1H), 7.19 (dd, *J*=8.4, 1.6 Hz, 1H), 4.16 (s, 3H), 3.16 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 135.5, 132.1, 129.4, 123.1, 121.4, 108.4, 74.5, 65.5, 51.3, 24.8; IR (ATR) 2944, 1677, 1496, 1340, 1268, 1228 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}ClN_2O_2$ ($M+H^+$) 255.0900, found 255.0893.

6-Bromo-1-methoxybenzimidazole (13). White solid; mp=46-47 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.66 (d, *J*=2.0 Hz, 1H), 7.63 (d, *J*=8.8 Hz, 1H), 7.38 (dd, *J*=8.4, 1.6 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.1, 130.3, 126.0, 122.3, 117.1, 111.5, 67.4; IR (ATR) 1462, 1347, 1220, 1086, 952 cm^{-1}; HRMS (ESI) calcd for $C_8H_8BrN_2O$ ($M+H^+$) 226.9820, found 226.9814.

6-Bromo-1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (14). Orange oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.32 (dd, *J*=8.4, 1.8 Hz, 1H), 4.15 (s, 3H), 3.15 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.3, 136.0, 132.6, 125.8, 121.8, 116.9, 111.5, 74.6, 65.6, 51.4, 24.8; IR (ATR) 2941, 1461, 1355, 1240, 1177 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}BrN_2O_2$ ($M+H^+$) 299.0395, found 299.0390.

6-Fluoro-1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (16). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J*=8.8, 4.8 Hz, 1H), 7.07 (dd, *J*=8.0, 2.4 Hz, 1H), 6.95 (td, *J*=9.6, 2.4 Hz, 1H), 4.13 (s, 3H), 3.14 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, $J^{C\text{-}F}$=241.0 Hz), 152.2 (d, $J^{C\text{-}F}$=3.0 Hz), 133.2, 131.5 (d, $J^{C\text{-}F}$=13.0 Hz), 121.4 (d, $J^{C\text{-}F}$=10.0 Hz), 110.8 (d, $J^{C\text{-}F}$=25.0 Hz), 95.0 (d, $J^{C\text{-}F}$=28.0 Hz), 74.4, 65.2, 51.3, 24.7; IR (ATR) 1486, 1448, 1172, 1067, 965, 811 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}FN_2O_2$ ($M+H^+$) 239.1196, found 239.1191.

1-Methoxy-6-methylbenzimidazole (18). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.65 (d, *J*=8.4 Hz, 1H), 7.29 (s, 1H), 7.11 (dd, *J*=8.0, 1.2 Hz, 1H), 4.17 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.0, 133.8, 129.4, 124.2, 120.4, 108.1, 67.1, 21.7; IR (ATR) 2922, 1457, 1060, 965, 806 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}N_2O$ ($M+H^+$) 163.0871, found 163.0867.

1-Methoxy-2-(2-methoxy-2-propyl)-6-methylbenzimidazole (19). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J*=8.4 Hz, 1H), 7.21 (d, *J*=1.2 Hz, 1H), 7.06 (dd, *J*=8.4, 1.2 Hz, 1H), 4.15 (s, 3H), 3.15 (s, 3H), 2.48 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.8, 135.1, 133.6, 131.6, 123.9, 119.9, 108.1, 74.5, 65.1, 51.3, 24.9, 21.7; IR (ATR) 2947, 1242, 1176, 810 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_2O_2$ ($M+H^+$) 235.1446, found 235.1441.

2-(2-Hydroxy-2-propyl)-1-methoxy-6-methylbenzimidazole (20). White solid; mp=99-100 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J*=8.4 Hz, 1H), 7.22 (s, 1H), 7.08 (dd, *J*=8.4, 1.2 Hz, 1H), 4.21 (s, 3H), 3.44 (br s, 1H), 2.50 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 135.0, 133.5, 131.4, 124.1, 119.9, 108.3, 69.8, 65.6, 28.8, 21.8; IR (ATR) 3241, 1145, 951, 815 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_2$ ($M+H^+$) 221.1290, found 221.1285.

Methyl 1-methoxybenzimidazole-6-carboxylate (22). White solid; mp=126-127 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 8.19 (s, 1H), 7.99 (dd, *J*=8.4, 1.2 Hz, 1H), 7.78 (d, *J*=8.4 Hz, 1H), 4.22 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 142.6, 140.0, 129.0, 125.6, 123.9, 120.7, 110.9, 67.7, 52.2; IR (ATR) 1698, 1441, 1320, 1280, 1226 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_3$ ($M+H^+$) 207.0769, found 207.0763.

1,5-Dimethoxybenzimidazole (25). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.23 (d, *J*=2.4 Hz, 1H), 6.98 (dd, *J*=8.4, 2.4 Hz, 1H), 4.15 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 140.3, 137.4, 123.9, 114.1, 108.8, 102.7, 67.2, 55.7; IR (ATR) 1213, 1125, 969, 803 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}N_2O_2$ ($M+H^+$) 179.0820, found 179.0820.

5-Chloro-1-methoxybenzimidazole (27). Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.75 (d, *J*=1.8 Hz, 1H), 7.39 (d, *J*=8.4 Hz, 1H), 7.29 (dd, *J*=9.0, 1.8 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 138.5, 128.1, 127.8, 124.1, 120.5, 109.1, 67.3; IR (ATR) 1457, 1309, 1054, 965, 898 cm^{-1}; HRMS (ESI) calcd for $C_8H_7ClN_2O$ ($M+Na^+$) 205.0144, found 205.0139.

5-Chloro-1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (28). Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J*=1.2 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.28 (dd, *J*=8.4, 1.8 Hz, 1H), 4.18 (s, 3H), 3.18 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 137.8, 130.2, 128.0, 124.0, 120.3, 109.2, 74.6, 65.5, 51.4, 24.8; IR (ATR) 2938, 1700, 1608, 1575, 1493, 1245 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}ClN_2O_2$ ($M+H^+$) 255.0900, found 255.0901.

5-Bromo-1-methoxybenzimidazole (30). Faint yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.91 (d, *J*=1.6 Hz, 1H), 7.43 (dd, *J*=8.8, 2.0 Hz, 1H), 7.35 (d, *J*=8.8 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.4, 128.2, 126.8, 123.7, 115.6, 109.7, 67.4; IR (ATR) 1454, 1308, 1175, 1066, 729 cm^{-1}; HRMS (ESI) calcd for $C_8H_8BrN_2O$ ($M+H^+$) 226.9820, found 226.9815.

5-Bromo-1-methoxy-2-(2-methoxy-2-propyl)benzimidazole (31). Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J*=1.6 Hz, 1H), 7.41 (dd, *J*=8.4, 1.6 Hz, 1H), 7.31 (d, *J*=8.8 Hz, 1H), 4.17 (s,

3H), 3.17 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 138.3, 130.5, 126.6, 123.4, 115.2, 109.6, 74.6, 65.5, 51.4, 24.8; IR (ATR) 1454, 1308, 1246, 1176, 1066 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}BrN_2O_2$ ($M+H^+$) 299.0395, found 299.0376.

1-Methoxy-5-methylbenzimidazole (33). Orange oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.56 (s, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.17 (d, *J*=7.8 Hz, 1H), 4.17 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.9, 137.4, 132.3, 127.4, 125.2, 120.6, 107.9, 21.5; IR (ATR) 2931, 1686, 1607, 1523, 1341, 1077 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}N_2O$ ($M+H^+$) 163.0871, found 163.0866.

1-Methoxy-5-methyl-(2-methoxy-2-propyl)benzimidazole (34). Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.14 (dd, *J*=8.0, 0.8 Hz, 1H), 4.17 (s, 3H), 3.17 (s, 3H), 2.47 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 137.4, 132.0, 129.6, 124.9, 120.2, 107.9, 74.6, 65.2, 51.4, 25.0, 21.5; IR (ATR) 2939, 1455, 1314, 1248, 1067 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_2O_2$ ($M+H^+$) 235.1446, found 235.1439.

1-Methoxy-(2-hydroxy-2-propyl)-5-methylbenzimidazole (35). White solid; mp=99-100 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.14 (dd, *J*=8.4, 1.2 Hz, 1H), 4.20 (s, 3H), 3.45 (br s, 1H), 2.47 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 137.3, 132.3, 129.3, 124.7, 120.1, 108.0, 69.7, 65.6, 28.7, 21.5; IR (ATR) 3242, 1372, 1309, 1236, 1145 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_2$ ($M+H^+$) 221.1290, found 221.1285.

1,6-Dimethoxy-2-(1-methoxycyclohexyl)benzimidazole (37). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J*=9.6 Hz, 1H), 6.88 (dd, *J*=9.6, 2.4 Hz, 1H), 6.87 (s, 1H), 4.16 (s, 3H), 3.89 (s,

3H), 3.10 (s, 3H), 2.34-2.31 (m, 2H), 2.16-2.10 (m, 2H), 1.76-1.64 (m, 2H), 1.62-1.56 (m, 3H), 1.42-1.35 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 149.9, 131.8, 131.4, 120.9, 111.7, 91.3, 75.8, 64.9, 55.7, 50.4, 32.5, 25.5, 21.7; IR (ATR) 2944, 1739, 1450, 1365, 1207 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}N_2O_3$ ($M+H^+$) 291.1708, found 291.1701.

1,6-Dimethoxy-2-(1-hydroxycyclohexyl)benzimidazole (38). White solid; mp=132-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J*=8.4, 1.2 Hz, 1H), 6.87 (dd, *J*=8.4, 2.4 Hz, 1H, 6.86 (s, 1H), 4.19 (s, 3H), 3.88 (s, 3H), 2.87 (br s, 1H), 2.17 (td, *J*=12.8, 4.0 Hz, 2H), 2.02-1.99 (m, 2H), 1.85-1.77 (m, 2H), 1.72-1.62 (m, 3H), 1.42-1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 153.2, 131.7, 131.5, 121.0, 111.7, 91.8, 71.3, 65.5, 55.9, 36.1, 25.3, 21.6; IR (ATR) 3281, 2940, 1504, 1451, 1435, 1237 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_3$ ($M+H^+$) 277.1552; found: 277.1547.

6-Bromo-1-methoxy-(1-methoxy-1-phenylethyl)benzimidazole (40). Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J*=8.8, 0.4 Hz, 1H), 7.51 (d, *J*=1.6 Hz, 1H), 7.38 (dd, *J*=8.8, 1.6 Hz, 1H), 7.42-7.40 (m, 2H), 7.35-7.24 (m, 3H), 3.53 (s, 3H), 3.29 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 144.0, 136.1, 128.2, 127.4, 125.9, 125.2, 122.0, 117.0, 111.6, 110.0, 78.3, 64.8, 51.4, 25.0; IR (ATR) 1437, 1373, 1245, 1185, 981, 792 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_2$ ($M+H^+$) 361.0551, found 361.0549.

6-Bromo-(1-hydroxy-1-phenylethyl)-1-methoxybenzimidazole (41). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.4 Hz, 1H), 7.50 (d, *J*=1.6 Hz, 1H), 7.48-7.46 (m, 2H), 7.39 (dd, *J*=8.4, 1.6 Hz, 1H), 7.38-7.27 (m, 3H), 3.90 (br s, 1H), 3.39 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 144.4, 136.0, 132.0, 128.6, 127.9, 126.1, 125.2, 122.0, 116.9, 111.5, 73.4, 65.0,

28.6; IR (ATR) 3233, 1449, 1364, 1251, 1089 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_2$ ($M+H^+$) 347.0395, found 347.0395.

6-Chloro-2-(2-hydroxy-2-propyl)-1-methoxybenzimidazole (42). White solid; mp=94-95 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=8.8 Hz, 1H), 7.43 (d, *J*=2.0 Hz, 1H), 7.23 (dd, *J*=8.8, 2.0 Hz, 1H), 4.22 (s, 3H), 3.19 (br s, 1H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 135.6, 131.8, 129.2, 123.3, 121.3, 108.6, 69.9, 66.0, 28.7; IR (ATR) 3286, 1457, 1309, 1054, 965 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}ClN_2O_2$ ($M+H^+$) 241.0743, found 241.0739.

6-Bromo-2-(2-hydroxy-2-propyl)-1-methoxybenzimidazole (43). White solid; mp=118-119 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.36 (dd, *J*=8.4, 0.8 Hz, 1H), 4.21 (s, 3H), 3.36 (br s, 1H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 135.9, 132.2, 126.0, 121.7, 116.6, 111.5, 69.8, 66.0, 28.7; IR (ATR) 3332, 1458, 1269, 1104, 729 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}BrN_2O_2$ ($M+H^+$) 285.0238, found 285.0233.

6-Fluoro-2-(2-hydroxy-2-propyl)-1-methoxybenzimidazole (44). White solid; mp=123-124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J*=9.2, 4.8 Hz, 1H), 7.10 (dd, *J*=8.0, 2.4 Hz, 1H), 6.99 (ddd, *J*=9.6, 8.8, 2.4 Hz, 1H), 4.19 (s, 3H), 3.46 (br s, 1H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (d, $J^{C\text{-}F}$=241.0 Hz), 155.0 (d, $J^{C\text{-}F}$=3.0 Hz), 133.2, 131.2 (d, $J^{C\text{-}F}$=14.0 Hz), 121.3 (d, $J^{C\text{-}F}$=10.0 Hz), 111.0 (d, $J^{C\text{-}F}$=25.0 Hz), 95.3 (d, $J^{C\text{-}F}$=28.0 Hz), 69.8, 65.7, 28.7; IR (ATR) 3232, 1488, 1438, 1363, 1172, 960, 833 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}FN_2O_2$ ($M+H^+$) 225.1039, found 225.1035.

5-Chloro-2-(2-hydroxy-2-propyl)-1-methoxybenzimidazole (45). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=2.0 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 7.26 (dd, *J*=8.8, 2.0 Hz, 1H), 4.21 (s, 3H), 3.71 (br s, 1H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 1376, 129.8, 128.1, 123.7, 120.1, 109.2, 69.8, 65.9, 28.6; IR (ATR) cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}ClN_2O_2$ ($M+H^+$) 241.0744, found 241.0727.

5-Bromo-2-(2-hydroxy-2-propyl)-1-methoxybenzimidazole (46). White solid; mp=109-110 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.40 (dd, *J*=8.8, 1.6 Hz, 1H), 7.29 (d, *J*=8.8 Hz, 1H), 4.20 (s, 3H), 3.49 (br s, 1H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.1, 130.1, 126.4, 123.2, 115.4, 109.7, 69.8, 66.0, 28.7; IR (ATR) 3257, 1455, 1309, 1175, 918, 731cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}BrN_2O_2$ ($M+H^+$) 285.0239, found 285.0233.

1,6-Dimethoxy-2-(1-hydroxy-1,1-diphenylmethyl)benzimidazole (48). Red viscous oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.21 (m, 2H), 7.19-7.16 (m, 1H), 7.15 (d, *J*=1.8 Hz, 1H), 7.14-7.13 (m, 1H), 7.09-7.02 (m, 6H), 7.01 (d, *J*=9.0 Hz, 1H), 6.81 (dd, *J*=9.0, 3.0 Hz, 1H), 6.33 (br s, 1H), 3.72 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 142.9, 142.6, 138.7, 135.9, 134.1, 130.4, 128.0, 127.6, 127.3, 127.0, 126.3, 126.0, 122.6, 120.5, 108.9, 55.9, 42.7; IR (ATR) 2835, 1529, 1493, 1228, 1040 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}N_2O_3$ ($M+H^+$) 361.1552, found 361.1548.

1-Benzyloxy-2-(2-benzyloxy-2-propyl)-6-methoxybenzimidazole (50). Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J*=8.8 Hz, 1H), 7.38-7.20 (m, 10H), 6.87 (dd, *J*=8.8, 2.4 Hz, 1H), 6.66 (d, *J*=2.8 Hz, 1H), 5.18 (s, 2H), 4.48 (s, 2H), 3.78 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 150.9, 138.4, 134.2, 132.9, 131.2, 129.3, 129.1, 128.6, 128.2, 127.3, 126.9, 121.0, 1119,

92.0, 79.8, 74.7, 65.6, 55.7, 25.5; IR (ATR) 2938, 1625, 1490, 1454, 1381, 1306 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_3$ ($M+H^+$) 403.2022, found 403.2014.

1-Benzyloxy-2-(2-hydroxyl-2-propyl)-6-methoxybenzimidazole (51). White solid; mp=118-119 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.8 Hz, 1H), 7.53-7.50 (m, 2H), 7.45-7.42 (m, 3H), 6.85 (dd, *J*=8.8, 2.4 Hz, 1H), 6.69 (d, *J*=2.4 Hz, 1H), 5.36 (s, 2H), 3.79 (s, 3H), 3.46 (br s, 1H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.5, 133.9, 132.4, 131.2, 129.5, 129.4, 128.9, 120.8, 111.7, 92.2, 80.3, 69.9, 55.7, 28.9; IR (ATR) 3240, 1627, 1491, 1452, 1250, 1213 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3$ ($M+H^+$) 313.1552, found 313.1547.

1-(2-Propen-1-yloxy)-6-methoxybenzimidazole (52). Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.61 (dd, *J*=9.6, 1.2 Hz, 1H), 6.90-6.87 (m, 2H), 6.07 (ddt, *J*=17.2, 10.4, 6.8 Hz, 1H), 5.33 (dq, *J*=17.2, 1.2 Hz, 1H), 4.71 (dt, *J*=6.4, 1.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 137.6, 133.7, 130.5, 130.3, 123.1, 121.3, 112.1, 91.6, 79.7, 55.7; IR (ATR) 1624, 1495, 1224, 1061, 932, 815cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}N_2O_2$ ($M+H^+$) 205.0977, found 205.0961.

1-(2-Propen-1-yloxy)-2-(2-(2-propen-1-yloxy)-2-propyl)-6-methoxybenzimidazole (53). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J*=8.8, 0.8 Hz, 1H), 6.87 (dd, *J*=8.4, 2.4 Hz, 1H), 6.85 (d, *J*=2.0 Hz, 1H), 6.15 (ddt, *J*=16.8, 10.4, 6.4, 1H), 5.87 (ddt, *J*=17.2, 10.4, 5.2 Hz, 1H), 5.50 (dq, *J*=17.2, 1.2 Hz, 1H), 5.41 (dd, *J*=17.2, 1.2 Hz, 1H), 5.23 (dq, *J*=17.2, 1.6 Hz, 1H), 5.10 (dq, *J*=10.4, 1.6 Hz, 1H), 4.84 (dt, *J*=6.4, 1.2 Hz, 2H), 3.87 (s, 3H), 3.85 (dt, *J*=5.2, 1.6 Hz, 2H), 1.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 150.7, 134.8, 132.7, 131.1, 130.9, 121.0, 120.9, 116.1,

111.7, 91.9, 78.7, 74.2, 64.5, 55.7, 25.3; IR (ATR) 2939, 1626, 1490, 1212, 1158, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}N_2O_3$ ($M+H^+$) 303.1708, found 303.1702.

2-(2-Hydroxy-2-propyl)-6-methoxy-1-(2-propen-1-yloxy)benzimidazole (54). White solid; mp=110-111 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J*=8.4, 0.8 Hz, 1H), 6.87 (dd, *J*=8.8, 2.4 Hz, 1H), 6.84 (d, *J*=2.0 Hz, 1H), 6.13 (ddt, *J*=16.8, 10.4, 6.4 Hz, 1H), 5.52 (dq, *J*=17.2, 1.2 Hz, 1H), 5.44 (dq, *J*=10.8, 1.2 Hz, 1H), 4.86 (d, *J*=6.4 Hz, 2H), 3.86 (s, 3H), 3.48 (br s, 1H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.6, 132.3, 131.2, 130.4, 121.5, 120.9, 111.7, 92.3, 79.0, 69.7, 55.8, 28.8; IR (ATR) 3208, 2991, 1490, 1252, 1252, 1176 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_3$ ($M+H^+$) 263.1396, found 263.1390.

8-Methoxy-4,4-dimethyl-4*H*-benzo[4,5]imidazo[1,2-*b*]dioxazine (55). White solid; mp=121-122 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J*=8.8, 1.2 Hz, 1H), 6.88 (dd, *J*=8.4, 2.4 Hz, 1H), 6.86 (d, *J*=2.4 Hz, 1H), 5.44 (s, 2H), 3.83 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 146.3, 131.6, 129.0, 120.4, 112.6, 91.3, 91.2, 75.8, 55.8, 27.4; IR (ATR) 1523, 1451, 1234, 1209, 1148 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3$ ($M+H^+$) 235.1082, found 235.1077.

6-Methoxy-1-(2-propyn-1-yloxy)benzimidazole (56). Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.62 (d, *J*=8.8 Hz, 1H), 6.92 (d, *J*=2.0 Hz, 1H), 6.90 (dd, *J*=8.8, 2.4 Hz, 1H), 4.86 (d, *J*=2.4 Hz, 2H), 3.85 (s, 3H), 2.68 (t, *J*=2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.8, 133.6, 130.1, 121.5, 112.4, 91.6, 79.1, 76.4, 66.0, 55.8; IR (ATR) 3286, 1626, 1496, 1238, 1021; HRMS (ESI) calcd for $C_{11}H_{11}N_2O_2$ ($M+H^+$) 203.0820, found 203.0811.

2-(2-Hydroxy-2-propyl)-6-methoxy-1-(2-propyn-1-yloxy)benzimidazole (57). White solid; mp=150-151 ^{o}C (dec.); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.4 Hz, 1H), 6.89 (d, *J*=1.8 Hz, 1H), 6.87 (dd, *J*=8.4, 2.4 Hz, 1H), 5.26 (d, *J*=2.4 Hz, 2H), 3.87 (s, 3H), 2.89 (br s, 1H), 2.33 (t, *J*=3.0 Hz, 1H), 1.77 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.8, 156.2, 136.4, 135.7, 120.2, 111.4, 93.6, 77.8, 73.2, 71.2, 55.9, 34.5, 29.3; IR (ATR) 3282, 1627, 1490, 1214, 1146 cm-1; HRMS (ESI) calcd for $C_{14}H_{16}N_2O_3$ (M+Na$^+$) 283.1058, found 283.1042.

1-(3-Butyn-2-yloxy)-6-methoxybenzimidazole (58). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.62 (d, *J*=9.6 Hz, 1H), 6.89 (d, *J*=2.8 Hz, 1H), 6.88 (dd, *J*=9.6, 2.8 Hz, 1H), 5.02 (dq, *J*=6.4, 2.0 Hz, 1H), 3.85 (s, 3H), 2.63 (d, *J*=2.0 Hz, 1H), 1.70 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 138.3, 133.6, 130.7, 121.3, 112.1, 92.0, 80.6, 76.7, 74.1, 55.8, 20.3; IR (ATR) 1624, 1495, 1234, 1061, 816; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_3$ (M+H$^+$) 217.0977, found 217.0968.

1-(3-Butyn-2-yloxy)-2-(2-hydroxy-2-propyl)-6-methoxybenzimidazole (59). White solid; mp=131-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$δ 7.54 (d, *J*=8.8 Hz, 1H), 7.13 (d, *J*=2.4 Hz, 1H), 6.86 (dd, *J*=8.8, 2.4 Hz, 1H), 5.52 (dq, *J*=6.8, 2.0 Hz, 1H), 3.86 (s, 3H), 2.78 (br s, 1H), 2.56 (d, *J*=2.0 Hz, 1H), 1.83 (s, 3H), 2.74 (d, *J*=1.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 153.7, 133.9, 131.0, 120.5, 112.0, 93.9, 81.9, 74.3, 70.2, 55.8, 29.7, 28.4, 20.7; IR (ATR) 3168, 1489, 1251, 1217, 1179 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3$ (M+H$^+$) 275.1396, found 275.1391.

1-Acetoxy-2-(2-acetoxy-2-propyl)-6-methoxybenzimidazole (60). Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J*=8.4 Hz, 1H), 6.87 (dd, *J*=8.4, 2.4 Hz, 1H), 6.57 (d, *J*=2.4 Hz, 1H), 3.84 (s, 3H), 2.46 (s, 3H), 1.82 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 157.5, 150.4,

133.4, 130.8, 120.9, 112.0, 91.6, 55.8, 43.0, 31.5, 27.1, 18.9, 12.4; IR (ATR) 1809, 1630, 1491, 1213, 1158 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_5$ ($M+H^+$) 307.1294, found 307.1275.

1-Acetoxy-2-(1-propen-2-yl)-6-methoxybenzimidazole (61). Pale yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J*=9.0 Hz, 1H), 6.89 (dd, *J*=9.0, 2.4 Hz, 1H), 6.63 (d, *J*=2.4 Hz, 1H), 5.69 (pent, *J*=1.2 Hz, 1H), 5.50 (pent, *J*=1.2 Hz, 1H), 3.84 (s, 3H), 2.40 (s, 3H), 2.27 (dd, *J*=1.8, 1.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 157.7, 148.3, 133.3, 133.0, 132.3, 121.2, 118.3, 112.4, 91.6, 55.8, 21.2, 18.3; IR (ATR) 1805, 1623, 1491, 1221, 1157, 813; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_3$ ($M+H^+$) 247.1083, found 247.1066.

2,4-Dinitro-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)benzenamine. Red oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J*=2.8 Hz, 1H), 8.20 (dd, *J*=9.6, 2.8 Hz, 1H), 7.04 (d, *J*=9.6 Hz, 1H), 5.71 (sept, *J*=1.2 Hz, 1H), 3.09 (s, 3H), 1.71 (d, *J*=1.2 Hz, 3H), 1.42 (d, *J*=1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 141.3, 136.8, 132.3, 127.7, 127.0, 123.2, 117.3, 40.7, 21.4, 17.5; ; IR (ATR) 1601, 1580, 1501, 1311, 1137 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}N_3O_4$ ($M+H^+$) 252.0984 , found 252.0980.

Methyl 4-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)amino-3-nitrobenzoate. Red oil; ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, *J*=1.8 Hz, 1H), 7.96 (dd, *J*=9.0, 2.4 Hz, 1H), 6.99 (d, *J*=9.0 Hz, 1H), 5.64 (sept, *J*=1.2 Hz, 1H), 3.87 (s, 3H), 3.02 (s, 3H), 1.67 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 146.3, 138.1, 133.5, 130.3, 128.2, 127.6, 118.7, 117.5, 52.0, 40.3, 21.4, 17.4; IR (ATR) 1704, 1607, 1525, 1290, 1259, 1126 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}N_2O_4$ ($M+H^+$) 265.1188, found 265.1171.

5-Chloro-2-nitro-*N*-methyl-*N*-(2-methyl-1-propen-1-yl)benzenamine. Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J*=8.4 Hz, 1H), 7.01 (d, *J*=1.8 Hz, 1H), 6.74 (dd, *J*=8.4, 1.8 Hz, 1H), 5.60 (sept, *J*=1.8 Hz, 1H), 2.97 (s, 3H), 1.68 (d, *J*=1.2 Hz, 3H), 1.43 (d, *J*=1.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 138.8, 137.7, 129.1, 127.7, 127.2, 118.5, 117.7, 40.5, 21.5, 17.5; IR (ATR) 1596, 1514, 1487, 1340, 1288 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}ClN_2O_2$ ($M+H^+$) 241.0743, found 241.0733.

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