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Microwave-Assisted Nickel-Catalyzed Synthesis of Benzimidazoles: Ammonia as a Cheap and Nontoxic Nitrogen Source

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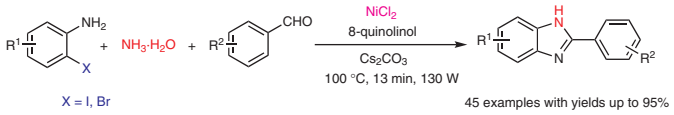

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Abstract An efficient and convenient Ni-catalyzed C–N bond formation for the synthesis of various benzimidazoles from various 2-haloanilines, aldehydes, and ammonia in a concise manner is reported. This protocol uses commercially available, nonhazardous, clean ammonia as a reaction partner instead of other nitrogen sources. Benzimidazoles, as the sole products, were obtained in high to excellent yields (up to 95%).

Key words nickel catalysis, C–N bond formation, benzimidazoles, microwave heating, ammonia

Benzimidazoles are important building blocks found in many biologically and therapeutically active compounds, natural products, and functional materials.[1] They show medicinal activities such as anticonvulsant, anticancer, antiulcer, antihypertensive, antibacterial, and antihistaminic properties (Figure 1).[2] In addition, they have applications in the fields of dyes, chemosensing, and fluorescence.[3] Therefore, many synthetic techniques for accessing these particular heterocycles have become established in recent years. The majority of the reported procedures for synthesizing benzimidazoles rely on the reactions of *o*-phenylenediamines with carboxylic acids, acid chlorides, or carbaldehydes in the presence of acids and oxidizing agents at elevated temperature [Scheme 1(a)].[4] However, many of these reported procedures suffer from harsh reaction conditions, prolonged reaction times, and environmentally unfriendly media. Therefore, the development of mild and efficient protocols for synthesizing these valuable heterocyclic entities remains a challenging problem.

During recent decades, efficient syntheses of benzimidazoles from 2-haloacetanilides,[5a] arylbenzimidamides,[5b] 2-haloarylamidines,[5c] or arylamino oximes[5d] have been reported [Scheme 1(b)]. Syntheses of benzimidazoles catalyzed by various transition metals, such as Fe, Co, Zn, Cu, Ce, or Pd, have also been developed.[6] Although the reactions are efficiently promoted by these catalysts, some of these methods have one or more shortcomings, such as the use of stoichiometric or larger quantity of reagents, the need for additives and/or harsh conditions, or the occurrence of side reactions. Consequently, there is a need for a cheap, clean, transition-metal-catalyzed, convenient reaction to increase the atom economy of the process. In this respect, nickel emerges as an important catalyst in the view of its abundance and low cost. In 2003, Schneider and Fort and their co-workers reported a method that uses Ni catalysts to synthesize indoles, quinolines, benzazepines, and benzoxazepines through intramolecular coupling of aryl chlorides with amines.[7] Unfortunately, Ni catalysts have rarely been used in studies on benzimidazoles.

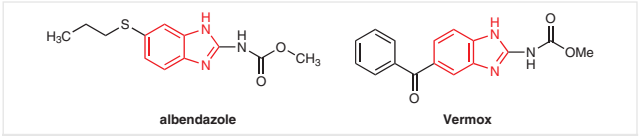
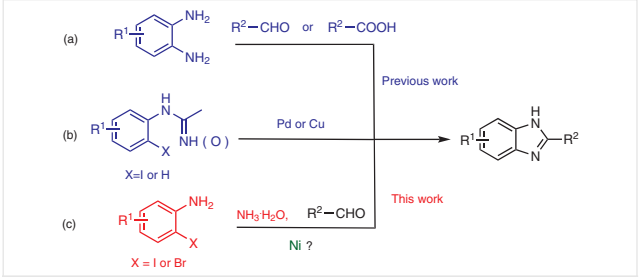


Figure 1 Marketed drugs containing a benzimidazole moiety



Scheme 1 Various synthetic routes to benzimidazoles derivatives

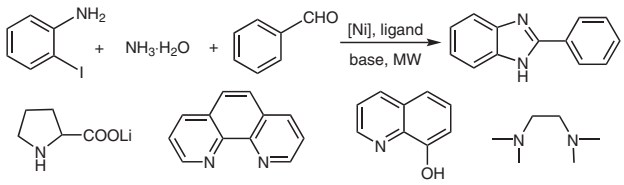
Unlike other nitrogen containing-compounds such as amidine hydrochlorides,[8a] 2-aminobenzylamines,[8b] NaN_3,[8c] or nitriles[8d] that can act as nitrogen sources for the synthesis of organic amino compounds, ammonia is among the most abundant and least expensive inorganic chemicals. In 2009, Xia and Taillefer discovered a simple and efficient method for transforming aryl iodides or bromides into aniline derivatives by using ammonia in the presence of $Cu(acac)_2$ as a catalyst in one step.[9] Ma and co-workers reported the synthesis of benzimidazoles by a CuI/L-proline catalyzed coupling of aqueous ammonia with 2-iodoacetanilides.[5a] The successful use of ammonia as a nitrogen source in the one-pot synthesis of aniline derivatives suggested the possibility of the synthesis of benzimidazoles from ammonia. In addition, microwave irradiation is of great importance in the context of green synthesis and sustainable chemistry, and the combination of microwave heating and the absence of an organic solvent is a way forward in future green catalytic protocols.

In a continuation of our ongoing researches,[10] we report an economical and simple microwave-assisted nickel-catalyzed protocol for the synthesis of benzimidazoles by using 2-haloanilines, ammonia, and aldehydes [Scheme 1(c)]. To the best of our knowledge, there has been no report of a Ni-catalyzed C–N bond formation for the synthesis of benzimidazoles.

We started our investigation by using 2-iodoaniline, ammonia, and benzaldehyde as model reactants, and we determined the optimal conditions for the reaction (Table 1). Initially, among the various nickel salts tested with the same ligand **L1**, $NiCl_2$ exhibited a higher catalytic ability than did $Ni(NO_3)_2$, $Ni(OAc)_2$, $NiSO_4$, or $Ni(OH)_2$ (Table 1, entries 1–5). Screening of several ligands (entries 5–8) indicated the most suitable one was **L3** (entry 7), indicating that the specific structures of quinolin-8-ol might be the key to a successful catalyst system. Note that in control experiments, no significant promotion was observed under similar reaction conditions in the absence of $NiCl_2$ and that only a trace of the product was obtained under ligand-free conditions (entries 9 and 10). The experiments showed that various widely used bases such as Na_2CO_3 and K_2CO_3 had a remarkable effect on the reactions, and that $Cs_2CO_3$was the best among the bases tested (entries 11–15). Further experiments revealed that lowering the reaction temperature to less than 100 °C had a negative effect on the reaction (entry 16), and that a reaction time of around 13 minutes was optimal (entry 19). Thus, the optimal catalytic conditions involve the use of 10 mol% $NiCl_2$ and ligand **L3** with Cs_2CO_3 as an additive at 100 °C for 13 minutes with irradiation by microwaves at 130 W (entry 19).

Having established the optimal reaction conditions, we turned our attention to exploring the scope of the method. As shown in Table 2, various 2-haloanilines and aldehydes were transformed into the corresponding benzimidazoles

Table 1 Optimization of the Catalytic Reaction[a]



L1 L2 L3 L4

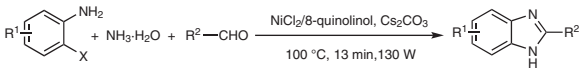
Entry	Ni source	Ligand	Base	Temp (°C)	Time (min)	Yield[b] (%)
1	$Ni(NO_3)_2$	**L1**	NaOH	100	15	63
2	$Ni(OAc)_2$	**L1**	NaOH	100	15	48
3	$NiSO_4$	**L1**	NaOH	100	15	35
4	$Ni(OH)_2$	**L1**	NaOH	100	15	23
5	$NiCl_2$	**L1**	NaOH	100	15	67
6	$NiCl_2$	**L2**	NaOH	100	15	64
7	$NiCl_2$	**L3**	NaOH	100	15	85
8	$NiCl_2$	**L4**	NaOH	100	15	46
9	$NiCl_2$	–	NaOH	100	15	10
10	–	**L3**	NaOH	100	15	trace
11	$NiCl_2$	**L3**	KOH	100	15	72
12	$NiCl_2$	**L3**	K_2CO_3	100	15	87
13	$NiCl_2$	**L3**	Na_2CO_3	100	15	80
14	$NiCl_2$	**L3**	Cs_2CO_3	100	15	92
15	$NiCl_2$	**L3**	–	100	15	trace
16	$NiCl_2$	**L3**	Cs_2CO_3	90	15	69
17	$NiCl_2$	**L3**	Cs_2CO_3	110	15	88
18	$NiCl_2$	**L3**	Cs_2CO_3	100	11	86
19	**$NiCl_2$**	**L3**	**Cs_2CO_3**	**100**	**13**	**92**

[a] Reaction conditions: 2-iodoaniline (0.5 mmol), PhCHO (0.6 mmol), 25–28% aq NH_3 (2 mL), Ni source (10 mol%), ligand (10 mol%), base (1.0 mmol), MW (130 W).
[b] Determined by GC with 1,4-dichlorobenzene as internal standard.

in high to excellent yields of 76 to 95%. These studies clearly revealed that substrates having electron-donating and electron-withdrawing groups are compatible with this process, affording the corresponding substituted benzimidazoles in high yields. 2-Bromanilines also reacted with ammonia and aldehydes under the same conditions, albeit with slightly lower yields than the corresponding 2-iodoanilines. Note that the reaction is absolute clean, producing 2-substituted benzimidazoles exclusively, with no byproducts being detected. Electron-donating *o*-haloanilines as substrates appeared to be more suitable for the catalysis (Table 2, entries 2–9). We then examined the general applicability of this method to a variety of aldehydes. Aldehydes bearing electron-donating groups gave better results than did those with electron-withdrawing groups (entries 10–14). This is because an aldehyde with a strongly electron-donating sub-

stituent (OMe; entry 11) forms the corresponding *N*-phenylformimine more readily than does an aldehyde with an electron-withdrawing group substituent.

Table 2 Substrate Scope[a]

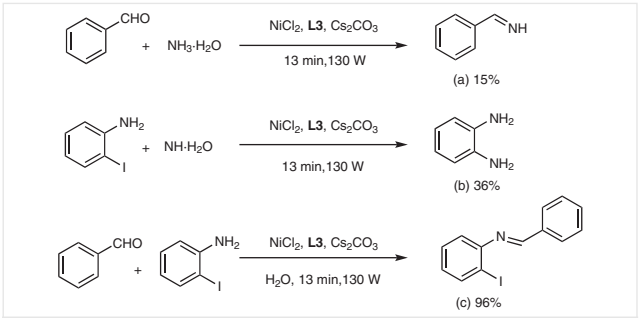


Entry	R^1	R^2	Product	Yield[b] (%)
1	H	Ph	**2a**	92 (X = I) 83 (X = Br)
2	4-O_2N	Ph	**2b**	82 (X = I) 78 (X = Br)
3	4-Cl	Ph	**2c**	89 (X = I) 83 (X = Br)
4	4-Br	Ph	**2d**	84 (X = I) 76 (X = Br)
5	4-Me	Ph	**2e**	95 (X = I) 86 (X = Br)
6	4-Me	3-pyridyl	**2f**	92 (X = I) 78 (X = Br)
7	4-Me	2-FC_6H_4	**2g**	86 (X = I) 79 (X = Br)
8	4-Me	2,4-$Me_2C_6H_3$	**2h**	89 (X = I) 81 (X = Br)
9	4,5-dichloro	Ph	**2i**	84 (X = I) 76 (X = Br)
10	H	4-Tol	**2j**	93 (X = I) 82 (X = Br)
11	H	4-$MeOC_6H_4$	**2k**	95 (X = I) 81 (X = Br)
12	H	4-ClC_6H_4	**2l**	92 (X = I) 79 (X = Br)
13	H	4-$O_2NC_6H_4$	**2m**	89 (X = I) 78 (X = Br)
14	H	2-ClC_6H_4	**2n**	87 (X = I) 78 (X = Br)
15	H	2-FC_6H_4	**2o**	85(X = I) 76 (X = Br)
16	H	2-HOC_6H_4	**2p**	92 (X = I) 80 (X = Br)
17	H	3-FC_6H_4	**2r**	85 (X = I) 79 (X = Br)
18	H	3-NCC_6H_4	**2s**	89 (X = I) 81 (X = Br)
19	H	3-hydroxy-4-methoxyphenyl	**2t**	88 (X = I) 81 (X = Br)
20	H	2-pyridyl	**2u**	82 (X = I) 77 (X = Br)
21	H	*i*-Pr	**2v**	85 (X = I) 79 (X = Br)
22	H	CH(Me)Pr	**2w**	82 (X = I) 77 (X = Br)

[a] Reaction conditions: haloaniline (0.5 mmol), ArCHO (0.6 mmol), 25–28% aq NH_3 (2 mL), $NiCl_2$ (10 mol%), **L3** (10 mol%), Cs_2CO_3(1.0 mmol), MW (130 W), 100 °C, 13 min.
[b] Isolated yield.

Moreover, the good yields obtained in the reactions of 4-chloro-2-iodoaniline and 4-bromo-2-iodoaniline implied that there was good chemoselectivity between iodide, bromide, and chloride functional groups (Table 2, entries 3, 4, and 9). Furthermore, the catalytic system also tolerated a variety of functional groups, including nitro, cyanide, methyl, methoxy, and hydroxy groups. Heterocyclic compound, such as pyridine-2-carboxaldehyde, also afforded the corresponding products in good yields (entry 20). The protocol was also equally efficient towards nonactivated aliphatic aldehydes (entries 21 and 22).

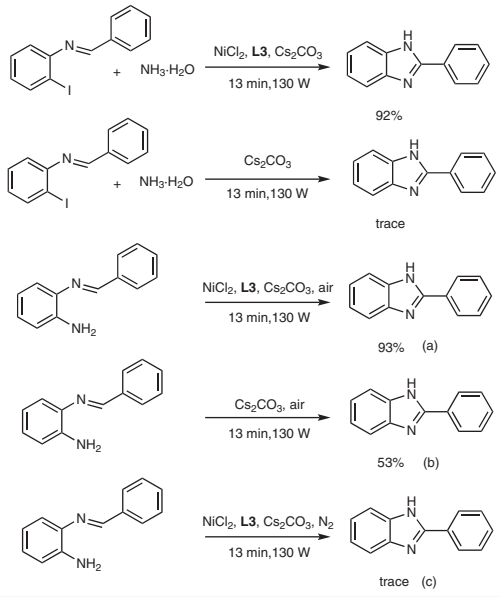
Preliminary mechanistic studies of the reaction were next conducted. As a first step, we turned our attention to exploring the possible intermediates in the reaction under the optimal catalytic conditions. The results are shown in Scheme 2.



Scheme 2 Formation of possible intermediates

Among the reactions shown in Scheme 2, we found that the reaction of benzaldehyde with 2-iodoaniline gave the best yield of an intermediate (a 96% yield of the corresponding *N*-phenylformimine), indicating that this is an intermediate in the reaction. The second step is the reaction of the *N*-phenylformimine with ammonia, as shown in Scheme 3. We found that $NiCl_2$ and quinolin-8-ol are extremely important, and that the reaction does not proceed in the absence of either. Finally, we conducted a study on the intermediate **III**. The yield of the desired product 2-phenyl-1*H*-benzimidazole reached 93% only when $NiCl_2$ was added to the reaction under an air atmosphere [Scheme 3(a)]. In the absence of $NiCl_2$, the yield decreased substantially [Scheme 3(b)]. Moreover, the reaction did not proceed under a N_2 atmosphere [Scheme 3(c)]. Therefore, $NiCl_2$ and O_2 are essential for the reaction to occur.

On the basis of these results and reports in the literature,[11] a possible reaction pathway for the synthesis of benzimidazoles is proposed, as shown in Scheme 4. Initially, 2-iodoaniline and benzaldehyde react to form an *N*-phenylformimine. Then, Ni(II)-catalyzed intermolecular N-arylation between the *N*-phenylformimine and ammonia provides the Ni(IV) intermediate **II**.[11d] Intermediate **III** then undergo intramolecular addition to produce intermediate

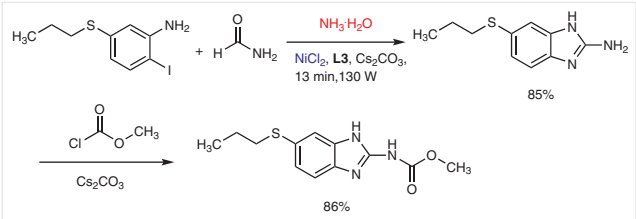


Scheme 3 Control experiments

IV.[11e–g] In the final step, the dihydrobenzimidazole **IV** undergoes $NiCl_2$-catalyzed oxidation by atmospheric oxygen to form the benzimidazole product.[11h]

Finally, the catalytic system was extended to a synthesis of albendazole, an efficient and low-toxicity broad-spectrum anthelmintic, in a good total yield of 73% (Scheme 5). This product was formerly obtained by a more-complicated multistep procedure.

In summary, we have developed an efficient, clean and inexpensive catalytic protocol for the synthesis of benzimidazoles from 2-haloanilines, ammonia, and aldehydes in the presence of $NiCl_2$ and 8-hydroxyquinoline as a robust catalytic system under mild reaction conditions.[12] This catalytic system provides an attractive method for the synthesis of wide range of benzimidazoles by using ammonia as the nitrogen source. This protocol further expands the scope of nickel-catalyzed C–N bond-formation reactions.



Scheme 5 Synthesis of albendazole

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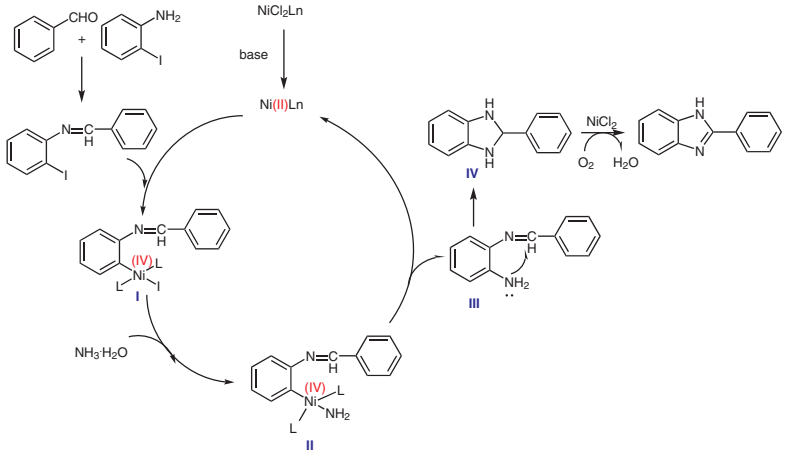
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610843.

References and Notes

(1) (a) Yadav, G.; Ganguly, S. *Eur. J. Med. Chem.* **2015**, *97*, 419. (b) Schiffmann, R.; Neugebauer, A.; Klein, C. D. *J. Med. Chem.* **2006**, *49*, 511. (c) Verma, R. P. *Bioorg. Med. Chem.* **2005**, *13*, 1059. (d) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208. (e) Narasimhan, B.; Sharma, D.; Kumar, P. *Med. Chem. Res.* **2012**, *21*, 269. (f) Ziarati, A.; Badiei, A.; Ziarani, G. M.; Eskandarloo, H. *Catal. Commun.* **2017**, *95*, 77.

(2) (a) Hu, L.; Kully, M. L.; Boykin, D. W.; Abood, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3374. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 4338. (d) Majik, M. S.; Tilvi, S.; Mascarenhas, S.; Kumar, V.;



Scheme 4 Proposed reaction mechanism

Chatterjee, A.; Banerjee, M. *RSC Adv.* **2014**, *4*, 28259. (e) Sharma, P.; Reddy, T. S.; Kumar, N. P.; Senwar, K. R.; Bhargava, S. K.; Shankaraiah, N. *Eur. J. Med. Chem.* **2017**, *138*, 234.

(3) (a) Song, W.; Shi, L.; Gao, L.; Hu, P.; Mu, H.; Xia, Z.; Huang, J.; Su, J. *ACS Appl. Mater. Interfaces* **2018**, *10*, 5714. (b) Bouwman, E.; Driessen, W. L.; Reedijk, J. *Coord. Chem. Rev.* **1990**, *104*, 143.

(4) (a) Hu, Z.; Zhao, T.; Wang, M.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.* **2017**, *82*, 3152. (b) Ghosh, P.; Subba, R. *Tetrahedron Lett.* **2015**, *56*, 2691. (c) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Catal. Commun.* **2007**, *8*, 1126. (d) Shelkar, R.; Sarode, S.; Nagarkar, J. *Tetrahedron Lett.* **2013**, *54*, 6986.

(5) (a) Diao, X.; Wang, Y.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 7974. (b) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem. Eur. J.* **2009**, *15*, 7292. (c) Deng, X.; Mani, N. S. *Eur. J. Org. Chem.* **2010**, 680. (d) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576.

(6) (a) Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, 1380. (b) Chari, M. A.; Shobha, D.; Sasaki, T. *Tetrahedron Lett.* **2011**, *52*, 5575. (c) Nale, D. B.; Bhanage, B. M. *Synlett* **2015**, *26*, 2835. (d) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742. (e) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *7*, 8719. (f) Lygin, A. V.; de Meijere, A. *Eur. J. Org. Chem.* **2009**, 5138. (g) Martins, G. M.; Puccinelli, T.; Gariani, R. A.; Xavier, F. R.; Silveira, C. C.; Mendes, S. R. *Tetrahedron Lett.* **2017**, *58*, 1969. (h) De Luca, L.; Porcheddu, A. *Eur. J. Org. Chem.* **2011**, 5791.

(7) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311.

(8) (a) Qu, Y.; Pan, L.; Wu, Z.; Zhou, X. *Tetrahedron* **2013**, *69*, 1717. (b) Saha, M.; Mukherjee, P.; Das, A. R. *Tetrahedron Lett.* **2017**, *58*, 1046. (c) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577. (d) Yu, J.; Xia, Y.; Lu, M. *Appl. Organomet. Chem.* **2014**, *28*, 764.

(9) Xia, N.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 337.

(10) (a) Ke, F.; Chen, X.; Li, Z.; Xiang, H.; Zhou, X. *RSC Adv.* **2013**, *3*, 22837. (b) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* **2011**, *13*, 454. (c) Li, Z.; Ke, F.; Deng, H.; Xu, H.; Xiang, H.; Zhou, X. *Org. Biomol. Chem.* **2013**, *11*, 2943.

(11) (a) Chen, Z.; Li, H.; Cao, G.; Xu, J.; Miao, M.; Ren, H. *Synlett.* **2017**, *28*, 504. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (c) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922. (d) Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* **2007**, *72*, 5069. (e) Sutapin, C.; Chirachanchai, S. *Synth. Commun.* **2018**, *48*, 650. (f) Sharghi, H.; Asemani, O.; Khalifeh, R. *Synth. Commun.* **2008**, *38*, 1128. (g) Zhang, C.; Zhang, L.; Jiao, N. *Green Chem.* **2012**, *14*, 3273. (h) Yu, J.; Lu, M. *Res. Chem. Intermed.* **2016**, *42*, 471.

(12) **Benzimidazoles 2a–w; General Procedure**

A 10 mL glass tube was charged with the appropriate 2-haloaniline (0.5 mmol), 25–28% aq NH_3 (2 mL), the appropriate aldehyde (0.6 mmol), $NiCl_2$ (11.88 mg, 0.05 mmol), quinolin-8-ol (7.258 mg, 0.05 mmol), and Cs_2CO_3 (325.82 mg, 1.0 mmol). The vessel was then sealed with a septum and placed in the cavity of a Discover microwave synthesizer (CEM Corp., Buckingham, UK), and irradiated at 130 W. The temperature was ramped from r.t. to the desired temperature of 100 °C, then held at this temperature for 13 min. The mixture was stirred continuously during the reaction. The mixture was then allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) to afford the corresponding product. The structures of the products were confirmed by NMR and MS spectroscopic analyses.

2-Phenyl-1*H*-benzo[*d*]imidazole (2a)

Light-yellow solid; yield: 89.24 mg (92%). ^{1}H NMR (400 MHz, MeCN-d_3): δ = 7.26–7.28 (m, 2 H), 7.55–7.64 (m, 5 H), 8.13 (d, *J* = 4.0 Hz, 2 H), 10.96 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.70, 144.29, 135.48, 130.65, 130.30, 129.42, 126.91, 123.00, 122.14, 119.35, 111.79. ESI-MS: *m/z* = 195.1 $[M + H]^+$.