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Hydrogen-Bond-Driven Electrophilic Activation for Selectivity Control: Scope and Limitations of Fluorous Alcohol-Promoted Selective Formation of 1,2-Disubstituted Benzimidazoles and Mechanistic Insight for Rationale of Selectivity

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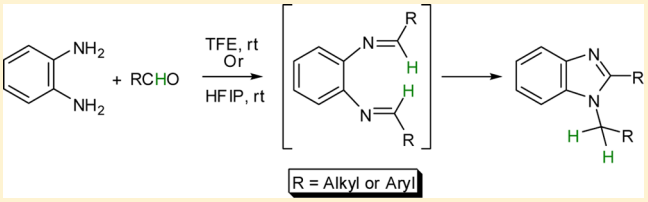
Supporting Information

ABSTRACT: Hydrogen-bond-driven electrophilic activation for selectivity control during competitive formation of 1,2-disubstituted and 2-substituted benzimidazoles from *o*-phenylenediamine and aldehydes is reported. The fluorous alcohols trifluoroethanol and hexafluoro-2-propanol efficiently promote the cyclocondensation of *o*-phenylenediamine with aldehydes to afford selectively the 1,2-disubstituted benzimidazoles at rt in short times. A mechanistic insight is invoked by NMR, mass spectrometry, and chemical studies to rationalize the selectivity. The ability of the fluorous alcohols in promoting the reaction and controlling the selectivity can be envisaged from their better hydrogen bond donor (HBD) abilities compared to that of the other organic solvents as well as of water. Due to the better HBD values, the fluorous alcohols efficiently promote the initial bisimine formation by electrophilic activation of the aldehyde carbonyl. Subsequently the hydrogen-bond-mediated activation of the in situ-formed bisimine triggers the rearrangement via 1,3-hydride shift to form the 1,2-disubstituted benzimidazoles.



INTRODUCTION

The broad range of biological activities of compounds with the 1,2-disubstituted benzimidazole moiety[1] make them highly sought as synthetic targets. This has generated interest to develop synthetic methods that follow diverse strategies (Scheme 1). The reported procedures for the construction of the 1,2-disubstituted benzimidazole scaffold may be classified under three broad categories: oxidative cyclocondensation, C-1 or N-2 alkylation/arylation of the preformed N-2 substituted or C-1 substituted benzimidazole, respectively, and transition metal-catalyzed inter/intramolecular N-arylation. The cyclocondensation involves the treatment of (i) *N*-alkyl-*N*-acyl-*o*-phenylenediamine (route A),[1g,2] or (ii) *N*-alkyl-*o*-phenylenediamine with aldehyde[1g,3] (route B). The C-1 or N-2 alkylation/arylation procedures involve (i) N-alkylation of 2-substituted benzimidazole,[1b,d,i] (route C) or (ii) Suzuki coupling of aryl boronic acids with 1-iodo-2-alkylbenzimidazoles[4] (route D). The transition metal-catalyzed N-arylation routes are (i) copper-catalyzed amidation of *o*-halo N-alkylated anilines followed by cyclodehydration of the *N*-alkyl-*N*-acyl *o*-phenylenediamine[5] intermediate (route E), (ii) copper/palladium-catalyzed amination of *o*-halo N-acylated anilines followed by cyclodehydration of the *N*-alkyl-*N*-acyl *o*-phenylenediamine[6] intermediate (route F), and (iii) palladium-catalyzed intramolecular aryl-amination of (*o*-bromo/iodophenyl)amidines[7] or bis(trifluoroacetoxy)iodobenzene-mediated intramolecular cyclization of *N*-alkyl-*N*′-arylamidines[8] (route G). These routes require metal catalysts and special efforts to prepare the desired starting materials. Thus, a direct one-pot cyclocondensation of *o*-phenylenediamine with aldehydes (route H) appears to be a straightforward approach.

The selectivity control[9] often becomes the synthetic bottleneck and is an important conceptual advancement in organic synthesis. Such a situation has high potential to occur during the direct cyclocondensation of *o*-phenylenediamines with aldehydes, as it poses a selectivity problem due to competitive formation of the 1,2-disubstituted and the 2-substituted benzimidazoles (Scheme 2).

Although the condensation of *o*-phenylenediamine with aldehydes (route H) is performed under varied catalytic assistance[10] to construct the benzimidazole scaffold, the critical issue of selectivity control due to the competitive formation of 1,2-disubstituted and 2-substituted benzimidazoles is inadequately addressed. We describe herein an efficient metal/Lewis acid-free protocol for selective formation of the 1,2-disubstituted benzimidazoles.

RESULTS AND DISCUSSION

We realized that the best examples of selectivity control are demonstrated by Nature's way to synthesize organic molecules. Anticipating that the strong Lewis/Brönstead acid catalysts used for electrophilic activation of the aldehyde carbonyl might cause a lack of selectivity, we opted for Nature's synthetic tools

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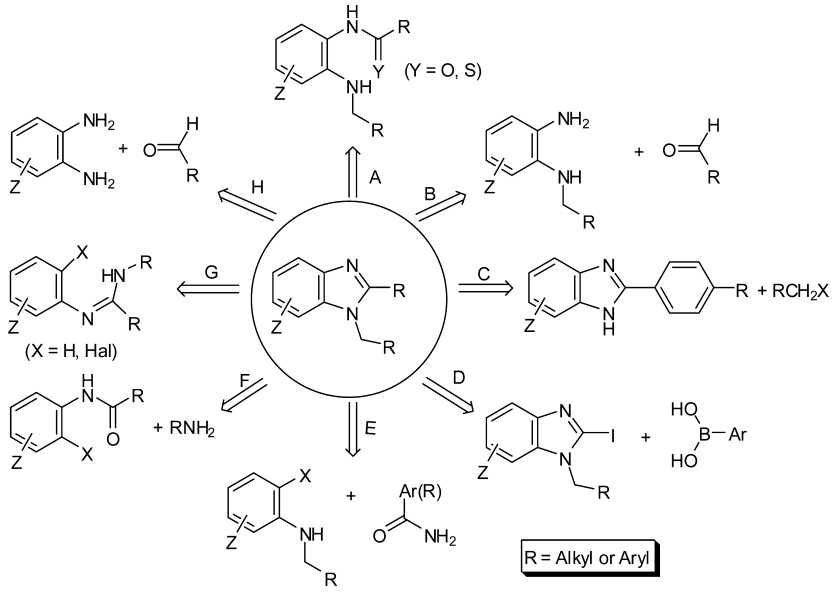
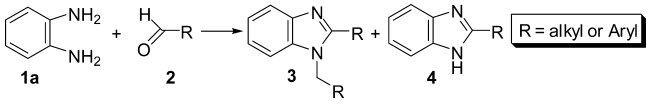
Scheme 1. Synthetic Strategies for 1,2-Disubstituted Benzimidazoles



Scheme 2. The Issue of Selectivity in the Formation of the 1,2-Disubstituted and 2-Substituted Benzimidazoles during the Condensation of *o*-Phenylenediamine with Aldehydes



of noncovalent interactions. Noncovalent synthesis is Nature's strategy to construct molecular architecture with a high precision of selectivity that is required for various biological functions and is the central theme of drug−receptor interaction.[11] The hydrogen bond (H-B) is the backbone of noncovalent synthesis[12] and is a frequently adopted synthetic tool by organic chemists.[13] Therefore, we resorted to a milder hydrogen-bond-driven[14] electrophilic activation strategy.

In a model study, *o*-phenylenediamine (**1a**) was treated with benzaldehyde (**2a**) in different solvents with varying hydrogen bond donor (HBD) ability in the absence of metal/Lewis acid catalyst (Table 1).

Poor conversion with competitive formation of **3a** and **4a** took place under neat conditions and in solvents with poor HBD (α) values[15] (entries 2−11, Table 1). Moderate results (total yields of **3a** and **4a**) were obtained in water and other protic polar solvents [such as alcohols and polyhydric alcohols (glycerol,[16] PEGs)] (entries 12−19, Table 1) with competitive formation of **4a**. Delightfully, we observed complete selectivity toward **3a** in excellent yields in trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP), as these have the highest α values, 1.51 and 1.96, respectively.[15]

The effect of various reaction parameters (temperature, time, molar equivalents of **1a** and **2a**, and amounts of TFE/HFIP) were assessed (Table 2). A decrease in selectivity was observed by lowering the reaction temperature to 0 °C to −40 °C with competitive formation of **4a**. The use of equimolar amounts of **1a** and **2a** also afforded **3a** as the major product and indicated the ability of TFE/HFIP to drive the selectivity toward **3a** although there is a general trend for competitive formation of **4a** at lower temperature. Most significantly, the TFE/HFIP is not required in large quantities and only 3 molar equiv (with respect to **1a**) is sufficient. The best operational condition is the treatment of **1a** with **2a** (2 equiv) in the presence of TFE/HFIP (3 equiv) at rt. However, the reactions are completed in shorter time (10 and 5 min, in 3 molar equiv of TFE and HFIP, respectively) at ∼80 °C with complete selectivity in favor of **3a**.

The superiority of TFE/HFIP was clearly established both in terms of the product yields as well as the selectivity by comparing the results obtained for the reaction of **1a** with **2a** with those obtained using a few reported catalysts (Table 3).

The general applicability of selective 1,2-disubstituted benzimidazole formation is demonstrated by the reaction of **1a** with various aldehydes (Table 4). Although the HFIP-promoted reactions take shorter time, TFE was chosen due to its ease of availability and low cost. Excellent results were obtained in short times (20−60 min) at rt. The reaction condition is compatible with various sensitive functional groups (entries 13−16). For substrates with an ortho substituent (entry 4) or bearing a strong electron-withdrawing group (entry 11), lack of selectivity was observed and the 2-substituted benzimidazole was the major product but the selectivity is directed toward 1,2-disubstituted benzimidazole at higher temperatures (∼80 °C).

To rationalize the role of TFE/HFIP on selectivity control, we set forth to understand the mechanistic course of the reaction. Two distinctly different pathways have been proposed (Scheme 3): (i) bisimine-rearrangement (path a)[10a,d,e,g,l,m,o,q,r] and (ii) monoimine-cyclocondensation−aminal/immonium-rearrangement (path b),[10l,17] reflecting inconsistent views without any distinct experimental evidence.

The TFE-promoted reaction of **1a** with PhCDO (2 equiv) afforded 2-phenyl-1-α-d_2-methylphenyl-1*H*-benzimidazole (**5**) (Figure 1). Although this observation justifies the proposal of a 1,3-hydride shift (Scheme 3), it remains inconclusive whether the rearrangement takes place via intermediate **III**[10o,q] (path a) or **V**/**VI** (path b).

Path b[10l,17] seems unlikely, as no ion peak corresponding to aminal **V** (condensation of **IV** with the aldehyde) or immonium ion **VI** was detected (LCMS) during the progress of the reaction of **1a** with **2a** (2 equiv). The formation of **3a** via **4a** is also ruled out, as no detectable amount of **3a** was formed by

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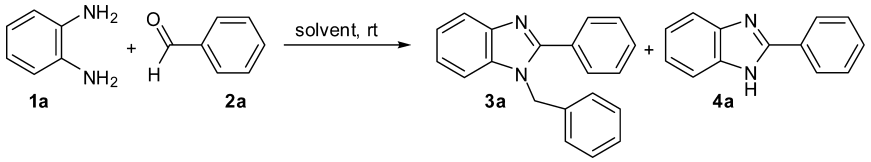
Table 1. Selectivity of Formation of 3a and 4a during the Reaction of 1a with 2a under Metal/Catalyst-Free Conditions[a]



1a 2a 3a 4a

		yield (%)[b]	
entry	solvent	3a	4a
1	neat	15	10
2	hexane	14	12
3	heptane	19	15
4	PhMe	32	20
5	1,4-dioxane	20	10
6	THF	22	15
7	DCE	14	27
8	DCM	15	12
9	CH_3CN	18	19
10	DMF	25	10
11	$MeNO_2$	30	15
12	Water	25	21
13	MeOH	35	25
14	EtOH	40	27
15	^{i}PrOH	32	25
16	^{t}BuOH	35	30
17	glycerol	20	15
18	PEG (2000)	30	20
19	PEG (400)	35	20
20	TFE	94	0
21	HFIP	95	0

[a] **1a** (0.10 g, 1 mmol) was treated with **2a** (0.21 g, 2 mmol, 2 equiv) in various solvents (1 mL) at rt for 1 h. [b] Isolated yields of **3a** and **4a** after purification.

treatment of the preformed **4a** with **2a** or benzyl alcohol in the presence of TFE or HFIP. Further exclusive formation of **3a** observed in comparable yields during the TFE-promoted reaction of **1a** with **2a** (2 equiv) under ambient temperature and nitrogen atmospheres also indicates that the 1,2-disubstituted benzimidazole formation does not proceed through imidazoline intermediate **IV**.[17b] Hence, we planned for various spectrometric studies to detect the intermediates involved during the progress of the reaction.

Mass spectrometric (+p ESI-MS) studies were performed during the TFE (3 mmol)-promoted reaction of **1a** (1 mmol) with **2a** (2 mmol) at rt. A sample aliquot from the reaction after 5 and 15 min exhibited ion peaks at m/z 285, which could be due to the bisimine or **3a**. The tandem mass (ms^2) of the ion with m/z 285 gave daughter ions at m/z 207 and 91 that are also obtained from the ms^2 of the authentic sample of **3a**. Thus, the mass study remains inconclusive with respect to the intermediacy of the bisimine (path a).

Next we performed time-dependent ^{1}H NMR experiments during the progress of the TFE-promoted reaction of **1a** (1 mmol) with **2a** (2 mmol) at rt for a sample aliquot withdrawn after 5, 15, and 30 min. A singlet at δ 8.55 was observed in the samples at 5 and 15 min reaction time with decreasing intensity and disappeared in the sample at 30 min reaction (Figure 2). To find out whether this was due to the monoimine or bisimine, the reaction of **1a** (1 mmol) with **2a** (2 mmol) in the presence of TFE (3 mmol) at rt was treated with $NaBH_4$ (3 equiv) after 5 min and stirred at rt for 1 h (Scheme 4). The LCMS of the crude reaction mixture exhibited ion peaks at m/z 285 and 289 which correspond to the ion peak of **3a** and the reduced product of the bisimine (bisreductive diamination of **2a** with **1a**), respectively. After purification (flash chromatography), *N*,*N*′-dibenzyl-1,2-phenylenediamine (**6**) was obtained (spectral data) and provided, for the first time, crucial evidence that the reaction proceeds via path a.

In the ^{1}H NMR spectrum, sample aliquots withdrawn after 5, 15, and 30 min of the reaction of **1a** (1 mmol) with **2a** (2 mmol) in MeOH (1 mL) at rt exhibited two singlets at δ 8.54 and 8.45 (Figure 2) corresponding to the bis- and monoimines, respectively. This justified the lack of selectivity observed in MeOH.

Therefore, the selectivity control for the formation of 1,2-disubstituted benzimidazole resides on the feasilibility of the formation of the bisimine under the prescribed set of experimental condition(s). The better HBD values of TFE and HFIP[15] enable them to act as effective electrophilic activating agents for bisimine formation and for promoting the subsequent mechanistic events (intramolecular nucleophilic attack followed by a 1,3-hydride shift) toward the selective formation of the 1,2-disubstituted imidazoles. The better HBD value of HFIP compared to that of TFE makes HFIP a better promoter as reflected by the shorter reaction time.

The formation of bisimine **II** is crucial and the determining factor for 1,2-disubstituted benzimidazole formation (hence directing/controlling the 1,2-disubstituted vs 2-substituted benzimidazole selectivity) as demonstrated by the reaction of **1a** with 2-methoxybenzaldehyde (2 equiv) that resulted in the formation of the 2-substituted benzimidazole as the major

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Table 2. Effect of Various Reaction Parameters on the Selectivity of Formation of 3a and 4a during the Condensation of 1a and 2a[a]

entry	equiv[b]	solvent	amount of solvent	temp (°C)	time (min)	yield (%)[c] 3a	yield (%)[c] 4a
1	2	TFE	1 mL	rt	60	94	0
2	2	HFIP	1 mL	rt	60	95	0
3	2	TFE	1 mL	−40	60	78	20
4	2	HFIP	1 mL	−40	60	89	10
5	2	TFE	1 mL	0	60	88	10
6	2	HFIP	1 mL	0	60	89	10
7	1	TFE	1 mL	rt	60	40	7
8	1	HFIP	1 mL	rt	60	44	5
9	1	TFE	1 mL	−40	60	36	27
10	1	HFIP	1 mL	−40	60	41	16
11	1	TFE	1 mL	0	60	35	17
12	1	HFIP	1 mL	0	60	41	16
13	2	TFE	5 mmol	rt	60	94	0
14	2	TFE	3 mmol	rt	60	94	0
15	2	TFE	2 mmol	rt	60	85	0
16	2	TFE	1 mmol	rt	60	76	0
17	2	HFIP	3 mmol	rt	60	95	0
18	2	HFIP	2 mmol	rt	60	87	0
19	2	HFIP	1 mmol	rt	60	83	0
20	2	TFE	3 mmol	rt	30	94	0
21	2	TFE	3 mmol	rt	20	85	0
22	2	TFE	3 mmol	rt	10	65	0
23	2	HFIP	3 mmol	rt	30	95	0
24	2	HFIP	3 mmol	rt	20	95	0
25	2	HFIP	3 mmol	rt	10	80	0
26	2	TFE	3 mmol	80	10	95	0
27	2	HFIP	3 mmol	80	5	95	0
28	2	glycerol	3 mmol	rt	60	trace	trace
29	2	glycerol	3 mmol	90	60	70	30
30	2	TFE	2 mmol	80	10	90	5
31	2	HFIP	2 mmol	80	5	95	0
32	2	TFE	1 mmol	80	10	80	15
33	2	HFIP	1 mmol	80	5	85	10

[a] **1a** (0.107 g, 1 mmol) was treated with **2a** (with varying molar equiv with respect to **1a**) in TFE/HFIP (except for entries 28 and 29) under various conditions. [b] Molar equivalent of **2a** used with respect to **1a**. [c] Isolated yields of **3a** and **4a** after purification.

product at rt (Table 4, entry 4, footnotes d and e). To demonstrate that in this case the bisimine formation does not occur, the reaction mixture of 2-methoxybenzaldehyde (2 mmol), **1a** (1 mmol), and TFE (3 mmol) at rt was treated with $NaBH_4$. The formation of N^1-(2-methoxybenzyl)benzene-1,2-diamine (**7**) (Scheme 4) proved that the lack of formation of the expected 1,2-disubstituted benzimidazole is due to the feasibilty of only monoimine formation. Similar implication of the steric factor in suppressing the bisimine formation (and hence directing the selectivity toward the 2-substituted benzimidazole) was also observed with pivaldehyde (sterically hindered aliphatic aldehyde) that gave the 2-substituted benzimidazole in 92% yield during the reaction with **1a** in the presence of TFE (3 equiv) at rt for 1 h (Table 4, entry 28).

In the case of electron-deficient aldehyde (Table 4, entry 11, footnote g) due to the highly electrophilic character of the aldehyde carbonyl, a rapid formation of the monoimine takes place, and before the second amino group of **1a** is involved in bisimine formation with another molecule of 4-nitrobenzaldehyde, it undergoes intramolecular nucleophilic attack on the C=N of the monoimine, leading to the formation of the imidazoline intermediate and finally to the 2-substituted benzimidazole. However, selective formation of the 1,2-disubstituted benzimidazole took place under heating, as this assisted the bisimine formation. Thus, it was anticipated that an increase in nucleophilicity of the amino group would induce the formation of the bisimine with 4-nitrobenzaldehyde and hence the corresponding 1,2-disubstituted benzimidazole. The formation of the 1,2-disubstituted benzimidazole, albeit in low (18%) yield, from the reaction of 3,4-dimethyl-*o*-phenylenediamine (1 mmol) with 4-nitrobenzaldehyde (2 mmol) at rt supported this hypothesis.

The specific role of TFE/HFIP through hydrogen-bond-driven electrophilic activation in promoting the tandem bisimine formation−rearrangement process for selective formation of the 1,2-disubstituted benzimidazoles is depicted in Scheme 5.

■ CONCLUSIONS

Hydrogen-bond-driven electrophilic activation for selectivity control is demonstrated for competitive formation of 1,2-disubstituted and 2-substituted benzimidazole during reaction of *o*-phenylenediamine with aldehydes at rt under metal/Lewis acid-free conditions. The fluorous alcohols trifluoroethanol and hexafluoro-2-propanol promote the condensation of *o*-phenylenediamine with 2 mol equiv of aldehydes to selectively form the 1,2-disubstituted benzimidazoles. The broad substrate scope with demonstrated chemoselectivity, metal/catalyst-free protocol, excellent yields, and room temperature reaction condition mark a few advantages. The mechanistic investigation through various spectroscopic and chemical (by first-time identification/isolation of the crucial intermediates) studies rationalize the origin of selectivity control and derives the influence of various factors (e.g., nature of the promoter, steric and electronic factors of the reactants) on the observed selectivity. The specific role of the fluorous alcohols in promoting the reaction has been envisaged through hydrogen-bond-driven electrophilic activation of the aldehyde in the initial bisimine formation stage and the subsequent rearrangement of the in situ-formed bisimine through a 1,3-hydride shift. The better HBD values of TFE and HFIP compared to other solvents justifies their superiority over other solvents in promoting the reaction and controlling the selectivity.

■ EXPERIMENTAL SECTION

General. The glassware to be used in reactions was thoroughly washed and dried in an oven, and the experiments were carried out with required precautions. Chemicals and all solvents were commercially available and used without further purification. The ^1H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CHCl_3$: 7.26/77.0) using TMS as an internal standard. Chemical shifts (δ) are given in ppm, and J values are given in hertz. The ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CDCl_3$ at 77.00 ppm. Splitting patterns were designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded under APCI mode of ionization. Infrared (IR) spectra were recorded in the range 4000−600 cm^{-1} either as neat for liquid or KBr pellets for solid samples. Purity of the compounds were checked on the silica gel GF-254 under UV at 254 nm. Melting points were measured using melting point

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Table 3. Selectivity in the Formation of 3a and 4a during the Reaction of 1a with 2a in the Presence of Various Reported Catalysts[a]

				yield (%)[d,e]			
entry	catalyst(mol %)[b]	equiv (1a:2a)[c]	time (h)	3a	4a	3a[f]	lit. ref
1	none	1:1	5	12	16	–	–
2	none	1:2	5	25	20	–	–
3	montmorilonite K-10 (10)[g]	1:1	10 min	21	32	–	10b
4	montmorilonite K-10 (10)[g]	1:2	10 min	75	18	90	10b
5	H_2SO_4–SiO_2 (10)	1:1	1.5	22	29	–	10c
6	H_2SO_4–SiO_2 (10)	1:2	1.5	58	27	75	10c
7	L-proline (10)	1:1	5	20	35	–	10e
8	L-proline (10)	1:2	5	68	26	95	10e
9	oxalic acid (10)	1:1	35 min	22	25	–	10d
10	oxalic acid (10)	1:2	35 min	65	22	97	10d
11	$Fe(ClO_4)_3$ (10)	1:1	10 min	20	30	–	10g
12	$Fe(ClO_4)_3$ (10)	1:2	10 min	48	25	90/10	10g
13	glyoxalic acid (75)	1:1	20 min	15	35	–	10h
14	glyoxalic acid (75)	1:2	20 min	68	21	95	10h
15	[Hmim][TFA] (10)	1:1	3	18	28	–	10i
16	[Hmim][TFA] (10)	1:2	3	71	25	86	10i
17	$SiO_2/ZnCl_2$ (25)	1:1	20 min	24	32	–	10l
18	$SiO_2/ZnCl_2$ (25)	1:2	20 min	62	28	72	10l
19	Amberlite-IR-20 (0.1 g)	1:1	1.45	23	26	–	10n
20	Amberlite-IR-20 (0.1 g)	1:2	1.45	60	31	95	10n
21	Me_3SiCl (50)	1:1	5	22	32	–	10o
22	Me_3SiCl (50)	1:2	5	68	15	87	10o
23	HOAc (3 mmol)[h]	1:2	30 min	65	30	–	10p
24	HOAc (10 mL)[h]	1:2	30 min	88	10	–	10p
23	SDS (10)	1:1	22 min	25	32	–	10q
24	SDS (10)	1:2	22 min	66	23	98	10q
25	$Mg(HSO_4)_2$ (30)	1:1	10 min	22	26	–	17
26	$Mg(HSO_4)_2$ (30)	1:2	10 min	60	28	90	17
27	$Mg(HSO_4)_2$ (30)	1:1	45	25	32	–	17
28	$Mg(HSO_4)_2$ (30)	1:2	45	64	26	92	17
29	[Hbim][BF_4] (75)[i]	1:1	5	20	28	–	17b
30	[Hbim][BF_4] (75)[i]	1:2	5	76	15	88	17b

[a] **1a** (2.5 mmol) was treated with **2a** in the presence of the catalyst (except for entries 1 and 2) under reported conditions. [b] Molar equivalent of the catalyst used with respect to **1a**. [c] Molar equivalent of **2a** used with respect to **1a**. [d] The isolated yield of **3a** and **4a** after column chromatographic purification obtained in performing the reaction under the present investigation. [e] The products were characterized by NMR (^{1}H and ^{13}C) and MS (APCI). [f] Yield of **3a** as reported in the cited literature except for entry 14. [g] A 10% w/w of the catalyst was used. [h] The reaction was performed using 1 mmol of **1a** at rt. [i] The reaction was carried out at 60 °C under N_2.

apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Typical Experimental Procedure for the Synthesis of 1-Benzyl-2-phenyl-1*H*-benzimidazole 3a. A mixture of **1a** (0.10 g, 1 mmol), **2a** (0.21 g, 2 mmol, 2 equiv), and TFE (0.30 g, 3 mmol, 217 μL) was stirred magnetically at rt for 30 min (complete consumption of **1**, TLC). The mixture was dissolved in EtOAc (3 mL), adsorbed on silica gel (0.5 g, 230–400 mesh), and concentrated under rotary vacuum evaporation. The resultant solid mass was charged onto a flash chromatography column and eluted with hexane–EtOAc (85:15) to afford **3a** (0.27 g, 95%) (entry 1, Table 4). White solid; mp = 130–132 °C; IR (KBr) ν_{max} = 3012, 2952, 1601, 1508, 1465, 1264, 1172, 1101, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.87 (d, J = 8 Hz, 1H), 7.70–7.68 (m, 2H), 7.47–7.44 (m, 3H), 7.33–7.29 (m, 4H), 7.24–7.21 (m, 2H), 7.12–7.09 (m, 2H), 5.46 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 154.2, 143.2, 136.4, 136.1, 130.1, 129.9, 129.3, 129.1, 128.7, 127.8, 126.0, 123.0, 122.7, 120.0, 110.5, 48.4. MS (APCI) m/z: 285.1 (M + H)$^+$.[10e] Unless otherwise mentioned, all reactions for generalization study under Table 4 were performed using 1 mmol of **1a** and 2 mmol of the respective aldehyde.

Effect of Steric Hindrance on Selectivity of Formation of 1,2-Disubstituted and 2-Substituted Benzimidazoles: Reaction of Pivalaldehyde with 1a in the Presence of Trifluoroethanol. 2-*tert*-Butyl-1*H*-benzimidazole (Entry 28, Table 4). A mixture of **1a** (108 mg, 1 mmol), pivalaldehyde (172 mg, 2 mmol, 2 equiv), and TFE (300 mg, 3 mmol, 217 μL) was stirred magnetically at rt for 60 min (complete consumption of **1**, TLC). The mixture was dissolved in EtOAc (3 mL), adsorbed on silica gel (0.5 g, 230–400 mesh), and concentrated under rotary vacuum evaporation. The resultant solid mass was charged onto a flash chromatography column and eluted with hexane–EtOAc (80:20) to afford 2-*tert*-butyl-1*H*-benzimidazole (0.16 g, 92%). White solid; mp = 320–322 °C; IR (KBr) ν_{max} = 3345, 2885, 1612, 1442, 1370, 1352, 1390, 1285, 1081 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz, TMS) δ: 7.53–7.52 (m, 1H), 7.41–7.39 (m, 1H), 7.14–7.07 (m, 2H), 1.39 (s, 9H). MS (APCI) m/z: 175.2 (M + H)$^+$.[18]

Investigation on the Progress of the Reaction for an Insight on the Mechanistic Course of the Reaction. Evidence for a 1,3-Hydride Shift through a Bisimine Intermediate. TFE-Promoted Reaction of 1a with Benzaldehyde-α-d_1. A mixture of **1a** (0.54 g, 0.5 mmol), benzaldehyde-α-d_1 (0.10 g, 1 mmol, 2 equiv), and TFE (0.15 g, 109 μL, 1.5 mmol) was stirred magnetically at rt for 30 min (complete consumption of **1**, TLC). The mixture was dissolved in EtOAc (3 mL), adsorbed on silica gel (0.5 g, 230–400 mesh), and concentrated under rotary vacuum evaporation. The resultant solid mass was charged onto a flash chromatography column and eluted with hexane–EtOAc (85:15) to afford 2-phenyl-1-α-d_2-methylphenyl-

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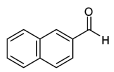
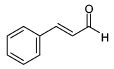
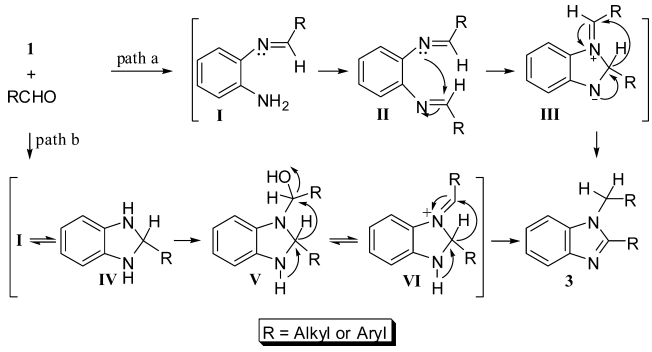
Table 4. TFE-Promoted Selective 1,2-Disubstituted Benzimidazole Formation during the Reaction of 1 with Various Aldehydes at rt under Metal/Catalyst-Free Conditions[a]

Entry	Aldehyde	Time	Yield (%)[b]
			
1	$R^1 = R^2 = R^3 = R^4 = R^5 = H$	30	94
2	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CH_3$	20	95
3	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCH_3$	20	96
4	$R^2 = R^3 = R^4 = R^5 = H$; $R^1 = OCH_3$	30	85[c,d,e]
5	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = N(CH_3)_2$	20	94
6	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Cl$	30	92
7	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Br$	30	93
8	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OH$	30	93
9	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CF_3$	30	90
10	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CN$	30	92
11	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NO_2$	30	75[f,g]
12	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCH_2Ph$	30	93
13	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCOPh$	30	92
14	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCOBu^t$	30	90
15	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OBoc$	30	95
16	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OTBDMS$	30	95
17	$R^1 = R^3 = R^5 = H$; $R^2 = R^4 = OCH_3$	30	91
18	$R^1 = R^4 = R^5 = H$; $R^2 = R^3 = OCH_3$	30	92
19	$R^1 = R^4 = R^5 = H$; $R^2 = OEt$; $R^3 = OH$	45	90
20		30	93
21		20	91
22		20	92
23		30	89
24		30	92
25		60	90
26		45	91
27		45	89
28		60	92[h]

[a] **1a** (0.107 g, 1 mmol) was treated with the aldehyde (0.21 g, 2 mmol, 2 equiv) in the presence of TFE (3 mmol) at rt. [b] Isolated yield of the 1,2-disubstituted benzimidazole after purification. [c] Reaction was performed at 80 °C. [d] 1,2-disubstituted and 2-substituted benzimidazoles were formed in 20% and 75% yields, respectively, at rt after 20 min. [e] 1,2-disubstituted and 2-substituted benzimidazoles were formed in 10% and 85% yields, respectively, at rt after 20 min in the presence of HFIP (3 mmol). [f] Reaction was performed at 80 °C and the 2-substituted benzimidazole was isolated in 20% yield in addition to the 1,2-disubstituted benzimidazole. [g] 2-aryl benzimidazole was formed in 93% yield at rt. [h] Yield of 2-substituted benzimidazole.

Scheme 3. Mechanism for Formation of 1,2-Disubstituted Benzimidazole



1*H*-benzimidazole (**5**) (0.13 g, 91%); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ = 7.90−7.87 (m, 1H), 7.92−7.69 (m, 2 H), 7.49 − 7.45 (m, 3 H), 7.37−7.31 (m, 4 H), 7.26−7.21 (m, 2 H), 7.14 − 7.11 (m, 2 H); MS (APCI) *m*/*z*: 287.2 $(M + H)^+$.[10o]

Evidence for the Intermediacy of Bisimine during the TFE-Promoted 1,2-Disubstituted Benzimidazole Formation. Formation of N^1,N^2-Dibenzylbenzene-1,2-diamine during the in Situ Reduction (with $NaBH_4$) of the Presumably Formed Bisimine during the Synthesis of the 1,2-Disubstituted Benzimidazole from 1a with 2a. A mixture of **1a** (0.10 g, 1 mmol), **2a** (0.21 g, 2 mmol, 2 equiv), and TFE (0.30 g, 3 mmol, 217 μL) was stirred magnetically at rt. After 5 min, $NaBH_4$ (3 mmol, 3 equiv) was added and the resultant mixture was stirred for further 30 min. The mixture was dissolved in EtOAc (3 mL), adsorbed on silica gel (0.5 g, 230−400 mesh), and concentrated under rotary vacuum evaporation. The resultant solid mass was charged onto a flash chromatography column and eluted with hexane−EtOAc (85:15) to afford N^1,N^2-dibenzylbenzene-1,2-diamine (**6**) (0.3 g, 10%). Low melting solid; IR (KBr) ν_{max} = 3441, 2979, 1610, 1455, 1326, 1265, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.39−7.35 (m, 4H), 7.34−7.32 (m, 4H), 7.29−7.27 (m, 2H), 6.80−6.78 (m, 2H), 6.72−6.70 (m, 2H), 4.31 (s, 4H), 3.64 (brs, 2H); MS (EI) *m*/*z*: 289.2 $(M + H)^+$.[19]

Evidence for the Intermediacy of Monoimine during the Reaction of 1a with Sterically Hindered Aldehyde Leading to the Formation of the 2-Substituted Benzimidazole. Formation of N^1-(2-Methoxybenzyl)benzene-1,2-diamine during the in Situ Reduction (with $NaBH_4$) of the Presumably Formed Monoimine during the Reaction of 1a with 2-Methoxybenzaldehyde That Led to the Formation of the 2-Substituted Benzimidazole. A mixture of **1a** (0.10 g, 1 mmol), 2-methoxybenzaldehyde (0.27 g, 1 mmol, 1 equiv), and TFE (0.30 g, 3 mmol, 217 μL) was stirred magnetically at rt. After 5 min, $NaBH_4$ (3 mmol, 3 equiv) was added and the resultant mixture was stirred for a further 30 min. The mixture was dissolved in EtOAc (3 mL), adsorbed on silica gel (0.5 g, 230−400 mesh), and concentrated under rotary vacuum evaporation. The resultant solid mass was charged onto a flash chromatography column and eluted with hexane−EtOAc (80:20) to afford N^1-(2-methoxybenzyl)benzene-1,2-diamine (**7**) (0.35 g, 15%). Light orange color oil; IR (KBr) ν_{max} = 3449, 2989, 2858, 1609, 1455, 1259, 1139, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.29−7.25 (m, 2H), 7.02−6.89 (m, 2H), 6.86−6.79 (m, 1H), 6.78−6.67 (m, 3H), 4.31 (s, 2H), 3.86 (s, 3H), 3.58 (brs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 157.5, 137.8, 134.7, 129.2, 128.4, 127.4, 120.6, 120.6, 118.9, 116.3, 112.6, 110.3, 55.4, 43.9. MS (EI) *m*/*z*: 228.3 $(M + H)^+$. Anal. Calcd For $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; O, 7.01%. Found: C, 73.69; H, 7.08; N, 12.29%.

1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-benzimidazole (Table 4, Entry 2). White solid (0.29 g, 95%); mp = 129−130 °C; IR (KBr) ν_{max} = 2959, 1618, 1605, 1402, 1252, 1128, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.85 (d, *J* = 8 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.31−7.18 (m, 5H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.99 (d, *J* = 7.7 Hz, 2H), 5.40 (s, 2H), 2.40 (s, 3H), 2.33 (s, 3H). MS (APCI) *m*/*z*: 313.4 $(M + H)^+$.[10e]

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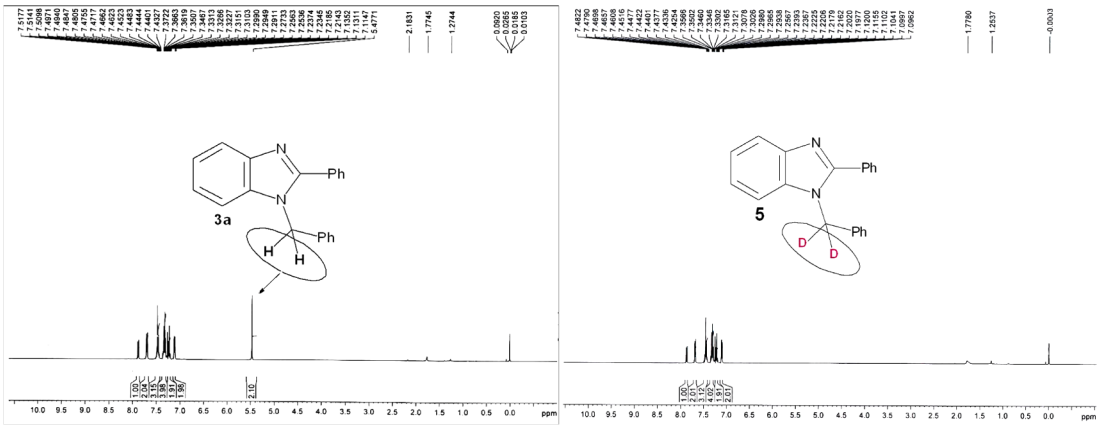


Figure 1. Evidence of a 1,3-hydride shift through the bisimine during TFE-promoted 1,2-disubstituted benzimidazole formation: (a) ^{1}H NMR spectrum of an authentic sample of **3** obtained from the reaction of **1a** (1 mmol) with **2a** (2 mmol) in TFE (3 mmol) at rt; (b) ^{1}H NMR spectrum of the product obtained from the reaction of **1a** (1 mmol) with PhCDO (2 mmol) in TFE (3 mmol) at rt.

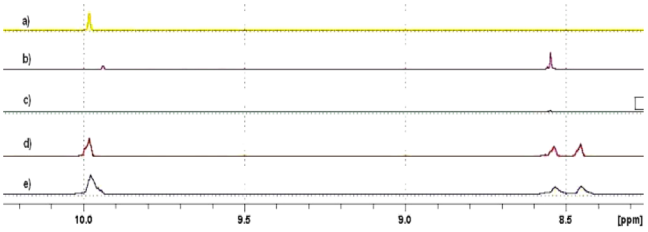


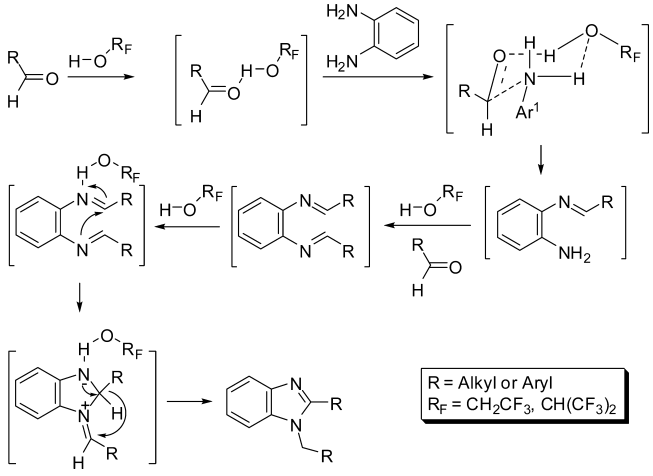
Figure 2. Time-dependent NMR study (δ 8.2−10.2) for reaction of **1a** (1 mmol) with **2a** (2 mmol) in TFE (3 mmol) and MeOH (1 mL): (a) **2a**; (b) reaction mixture in TFE after 5 min; (c) reaction mixture in TFE after 30 min; (d) reaction mixture in MeOH after 5 min; (e) reaction mixture in MeOH after 30 min.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (Table 4, Entry 3). White solid (0.33 g, 96%); mp = 130−131 °C; IR (KBr) ν_{max} = 3005, 2895, 1601, 4586, 1238, 1211, 1177, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.68 (d, J = 8.6 Hz, 3H), 7.44 (d, J = 8.5 Hz, 1H), 7.25−7.19 (m, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.49 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H); MS (APCI) m/z: 345.1 (M + H)$^+$.[10e]

1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-benzimidazole (Table 4, Entry 4, Footnote c). Off-white solid (0.29 g, 85%); mp = 150−152 °C; IR (KBr) ν_{max} = 3015, 2985, 1612, 1476, 1432, 1395, 1285, 1172, 1098; ^{1}H NMR (DMSO, 400 MHz, TMS) δ: 7.86 (d, J = 7.76 Hz, 1H), 7.69 (d, J = 7.96 Hz, 2H), 7.31 (t, J = 6.96 Hz, 1H), 7.26−7.22 (m, 1H), 7.20−7.19 (m, 3H), 7.11 (d, J = 8.04 Hz, 2H), 7.06 (d, J = 7.88 Hz, 2H), 5.44 (s, 2H), 2.32 (s, 3H), 2.29 (s, 3H); MS (EI) m/z: 345.4 (M + H)$^+$.[10n]

2-(2-Methoxyphenyl)-1*H*-benzimidazole (Table 4, Entry 4, Footnotes d and e). Off-white solid (0.168 g, 75% and 0.19 g, 85%, for footnotes d and e, respectively); mp = 176−177 °C; IR (KBr) ν_{max} = 3435, 3028, 1601, 1582, 1485, 1432, 1394, 1280, 1182, 1165, 1095; ^{1}H NMR (DMSO, 400 MHz, TMS) δ: 10.63 (brs, 1H), 8.60 (dd, J = 1.74 and 7.79 Hz, 1H), 7.82 (d, J = 6.65 Hz, 1H), 7.51 (d, J = 6.50 Hz, 1H), 7.46−7.42 (m, 1H), 7.29−7.28 (m, 2H), 7.18−7.14 (m, 1H), 7.09 (d, J = 11.25 Hz, 1H), 4.11 (s, 3H); MS (EI) m/z: 225.4 (M + H)$^+$.[20]

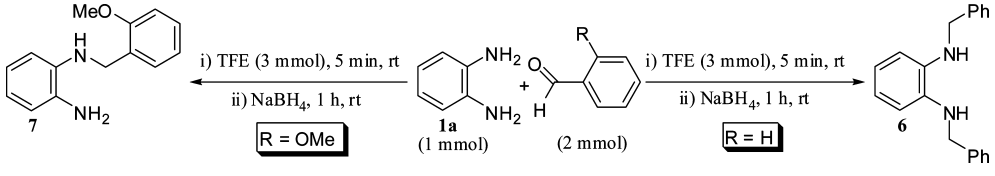
Scheme 5. Hydrogen-Bond-Driven Electrophilic Activation by Fluorous Alcohols for Selective Formation of 1,2-Disubstituted Benzimidazoles



4-[1-{4-(Dimethylamino)benzyl}-1*H*-benzimidazol-2-yl]-*N*,*N*-dimethylaniline (Table 4, Entry 5). White solid (0.35 g, 95%); mp = 254−255 °C; IR (KBr) ν_{max} = 2953, 2895, 1612, 1462, 1422, 1238, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.82 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.26−7.19 (m, 3H), 7.02 (d, J = 7.4 Hz, 2H), 6.73 (d, J = 7.6 Hz, 2H), 6.68 (d, J = 7.5 Hz, 2H), 5.37 (s, 2H), 3.01 (s, 6H), 2.93 (s, 6H). MS (APCI) m/z: 371.4 (M + H)$^+$.[10e]

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzimidazole (Table 4, Entry 6). White solid (0.32 g, 92%); mp = 136−137 °C; IR (KBr) ν_{max} = 2995, 2856, 1605, 1483, 1354, 1221, 1250, 1162, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.89−7.87 (m, 1H), 7.60 (td, J

Scheme 4. Trapping of the Presumably Involved Monoimine/Bisimine Intermediate during the Formation of 2-Substituted and 1,2-Disubstituted Benzimidazoles, Respectively, through Conversion to the Corresponding Reductive Amination Products by Treatment with $NaBH_4$



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= 8.6 and 2 Hz, 2H), 7.45 (td, J = 8.6 and 2.4 Hz, 2 H), 7.37−7.26 (m, 5H), 7.21 (d, J = 7.9 Hz, 1H), 7.05−7.02(m, 2H), 5.41 (s, 2H); MS (APCI) m/z: 354.2 $(M + H)^+$.[10e]

1-(4-Bromobenzyl)-2-(4-bromophenyl)-1*H*-benzimidazole (Table 4, Entry 7). White solid (0.40 g, 93%); mp = 139−141 °C; IR (KBr) ν_{max} = 3021, 2899, 1610, 1595, 1350, 1245, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.87 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.34−7.29 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 7.5 Hz, 2H), 5.38 (s, 2H). MS (APCI) m/z: 440.2 $(M + H)^+$.[10o]

4-[1-(4-Hydroxybenzyl)-1*H*-benzimidazol-2-yl]phenol (Table 4, Entry 8). Off-white solid (0.29 g, 93%); mp = 183−185 °C; IR (KBr) ν_{max} = 3450, 3022, 2895, 1618, 1355, 1242 cm^{-1}; ^1H NMR (DMSO, 400 MHz, TMS) δ: 7.64 (d, J = 6.72 Hz, 1H), 7.55 (d, J = 7.92 Hz, 2H), 7.40 (d, J = 6.72 Hz, 1H), 7.18 (s, 2H), 6.89 (d, J = 7.96 Hz, 2H), 6.81 (d, J = 7.76 Hz, 2H), 6.64 (d, J = 7.76 Hz, 2H), 5.40 (s, 2H). MS (EI) m/z: 318.2 $(M + H)^+$.[10n]

1-[4-(Trifluoromethyl)benzyl]-2-[4-(trifluoromethyl)phenyl]-1*H*-benzimidazole (Table 4, Entry 9). White solid (0.38 g, 90%); mp = 146−147 °C; IR (KBr) ν_{max} = 3019, 2956, 1605, 1586, 1256, 1109, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.91 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.38 (dt, J = 8.1 and 1.1 Hz, 1H), 7.30 (dt, J = 8.1 and 1.1 Hz, 1H), 7.23−7.20 (m, 3H), 5.52 (s, 2H). MS (APCI) m/z: 421.2 $(M + H)^+$.[21]

4-[1-(4-Cyanobenzyl)-1*H*-benzimidazol-2-yl]benzonitrile (Table 4, Entry 10). White solid (0.31 g, 92%); mp = 136−137 °C; IR (KBr) ν_{max} =3031, 2965, 2866, 2229, 2221, 1610, 1485, 1365, 1254, 1165 cm^{-1}; ^1H NMR (DMSO, 400 MHz, TMS) δ: 7.64 (d, J = 6.72 Hz, 1H), 7.55 (d, J = 7.92 Hz, 2H), 7.40 (d, J = 6.72 Hz, 1H), 7.18 (s, 2H), 6.89 (d, J = 7.96 Hz, 2H), 6.81 (d, J = 7.76 Hz, 2H), 6.64 (d, J = 7.76 Hz, 2H), 5.40 (s, 2H). MS (EI) m/z: 318.2 $(M + H)^+$.[10f]

1-(4-Nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzimidazole (Table 4, Entry 11, Footnote f). Yellow solid (0.18 g, 75%); mp = 302−304 °C; IR (KBr) ν_{max} = 2985, 2853, 1610, 1526, 1450, 1375, 1230, 1141, 1052 cm^{-1}; ^1H NMR (DMSO, 400 MHz, TMS) δ: 8.42−8.32 (m, 4H), 8.26 (d, J = 8.48 Hz, 2H), 8.13 (d, J = 7.92 Hz, 1H), 7.36−7.23 (m, 2H), 7.02 (t, J = 7.56 Hz, 1H), 6.75 (d, J = 7.88 Hz, 1H), 6.57 (t, J = 7.48 Hz, 1H), 5.41 (s, 2H); MS (APCI) m/z: 375.2 $(M + H)^+$.[10n]

2-(4-Nitrophenyl)-1*H*-benzoimidazole (Table 4, Entry 11, Footnote g). Yellow solid; mp = 328−329 °C; IR (KBr) ν_{max} = 2985, 2853, 1610, 1526, 1450, 1375, 1230, 1141, 1052 cm^{-1}; ^{1} H NMR (DMSO, 400 MHz, TMS) δ: 8.53 (brs, 1H), 8.30 (s, 2H), 8.03 (d, J = 3.2 Hz, 2H), 7.33−7.22 (m, 4H). MS (APCI) m/z: 240.4 $(M + H)^+$.[10f]

1-[4-(Benzyloxy)benzyl]-2-(4-(benzyloxy)phenyl]-1*H*-benzimidazole (Table 4, Entry 12). White solid (0.46 g, 93%); mp = 127−128 °C; IR (KBr) ν_{max} = 3034, 2985, 2859, 1612, 1515, 1450, 1325, 1256, 1176, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.83 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.44−7.27 (m, 11H), 7.22−7.20 (m, 2H), 7.05−7.01 (m, 4H), 6.92 (d, J = 8.3 Hz, 2H), 5.38 (s, 2H), 5.11 (s, 2H), 5.03 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 160.1, 158.3, 154.1, 143.1, 136.7, 136.5, 136.1, 130.7, 128.74, 128.67, 128.6, 128.1, 128.0, 127.5, 127.2, 122.8, 122.7, 122.5, 119.7, 115.3, 115.1, 110.4, 70.1, 47.9. MS (APCI) m/z: 497.5 $(M + H)^+$; Anal. Calcd For $C_{34}H_{28}N_2O_2$: C, 82.23; H, 5.68; N, 5.64%. Found: C, 82.25; H, 5.67; N, 5.66%.

4-[1-(4-(Benzoyloxy)benzyl)-1*H*-benzimidazol-2-yl]phenyl Benzoate (Table 4, Entry 13). White solid (0.48 g, 92%); mp = 164−166 °C; IR (KBr) ν_{max} = 3025, 2980, 2848, 1603, 1509, 1338, 1245, 1196, 1068 cm^{-1}; ^1H NMR (DMSO, 400 MHz, TMS) δ: 8.23−8.18 (m, 5H), 8.10 (d, J = 8.64 Hz, 1H), 7.88 (d, J = 7.84 Hz, 1H), 7.79−7.76 (m, 2H), 7.70−7.62 (m, 3H), 7.54−7.49 (m, 4H), 7.37−7.31 (m, 3H), 7.28−7.23 (m, 3H), 5.51 (s, 2H); MS (EI) m/z: 525.3 $[M + H^+]$. ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 165.1, 164.9, 153.4, 152.3, 150.5, 143.0, 136.0, 133.8, 133.7, 130.5, 130.3, 130.2, 129.3, 129.2, 128.7, 128.6, 127.9, 127.6, 127.1, 123.4, 123.0, 122.5, 122.3, 120.0, 110.6, 48.0; MS (EI) m/z: 517.5 $(M + H)^+$. Anal. Calcd For $C_{34}H_{24}N_2O_4$: C, 77.85; H, 4.61; N, 5.34; O, 12.20%. Found: 77.86; H, 4.63; N, 5.35%.

4-[1-(4-Acetoxybenzyl)-1*H*-benzimidazol-2-yl]phenyl Acetate (Table 4, Entry 14). White solid (0.43 g, 90%); mp = 154−155 °C; IR (KBr) ν_{max} = 3028, 2990, 2862, 1756, 1748, 1608, 1520, 1320, 1250, 1168, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.86 (d, J = 7.96 Hz, 1H), 7.71−7.67 (m, 2H), 7.34−7.30 (m, 1H), 7.27−7.23 (m, 1H), 7.21−7.18 (m, 3H), 7.12−7.10 (m, 2H), 7.07−7.05 (m, 2H), 5.44 (s, 2H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 169.4, 169.1, 153.2, 151.9, 150.2, 143.1, 136.0, 133.7, 130.4, 127.5, 126.9, 123.3, 122.9, 122.3, 122.1, 120.0, 110.5, 47.9, 21.2, 21.1. MS (EI) m/z: 402.3 $(M + H)^+$. Anal. Calcd For $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00; O, 15.98%. Found: C, 72.00; H, 5.05; N, 7.03%.

1-[4-(*tert*-Butoxycarbonyloxy)benzyl]-2-[4-(*tert*-butoxycarbonyloxy)phenyl]-1*H*-benzimidazole (Table 4, Entry 15). White solid (0.49 g, 95%); mp = 135−136 °C; IR (KBr) ν_{max} = 3030, 2986, 2868, 1760, 1754, 1610, 1516, 1254, 1166, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.89 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 2H), 7.32−7.25 (m, 4H), 7.20−7.15 (m, 3H), 7.10 (d, J = 8.2 Hz, 2H), 5.43 (s, 2H), 1.56 (s, 9H), 1.55 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 153.2, 152.5, 151.7, 151.3, 135.8, 133.5, 131.5, 130.4, 127.1, 126.9, 123.4, 123.0, 122.0, 121.7, 120.9, 119.9, 110.5, 84.0, 83.8, 47.9, 27.7. MS (EI) m/z: 516.3 $(M + H)^+$. Anal. Calcd For $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42; O, 18.58%. Found: C, 69.78; H, 6.26; N, 5.43%.

1-[4-(*tert*-Butyldimethylsilyloxy)benzyl]-2-[4-(*tert*-butyldimethylsilyloxy)phenyl]-1*H*-benzimidazole (Table 4, Entry 16). Colorless liquid (0.51 g, 95%); IR (KBr) ν_{max} = 3035, 2986, 2862, 1615, 1450, 1338, 1268, 1186 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.83 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.30−7.21 (m, 3H), 6.96 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 7.9 Hz, 2H), 5.37 (s, 2H), 0.99 (s, 9H), 0.96 (s, 9H), 0.22 (s, 6H), 0.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 157.3, 155.2, 154.2, 143.1, 136.1, 130.7, 129.1, 127.3, 123.1, 122.7, 122.5, 120.5, 120.4, 119.7, 110.4, 48.0, 25.6, 18.25, 18.2, −4.39, −4.43. MS (EI) m/z: 545.2 $(M + H)^+$. Anal. Calcd For $C_{32}H_{44}N_2O_2Si_2$: C, 70.54; H, 8.14; N, 5.14; O, 5.87; Si, 10.31%. Found: C, 70.58; H, 8.17; N, 5.17%.

1-(3,5-Dimethoxybenzyl)-2-(3,5-dimethoxyphenyl)-1*H*-benzimidazole (Table 4, Entry 17). Semisolid (0.92 g, 91%); IR (KBr) ν_{max} = 3042, 2985, 2796, 1745, 1704, 1642, 1498, 1255, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.87 (d, J = 7.7 Hz, 1H), 7.27−7.39 (m, 3H), 6.85 (d, J = 2.2 Hz, 2H), 6.38−6.56 (m, 2H), 6.28 (d, J = 1.6 Hz, 2H), 5.40 (s, 2H), 3.78 (s, 6H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 161.4, 160.9, 154.0, 142.7, 139.0, 136.2, 131.4, 125.3, 122.9, 119.8, 110.5. 107.0, 104.4, 104.1, 102.8, 99.2, 55.3, 48.4.; MS (APCI) m/z: 405.2 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2O_4Na^+$ $[M + Na^+]$, 427.1628; Found 427.1625.

1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1*H*-benzimidazole (Table 4, Entry 18). White solid (0.93 g, 92%); mp = 142−144 °C; IR (KBr) ν_{max} = 3196, 2940, 2785, 1750, 1710, 1650, 1496, 1265, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.86 (d, J = 8 Hz, 1H), 7.29−7.21 (m, 5H), 6.92−6.93 (m, 1H), 6.81 (d, J = 4.9 Hz, 1H), 6.65 (d, J = 9.8 Hz, 2H), 5.40 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 154.1, 150.4, 149.5, 149.0, 148.5, 143.0, 136.3, 129.0, 126.0, 124.3, 222.9, 122.6, 122.5, 121.8, 119.7, 118.0, 112.3, 111.5, 110.9, 110.3, 108.9, 108.8, 55.9, 48.1. MS (APCI) m/z: 405.6 $(M + H)^+$. HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2O_4Na^+$ $[M + Na^+]$, 427.1628; Found 427.1629.

2-Ethoxy-3-((2-(3-ethoxy-4-hydroxyphenyl)-1*H*-benzo[*d*]-imidazol-1-yl)methyl)phenol (Table 4, Entry 19). White solid (0.91 g, 90%); mp = 200−201 °C; IR (KBr) ν_{max} = 3162, 2948, 27866, 1748, 1721, 1623, 1472, 1258, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 9.56 (s, 1H, OH), 8.96 (s, 1H, OH), 7.65−7.67 (m, 1H), 7.46−7.49 (m, 1H), 7.17−7.23 (m, 4H), 6.92 (d, J = 8.0 Hz, 1H), 6.62−6.67 (m, 2H), 6.36−6.38 (m, 1H), 5.42 (s, 2H), 3.91−3.96 (m, 2H), 3.81−3.86 (m, 2H), 1.22−1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 154.0, 148.9, 147.2, 147.1, 146.6, 142.9, 136.4, 128.3, 122.7, 122.5, 122.3, 121.5, 119.3, 119.0, 116.1, 116.0, 114.5, 112.2, 111.3, 64.2, 47.7, 15.1. MS (APCI) m/z: 405.5 $(M + H)^+$;

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HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2O_4Na^+$ [M + Na^+], 427.1628; Found 427.1625,

2-(Pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1*H*-benzimidazole (Table 4, Entry 20). White solid (0.26 g, 93%); mp = 129−130 °C; IR (KBr) ν_{max} = 3026, 2985, 2856, 1620, 1595, 1463, 1445, 1389, 1285, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 8.60−8.57 (m, 2H), 8.49−8.46 (m, 1H), 7.88−7.82 (m, 2 H), 7.49 (dt, J = 7.7 and 1.8 Hz, 1H), 7.38−7.36 (m, 1H), 7.33−7.24 (m, 3H), 7.16−7.13 (m, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.30 (s, 2H); MS (APCI) m/z: 287.3 $(M + H)^+$.[10e]

2-(Furan-2-yl)-1-(furan-2-ylmethyl)-1*H*-benzimidazole (Table 4, Entry 21). White solid (0.25 g, 93%); mp = 94−95 °C ; IR (KBr) ν_{max} = 3091, 2895, 1605, 1514, 1450, 1375, 1106, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.79−7.77 (m, 1H), 7.65 (s, 1H), 7.51−7.49 (m, 1H), 7.33−7.29 (m, 3H), 7.21 (d, J = 3.4 Hz, 1H), 7.61(t, J = 1.7 Hz, 1H), 6.28−6.23 (m, 2H), 5.64 (s, 2H); MS (APCI) m/z: 265.3 $(M + H)^+$.[10e]

2-(Thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1*H*-benzimidazole (Table 4, Entry 22). White solid (0.27 g, 92%); mp = 146−147 °C; IR (KBr) ν_{max} = 3024, 2884, 1615, 1525, 1425, 1362, 1282, 1161, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.84−7.82 (m, 1H), 7.52 (dd, J = 5.1 and 1.0 Hz, 1H), 7.47 (dd, J = 3.7 and 1 Hz, 1H), 7.38−7.36 (m, 1H), 7.33−7.28 (m, 2H), 7.24 (dd, J = 5.2 and 1.2 Hz, 1H), 7.15−7.13 (m, 1H), 6.95−6.93 (m, 1H), 6.87−6.86 (m, 1H), 5.71 (s, 2H); MS (APCI) m/z: 297.2 $(M + H)^+$.[10o]

1-((1*H*-Indol-3-yl)methyl)-2-(1*H*-indol-3-yl)-1*H*-benzimidazole (Table 4, Entry 23). Brown solid (0.32 g, 89%); mp = 254−256 °C; IR (KBr) ν_{max} = 3025, 2956, 1610, 1590, 1356, 1255, 1101, 1058 cm^{-1}; ^{1} H NMR (DMSO, 400 MHz, TMS) δ: 11.66 (s, 1H), 11.00 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.86 (s, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.54 (d, J = 7.1 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.26−7.13 (m, 5H), 7.03−7.01 (m, 2H), 6.83 (d, J = 7.4 Hz, 1H), 5.82 (s, 2H); MS (APCI) m/z: 363.2 $(M + H)^+$.[10f]

2-(Naphthalen-2-yl)-1-(naphthalen-2-ylmethyl)-1*H*-benzimidazole (Table 4, Entry 24). White solid (0.35 g, 92%); mp = 124−126 °C; IR (KBr) ν_{max} = 3055, 2899, 1602 1438, 1370, 1324, 1252, 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 8.20 (S, 1H), 7.94 (d, J = 8 Hz, 1H), 7.91−7.83 (m, 5H), 7.75−7.70 (m, 2H), 7.57 (s, 1H), 7.55−7.46 (m, 4H), 7.37−7.23 (m, 4H), 5.67 (s, 2H); MS (APCI) m/z: 385.3 $(M + H)^+$.[10g]

1-Cinnamyl-2-styryl-1*H*-benzimidazole (Table 4, Entry 25). Light red color oil (0.30 g, 90%); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 8.00 (d, J = 15.8 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.3 Hz, 2H), 7.39−7.20 (m, 11H), 7.09 (d, J = 15.8 Hz, 1H), 6.44−6.31 (m, 2H), 5.03 (d, J = 4.7 Hz, 2H); MS (EI) m/z: 336.2 $(M + H)^+$.[21]

2-Cyclohexyl-1-(cyclohexylmethyl)-1*H*-benzimidazole (Table 4, Entry 23). White solid (0.27 g, 91%); mp = 91−92 °C; IR (KBr) ν_{max} = 3011, 2956, 1611, 1445, 1325, 1228, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.76−7.71 (m, 1H), 7.31−7.27 (m, 1H), 7.23−7.18 (m, 2H), 3.91 (d, J = 7.4 Hz, 2H), 2.81−2.77 (m, 1H), 1.94−1.62 (m, 13H), 1.43−1.38 (m, 3H), 1.19−1.15 (m, 3H), 1.09−1.03 (m, 2H); MS (APCI) m/z: 297.4 $(M + H)^+$.[10j]

1-Butyl-2-propyl-1*H*-benzimidazole (Table 4, Entry 27). White solid (0.19 g, 89%); mp = 128−130 °C; IR (KBr) ν_{max} = 3035, 2868, 1610, 1518, 1416, 1259, 1186, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ: 7.75−7.71 (m, 1H), 7.33−7.29 (m, 1H), 7.26−7.22 (m, 2H), 4.10 (t, J = 7.48 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 1.99−1.90 (m, 2H), 1.83−1.75 (m, 2H), 1.46−1.36 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H). MS (EI) m/z: 217.2 $(M + H)^+$. [10l]

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra for all compounds.. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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