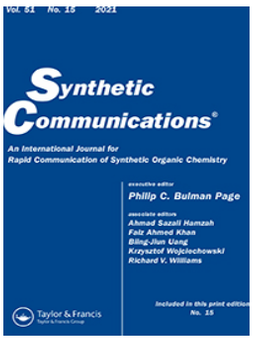

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Convenient synthesis of *N*-1-alkyl benzimidazoles via Pd catalyzed C–N bond formation and cyclization

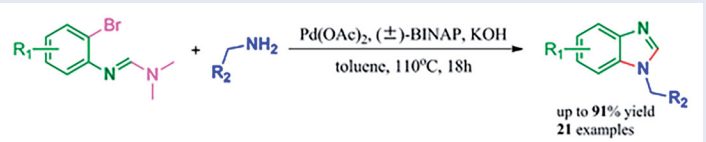
Fusheng Bie[a], Yongfeng Yao[b], Han Cao[a], Yijun Shi[a], Peng Yan[a], Jie Ma[a], Ying Han[a], and Xuejing Liu[a]

[a]Engineering and Technology Institute of LuNan Coal Chemical Engineering, ZaoZhuang University, Zaozhuang, P. R. China; [b]Zaozhuang Ecological Environment Monitoring Center, Zaozhuang, P. R. China

ABSTRACT

N-1-Alkyl-2-unsubstituted benzimidazoles were directly synthesized by intermolecular coupling of formimidamides with benzylamines; the syntheses were catalyzed by $Pd(OAc)_2$ in one pot, giving rise to moderate to good yields. Aromatic formamidines with various substituents as starting materials could be readily prepared from the reactions of the corresponding anilines and *N,N*-dimethylformamide dimethyl acetal in high yields.

GRAPHICAL ABSTRACT



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KEYWORDS
Aromatic formamidine; benzimidazole; catalysis; cyclization; palladium

Introduction

Benzimidazole scaffolds have played important roles in bioactive natural products, synthetic drugs, and agricultural chemicals after being discovered as the integral part of the structure of vitamin B_{12} in the 1950s.[1–3] A recent analysis found that benzimidazole scaffolds are the top five most commonly used five-membered heterocycle in the FDA-approved drugs.[4,5] Drugs consisting of such skeletons are widely applied to the treatment of many kinds of diseases, such as antihypertension,[6] anti-HIV,[7] anti-cancer,[8–11] anti-viral,[12,13] and anti-bacterial.[14,15] Additionally, the derivatives derived from substitutions at *N*-1-position occupy 46% of FDA-approved pharmaceuticals bearing a benzimidazole core, forming a vital branch due to their broad-spectral activities.[16–18] Numerous synthetic strategies have been introduced based on these important scaffolds to build an efficient route for the construction of benzimidazoles.[19–27] Generally, the benzimidazoles are cyclocondensed from suitably substituted 1,2-diaminoarenes with carboxylic acids or equivalents under harsh dehydrating conditions or oxidative coupling reactions with benzaldehydes.[28] The following-up

CONTACT Fusheng Bie fsbie@uzz.edu.cn Engineering and Technology Institute of LuNan Coal Chemical Engineering, ZaoZhuang University, Zaozhuang, P. R. China.

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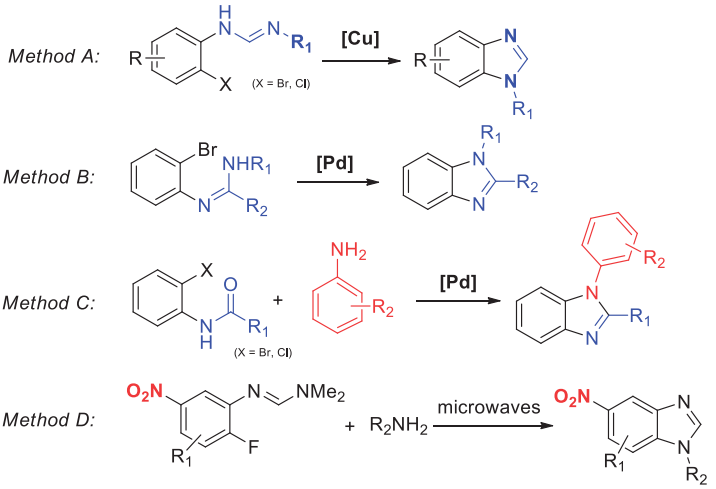


Scheme 1. Some typical methods for the synthesis of *N*-1-aryl-benzimidazoles.

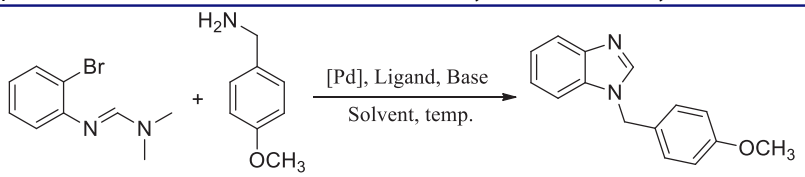
N-alkylation of the benzimidazole ring generally shows many critical weaknesses, such as low regioselectivity, sensitive to steric hindrance and laborious procedures. It is still a challenge to acquire conveniently *N*-alkyl-substituted benzimidazoles during this whole process.[29–33] Therefore, the development of an effective method for synthesis of *N*-1-aryl-substituted benzimidazoles will gain a considerable interest.

Other synthetic methodologies for *N*-1-aryl-benzimidazoles include Cu- and Pd-catalyzed intramolecular cyclization reactions (as illustrated in Scheme 1, methods A and B).[34–37] Buchwald et al. have developed a strategy which relies on the intermolecular formation of benzimidazoles by coupling 2-bromoacetanilides with anilines (cf. Scheme 1, method C)[38,39]; the strategy has involved various pre-prepared alkyl-amides *ortho* to a halide and gave both *2*- and *N*-substituted benzimidazoles. Clearly, most of the above synthetic routes required elaborately synthesized starting materials. Recently, we reported an intermolecular cyclization method for synthesis of *N*-1-alkyl benzimidazoles from formamidines and primary amines (Scheme 1, method D).[40] This method only worked efficiently with the formamidine ring which has a strong electron with-drawing group (such as -NO_2). Since formamidines can be prepared relatively easily, we envisioned that they can be coupled intermolecularly with various commercial amines, thus broadening the potential application of this method. Herein, we report a convenient synthetic strategy of constructing *N*-1-alkyl-2-unsubstituted benzimidazoles by intermolecular coupling of aryl formamidines with benzylamine in the presence of Pd catalyst.

Results and discussion

First, we commenced the synthesis of *N*-1-alkyl-2-unsubstituted benzimidazole from *N*′-(2-bromophenyl)-*N*,*N*-dimethylformimidamide (**1**), 4-methoxybenzylamine (**2a**), $Pd(OAc)_2$, sodium *t*-butoxide (*t*-BuONa) and (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((±)-BINAP) at 110 °C under argon (Table 1, entry 1). The desired product (**3a**) was isolated in a good yield (64%).

Table 1. Optimization of the reaction conditions for the synthesis of 1-benzylbenzimidazole.[a]



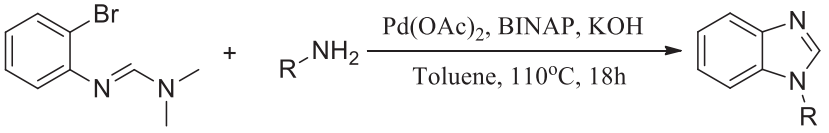
1 **2a** **3a**

Entry	Catalyst	Ligand	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	(±)-BINAP	t-BuONa	Toluene	110	64
2	$PdCl_2$	(±)-BINAP	t-BuONa	Toluene	110	37
3	$Pd_2(dba)_3$	(±)-BINAP	t-BuONa	Toluene	110	46
4	$Pd(PPh_3)_4$	(±)-BINAP	t-BuONa	Toluene	110	5
5	**$Pd(OAc)_2$**	**(±)-BINAP**	**KOH**	**Toluene**	**110**	**84**
6	$Pd(OAc)_2$	(±)-BINAP	t-BuOK	Toluene	110	68
7	$Pd(OAc)_2$	(±)-BINAP	NaH (60%)	Toluene	110	56
8	$Pd(OAc)_2$	(±)-BINAP	EtONa	Toluene	110	43
9	$Pd(OAc)_2$	(±)-BINAP	DBU	Toluene	110	4
10	$Pd(OAc)_2$	(±)-BINAP	DABCO	Toluene	110	3
11	$Pd(OAc)_2$	PPh_3	KOH	Toluene	110	33
12	$Pd(OAc)_2$	DPPF	KOH	Toluene	110	42
13	$Pd(OAc)_2$	DPPP	KOH	Toluene	110	40
14	$Pd(OAc)_2$	$PCy_3{\cdot}HBF_4$	KOH	Toluene	110	37
15	$Pd(OAc)_2$	TFP	KOH	Toluene	110	26
16	$Pd(OAc)_2$	(±)-BINAP	KOH	NMP	110	45
17	$Pd(OAc)_2$	(±)-BINAP	KOH	DMF	110	42
18	$Pd(OAc)_2$	(±)-BINAP	KOH	DMSO	110	8
19	$Pd(OAc)_2$	(±)-BINAP	KOH	Xylenes	110	77
20	$Pd(OAc)_2$	(±)-BINAP	KOH	CH_3CN	110	48
21	$Pd(OAc)_2$	(±)-BINAP	KOH	Dioxane	110	19
22	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	90	56
23	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	100	69
24	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	140	57
25	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	110	66[c]
26	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	110	87[d]
27	$Pd(OAc)_2$	(±)-BINAP	KOH	Toluene	110	90[e]
28	–	(±)-BINAP	KOH	Toluene	110	N.D.[f]
29	$Pd(OAc)_2$	–	KOH	Toluene	110	N.D.

[a]**1** (0.1 mmol), **2a** (0.1 mmol), solvent (0.5 mL), catalyst (5 mol%), ligand (10 mol%), base (2.2 equiv) in a sealed tube, argon protected, 18 h.
[b]Isolated yields.
[c]Reaction time: 6 h.
[d]Reaction time: 24 h.
[e]Catalyst: 10 mol%, ligand (20 mol%).
[f]Not detected.

Then we screened several common palladium catalysts and found that $Pd(OAc)_2$ was the most effective one in 5 mol% (Table 1, entries 1–4). Different kinds of bases were also employed and KOH gave the highest yield (Table 1, entries 5–10). On the other hand, the strong organic bases, such as 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO), did not work well due probably to the big steric hindrance of the organic bases. When the maneuverability and the product yield are compared, toluene was superior to other solvents such as *N*-methyl pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), xylenes, acetonitrile and dioxane (Table 1, entries 5 and 16–21). Moreover, 110 °C was proved to be the most suitable temperature (Table 1, entries 5 and 22–24), and (±)-BINAP served as the best

Table 2. The scope of different aromatic amines for the synthesis of benzimidazoles.[a]



1 **2** **3**

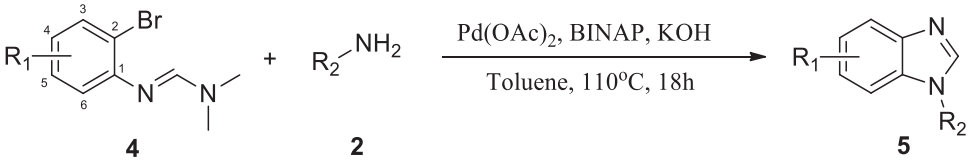
Entry	Amine (2)	Product (3)	Yield (%)[b]
1	**2b**, R = benzyl	**3b**	70
2	**2c**, R = 4-methylbenzyl	**3c**	79
3	**2d**, R = 1-phenylethyl	**3d**	55
4	**2e**, R = 4-(methoxycarbonyl)benzyl	**3e**	37
5	**2f**, R = 4-fluorobenzyl	**3f**	20
6	**2g**, R = 4-chlorobenzyl	**3g**	36
7	**2h**, R = 4-methoxyphenyl	–	N.D.[c]
8	**2i**, R = 3,4-dimethoxyphenyl	–	N.D.
9	**2j**, R = 3,4,5-trimethoxyphenyl	–	N.D.
10	**2k**, R = 4-methylphenyl	–	N.D.
11	**2l**, R = *n*-butyl	–	N.D.
12	**2m**, R = *t*-butyl	–	N.D.
13	**2n**, R = cyclohexyl	–	N.D.
14	**2o**, R = octadecyl	–	N.D.

[a]**1** (0.1 mmol), **2b–k** (0.1 mmol), toluene (0.5 mL), $Pd(OAc)_2$ (5 mol%), (±)-BINAP (10 mol%), KOH (2.2 equiv) in a sealed tube, argon protected.
[b]Isolated yields.
[c]Not detected.

ligand for the palladium catalyst among commercially available ligands trialed (Table 1, entries 5 and 11–15). Furthermore, we also investigated the effect of reaction time on the product yield and found that 18-h reaction time gave essentially the best results. When the reaction time was less than 18 h, the yield of the product deceased remarkably (Table 1, entry 25). However, when the reaction time was extended to 24 h, the yield of the product was not increased much (Table 1, entry 26). Obviously, 10 mol% catalyst gave a slightly better yield than 5 mol% catalyst (Table 1, entry 27); however, when the cost of the catalyst was taken into account, a 5 mol% catalyst was chosen. In fact, no desired product was observed when neither catalyst nor the ligand was added (Table 1, entries 28 and 29). After optimization of the reaction conditions, we chose $Pd(OAc)_2$ (5 mol%) and (±)-BINAP as the catalyst system, KOH as the base and toluene the solvent, widening our synthetic scope (Table 1, entry 5). These results were summarized in Table 2.

Generally, the electronic effect of the substituted groups played important roles in terms of the yields. The benzylamines with electron-donating groups gave rise to much better yields than electron-withdrawing groups (Table 1, entry 5; Table 2, entries 1–6). Product **3d** was obtained in a much lower yield due to the steric hindrance of methyl-group (Table 2, entries 1 and 3), indicating the importance played by the steric hindrance. Unfortunately, both phenylamines and aliphatic amines did not work in this catalyzed reaction system, even if they were substituted with strong electron-donating groups (Table 2, entries 7–14). In addition, we got the single crystal structure of **3b** (CCDC 1944526) which was shown in Figure S1 and Table S1 in Supporting Information.

Table 3. The scope of different aromatic formamidines for the synthesis of benzimidazoles.[a]

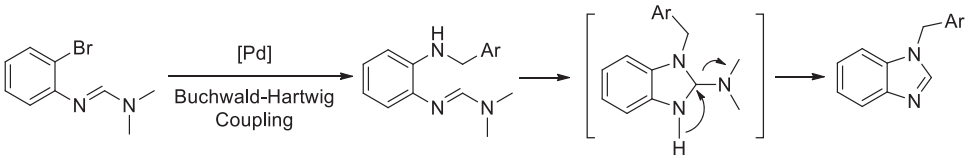


Entry	Formamidine (4)	Amine (2)	Product (5)	Yield (%)[b]
1	**4a**, R_1 = 5-F	**2a**, R_2 = 4-methoxybenzyl	**5a**	75
2	**4b**, R_1 = 5-Cl	**2a**, R_2 = 4-methoxybenzyl	**5b**	63
3	**4c**, R_1 = 5-Br	**2a**, R_2 = 4-methoxybenzyl	**5c**	60
4	**4d**, R_1 = 5-COOMe	**2a**, R_2 = 4-methoxybenzyl	**5d**	72
5	**4e**, R_1 = 5-Me	**2a**, R_2 = 4-methoxybenzyl	**5e**	57
6	**4f**, R_1 = 5-OMe	**2a**, R_2 = 4-methoxybenzyl	**5f**	52
7	**4g**, R_1 = 4-OMe	**2a**, R_2 = 4-methoxybenzyl	**5g**	81
8	**4h**, R_1 = 4-Me	**2a**, R_2 = 4-methoxybenzyl	**5h**	78
9	**4i**, R_1 = 4-COOMe	**2a**, R_2 = 4-methoxybenzyl	**5i**	45
10	**4j**, R_1 = 4-CF_3	**2a**, R_2 = 4-methoxybenzyl	**5j**	52
11	**4k**, R_1 = 6-Me	**2a**, R_2 = 4-methoxybenzyl	**5k**	59
12	**4l**, R_1 = 3-Me	**2a**, R_2 = 4-methoxybenzyl	**5l**	80
13	**4m**, R_1 = 3-CF_3	**2a**, R_2 = 4-methoxybenzyl	**5m**	91
14	**4m**, R_1 = 3-CF_3	**2c**, R_2 = 4-methylbenzyl	**5n**	87
15	**4m**, R_1 = 3-CF_3	**2b**, R_2 = 4-benzyl	**5o**	80
16	**4m**, R_1 = 3-CF_3	**2d**, R_2 = 1-phenylethyl	–	N.D.[c]

[a]**4a–m** (0.1 mmol), **2a–d** (0.1 mmol), toluene (0.5 mL), $Pd(OAc)_2$ (5 mol%), (±)-BINAP (10 mol%), KOH (2.2 equiv) in a sealed tube, argon protected.
[b]Isolated yields.
[c]Not detected.

To further expand the application scope, aromatic formamidines with various substituents were also investigated and the results are given in Table 3. Undoubtedly, both the position of substituents and the electronic effect are important factors influencing the product yields. Aromatic formamidines having 5-F, 5-Cl, 5-Br, and 5-COOMe substituents underwent reactions with yields ranging from 60 to 75% (Table 3, entries 1–4). On the other hand, formamidines possessing electron-donating substituents the 5-Me and 5-OMe leaded to a drop in the yield (Table 3, entries 5 and 6). These results indicated that the electron-withdrawing substituents on the *5*-position of the formamidines were favorable for the reaction. But the opposite tendency was occurred when the substituents on the *4*-positon of the formamidines. Under the same conditions, aromatic formamidines bearing electron-donating groups, such as 4-OMe and 4-Me, gave yields from 78% to 81% (Table 3, entries 7 and 8). Conversely, the electron-withdrawing groups, such as 4-COOMe and 4-CF_3, only gave yields from 45% to 52% (Table 3, entries 9 and 10). Aromatic formimidamide with 6-Me substituent gave a yield of 59% (Table 3, entry 11). Reactions of **4l** and **4m**, which contained steric groups on *3*-positon of the aromatic formamidines, proved to be much more efficient; the corresponding products **5l** and **5m** are in good yields (80 and 91% yield, respectively, Table 3, entries 12 and 13).

The same observation was also reported by Brain and coworkers.[35,36] The steric hindrance from 3-CF_3 group could be responsible for the relatively high yield. Finally, we chose the best aromatic formimidamide (**4m**) to react with different benzylamines. As expected, the yield of the product increased with the electron-donating capability of the



Scheme 2. The proposed reaction mechanism for the synthesis of *N*-substituted benzimidazoles.

para-position on benzylamines (Table 3, entries 13–15). Surprisingly, when a methyl-group on α-position of benzylamine was used, no reaction took place (Table 3, entry 16). This is ascribed probably to the steric interaction between 3-CF_3 and α-CH_3 in the cyclization step.

A plausible mechanism for the synthesis of *N*-1-alkyl-2-unsubstituted benzimidazoles is proposed. First, the Pd-catalyzed Buchwald-Hartwig coupling reaction occurs between bromide and amine.[27,41] Then the thermal cyclization proceeds, giving the corresponding benzimidazoles as products (Scheme 2).[42]

Conclusion

In summary, we have demonstrated a novel synthetic methodology involving Pd-catalyzed reactions; the methodology is an efficient way for the synthesis of *N*-substituted benzimidazoles. Aromatic formamidines as the starting materials can be simply obtained in high yields. The products benzimidazoles with various substituents are obtainable in moderate to good yields. The 2-unsubstituted position of acquired benzimidazoles could be further elaborated by attaching various substituents.[43–45] This synthetic strategy may show potential applications in the synthesis of biological and medical compounds.

Experimental

Unless otherwise noted, the chemical materials were purchased from commercial suppliers and used without further purification. The solvents were degassed by burbling with Argon before use. TLC analysis was performed on precoated plates (silica gel 60 F254) and visualized by UV light. Flash chromatography was performed with silica gel (mesh 200–300) in glass columns. ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra were obtained on a Bruker AVANCE NEO 400 MHz spectrometer at ambient temperature. Chemical shifts were reported in parts per million (δ) relative to residual solvent protons as internal standards. (^{1}H: $CDCl_3$: $\delta = 7.26$ ppm; acetone-d_6: $\delta = 2.05$ ppm. ^{13}C: $CDCl_3$: $\delta = 77.16$ ppm; acetone-d_6: $\delta = 29.84$ ppm and 206.26 ppm. Multiplicity: *s* = singlet; *d* = doublet; *t* = triplet; *q* = quartet; *br* = broad; *m* = multiplet). All the melting points were recorded on INESA (SGWX-4B) equipment without corrected. HRMS data were recorded on Agilent 6530 Accurate-Mass Q-TOF LCMS spectrometer by ESI in positive mode. X-ray data were obtained on an Agilent SuperNova CCD-based diffractometer (Cu Kα radiation, $\lambda = 1.54184$ Å).

General procedures for synthesis of aromatic formamidines

The raw materials were synthesized according to the literature.[46] The reactions were performed with different substituted 2-bromoanilines (typically, 0.01 mol) and *N*,*N*-dimethylformamide dimethyl acetal (DMF·DMA, 0.02 mol, 2.0 equiv) at 80 °C without solvent for about 6 h. The reactions were checked by TLC on silica gel plates using a mixture of petroleum and ethyl acetate as eluent. Then DMF·DMA was removed by high vacuum to generate the product which was used without further purification.

General procedures for synthesis of benzimidazoles

An oven-dried vial (20 mL) equipped with a stir bar was quickly added aromatic formimidamide (typically, 0.1 mmol), benzylamine (0.1 mmol, 1.0 equiv), catalyst (0.005 mmol, 0.05 equiv), ligand (0.01 mmol, 0.1 equiv) and base (0.22 mmol, 2.2 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. The pre-degassed solvent was added, and the reaction mixture was heated at 110 °C for 18 h. The reaction was monitored by TLC using a mixture of petroleum and ethyl acetate as eluent. After the reaction was completed, the mixture was cooled to room temperature, added 15 ml H_2O, and then extracted with ethyl acetate (3×10 ml). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtered, ethyl acetate was removed by vacuum. A sample was analyzed by ^{1}H-NMR ($CDCl_3$, 400 MHz) and gas chromatography-mass spectrometry (GC-MS) to obtain yield using internal standard and comparison with authentic samples. The crude mixture was purified by flash column chromatography with a gradient of petroleum ether and ethyl acetate to give the pure product.

Full experimental detail, ^{1}H and ^{13}C NMR spectra, Single crystal structure and data of **3b**. This material can be found via the "Supplementary Content" section of this article's webpage.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Han Cao http://orcid.org/0000-0001-7470-9213

References

[1] Tonelli, M.; Simone, M.; Tasso, B.; Novelli, F.; Boido, V.; Sparatore, F.; Paglietti, G.; Pricl, S.; Giliberti, G.; Blois, S.; et al. Antiviral Activity of Benzimidazole Derivatives. II. Antiviral Activity of 2-Phenylbenzimidazole Derivatives. *Biorg. Med. Chem.* **2010**, *18*, 2937–2953. DOI: 10.1016/j.bmc.2010.02.037.

[2] Shaharyar, M.; Abdullah, M. M.; Bakht, M. A.; Majeed, J. Pyrazoline Bearing Benzimidazoles: Search for Anticancer Agent. *Eur. J. Med. Chem.* **2010**, *45*, 114–119. DOI: 10.1016/j.ejmech.2009.09.032.

[3] Liu, C.; Ji, C.-L.; Hong, X.; Szostak, M. Palladium-Catalyzed Decarbonylative Borylation of Carboxylic Acids: Tuning Reaction Selectivity by Computation. *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 16721–16726. DOI: 10.1002/anie.201810145.

[4] Largeron, M.; Nguyen, K. M. H. Recent Advances in the Synthesis of Benzimidazole Derivatives from the Oxidative Coupling of Primary Amines. *Synthesis.* **2018**, *50*, 241–253. DOI: 10.1055/s-0036-1590915.

[5] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. DOI: 10.1021/jm501100b.

[6] Michel, M. C.; Foster, C.; Brunner, H. R.; Liu, L. A Systematic Comparison of the Properties of Clinically Used Angiotensin II Type 1 Receptor Antagonists. *Pharmacol. Rev.* **2013**, *65*, 809–848. DOI: 10.1124/pr.112.007278.

[7] Biron, K. K. Antiviral Drugs for Cytomegalovirus Diseases. *Antiviral Res.* **2006**, *71*, 154–163. DOI: 10.1016/j.antiviral.2006.05.002.

[8] Zimmermann, G.; Schultz-Fademrecht, C.; Küchler, P.; Murarka, S.; Ismail, S.; Triola, G.; Nussbaumer, P.; Wittinghofer, A.; Waldmann, H. Structure Guided Design and Kinetic Analysis of Highly Potent Benzimidazole Inhibitors Targeting the PDEδ Prenyl Binding Site. *J. Med. Chem.* **2014**, *57*, 5435–5448. DOI: 10.1021/jm500632s.

[9] Liang, Y.; Zheng, J.; Li, X.; Zheng, W.; Chen, T. Selenadiazole Derivatives as Potent Thioredoxin Reductase Inhibitors That Enhance the Radiosensitivity of Cancer Cells. *Eur. J. Med. Chem.* **2014**, *84*, 335–342. DOI: 10.1016/j.ejmech.2014.07.032.

[10] Cindrić, M.; Jambon, S.; Harej, A.; Depauw, S.; David-Cordonnier, M.-H.; Kraljević Pavelić, S.; Karminski-Zamola, G.; Hranjec, M. Novel Amidino Substituted Benzimidazole and Benzothiazole Benzo[b]Thieno-2-Carboxamides Exert Strong Antiproliferative and DNA Binding Properties. *Eur. J. Med. Chem.* **2017**, *136*, 468–479. DOI: 10.1016/j.ejmech.2017.05.014.

[11] Tahlan, S.; Kumar, S.; Kakkar, S.; Narasimhan, B. Benzimidazole Scaffolds as Promising Antiproliferative Agents: A Review. *BMC Chem.* **2019**, *13*, 66. DOI: 10.1186/s13065-019-0579-6.

[12] Kanwal, A.; Ahmad, M.; Aslam, S.; Naqvi, S. A. R.; Saif, M. J. Recent Advances in Antiviral Benzimidazole Derivatives: A Mini Review. *Pharm. Chem. J.* **2019**, *53*, 179–187. DOI: 10.1007/s11094-019-01976-3.

[13] Hue, B. T. B.; Nguyen, P. H.; De, T. Q.; Van Hieu, M.; Jo, E.; Van Tuan, N.; Thoa, T. T.; Anh, L. D.; Son, N. H.; Thanh, D. L. D.; et al. Benzimidazole Derivatives as Novel Zika Virus Inhibitors. *ChemMedChem.* **2020**, 15, 1453–1463. DOI: 10.1002/cmdc.202000124.

[14] Göker, H.; Karaaslan, C.; Püsküllü, M. O.; Yildiz, S.; Duydu, Y.; Üstündağ, A.; Yalcin, C. Ö. Synthesis and in Vitro Activity of Polyhalogenated 2-Phenylbenzimidazoles as a New Class of anti-MRSA and anti-VRE Agents. *Chem. Biol. Drug Des.* **2016**, *87*, 57–68. DOI: 10.1111/cbdd.12623.

[15] Bandyopadhyay, P.; Sathe, M.; Ponmariappan, S.; Sharma, A.; Sharma, P.; Srivastava, A. K.; Kaushik, M. P. Exploration of *in Vitro* Time Point Quantitative Evaluation of Newly Synthesized Benzimidazole and Benzothiazole Derivatives as Potential Antibacterial Agents. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7306–7309. DOI: 10.1016/j.bmcl.2011.10.034.

[16] Dubey, P. K.; Prasada Reddy, P. V. V.; Srinivas, K. Alternate Method for the Synthesis of *N*-Alkyl/Aralkyl-2-(α-Hydroxy Alkyl/Aralkyl) Benzimidazoles via Regiospecific Acetylation. *Synth. Commun.* **2007**, *37*, 1675–1681. DOI: 10.1080/00397910701265556.

[17] Meng, X.; Li, X.; Chen, W.; Zhang, Y.; Wang, W.; Chen, J.; Song, J.; Feng, H.; Feng, B. Facile One-Pot Synthesis of *N*-Alkylated Benzimidazole and Benzotriazole from Carbonyl Compounds. *J. Heterocyclic Chem.* **2014**, *51*, 349–356. DOI: 10.1002/jhet.1616.

[18] Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu, C. Metal-Free, Highly Efficient Organocatalytic Amination of Benzylic C–H Bonds. *Chem Commun.* **2013**, *49*, 3700–3702. DOI: 10.1039/c3cc41558a.

[19] Lygin, A.; de Meijere, V. A. Synthesis of 1-Substituted Benzimidazoles from o-Bromophenyl Isocyanide and Amines. *Eur. J. Org. Chem.* **2009**, *2009*, 5138–5141. DOI: 10.1002/ejoc.200900820.

[20] Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles. *J. Org. Chem.* **2009**, *74*, 8719–8725. DOI: 10.1021/jo901813g.

[21] Aridoss, G.; Laali, K. K. Building Heterocyclic Systems with $RC(or)^{2+}$ Carbocations in Recyclable Brønsted Acidic Ionic Liquids: Facile Synthesis of *1*-Substituted 1H-1,2,3,4-Tetrazoles, Benzazoles and Other Ring Systems with $CH(OEt)_3$ and $EtC(OEt)_3$ in $[EtNH_3][NO_3]$ and $[PMIM(SO_3H)][OTf]$. *Eur. J. Org. Chem.* **2011**, *2011*, 2827–2835. DOI: 10.1002/ejoc.201100128.

[22] Baars, H.; Beyer, A.; Kohlhepp, S.; Bolm, V. C. Transition-Metal-Free Synthesis of Benzimidazoles Mediated by KOH/DMSO. *Org. Lett.* **2014**, *16*, 536–539. DOI: 10.1021/ol403414v.

[23] Aksenov, A. V.; Smirnov, A. N.; Aksenov, N. A.; Bijieva, A. S.; Aksenova, I. V.; Rubin, M. Benzimidazoles and Benzoxazoles via the Nucleophilic Addition of Anilines to Nitroalkanes. *Org. Biomol. Chem.* **2015**, *13*, 4289–4295. DOI: 10.1039/c5ob00131e.

[24] Sun, X.; Lv, X.-H.; Ye, L.-M.; Hu, Y.; Chen, Y.-Y.; Zhang, X.-J.; Yan, M. Synthesis of Benzimidazoles via Iridium-Catalyzed Acceptorless Dehydrogenative Coupling. *Org. Biomol. Chem.* **2015**, *13*, 7381–7383. DOI: 10.1039/C5OB00904A.

[25] Wang, Z.; Zhao, Q.; Hou, J.; Yu, W.; Chang, J. Iodine-Mediated Direct Synthesis of Multifunctional 2-Aminobenzimidazoles from N-Substituted o-Diaminoarenes and Isothiocyanates. *Tetrahedron.* **2018**, *74*, 2324–2329. DOI: 10.1016/j.tet.2018.03.049.

[26] Dissanayake, D. M. M. M.; Vannucci, A. K. Transition-Metal-Free and Base-Free Electrosynthesis of 1H-Substituted Benzimidazoles. *ACS Sustainable Chem. Eng.* **2018**, *6*, 690–695. DOI: 10.1021/acssuschemeng.7b03029.

[27] Jiang, X.; Huang, Z.; Makha, M.; Du, C.-X.; Zhao, D.; Wang, F.; Li, Y. Tetracoordinate Borates as Catalysts for Reductive Formylation of Amines with Carbon Dioxide. *Green Chem.* **2020**, *22*, 5317–5324. DOI: 10.1039/D0GC01741H.

[28] Preston, P. N. Synthesis, Reactions, and Spectroscopic Properties of Benzimidazoles. *Chem. Rev.* **1974**, *74*, 279–314. DOI: 10.1021/cr60289a001.

[29] Bookser, B. C.; Weinhouse, M. I.; Burns, A. C.; Valiere, A. N.; Valdez, L. J.; Stanczak, P.; Na, J.; Rheingold, A. L.; Moore, C. E.; Dyck, B. Solvent-Controlled, Site-Selective N-Alkylation Reactions of Azolo-Fused Ring Heterocycles at N_1-, N_2-, and N_3-Positions, Including Pyrazolo[3,4-d]Pyrimidines, Purines, [1,2,3]Triazolo[4,5]Pyridines, and Related Deaza-Compounds. *J. Org. Chem.* **2018**, *83*, 6334–6353. DOI: 10.1021/acs.joc.8b00540.

[30] Lai, T.-T.; Xie, D.; Zhou, C.-H.; Cai, G.-X. Copper-Catalyzed Inter/Intramolecular N-Alkenylation of Benzimidazoles via Tandem Processes Involving Selectively Mild Iodination of sp3 C–H Bond at α-Position of Ester. *J. Org. Chem.* **2016**, *81*, 8806–8815. DOI: 10.1021/acs.joc.6b01465.

[31] Chen, S.; Graceffa, R. F.; Boezio, A. A. Direct, Regioselective *N*-Alkylation of 1,3-Azoles. *Org. Lett.* **2016**, *18*, 16–19. DOI: 10.1021/acs.orglett.5b02994.

[32] Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. A Versatile Approach to Ullmann C-N Couplings at Room Temperature: New Families of

Nucleophiles and Electrophiles for Photoinduced, Copper-Catalyzed Processes. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112. DOI: 10.1021/ja4060806.

[33] Chakraborty, A.; Debnath, S.; Ghosh, T.; Maiti, D.; Majumdar, K. S. An Efficient Strategy for *N*-Alkylation of Benzimidazoles/Imidazoles in SDS-Aqueous Basic Medium and *N*-Alkylation Induced Ring Opening of Benzimidazoles. *Tetrahedron.* **2018**, *74*, 5932–5941. DOI: 10.1016/j.tet.2018.08.029.

[34] Hirano, K.; Biju, A.; Glorius, T. F. Copper-Catalyzed Synthesis of *2*-Unsubstituted, *N*-Substituted Benzimidazoles. *J. Org. Chem.* **2009**, *74*, 9570–9572. DOI: 10.1021/jo902160y.

[35] Brain, C. T.; Brunton, S. A. An Intramolecular Palladium-Catalysed Aryl Amination Reaction to Produce Benzimidazoles. *Tetrahedron Lett.* **2002**, *43*, 1893–1895. DOI: 10.1016/S0040-4039(02)00132-6.

[36] Brain, C. T.; Steer, J. T. An Improved Procedure for the Synthesis of Benzimidazoles, Using Palladium-Catalyzed Aryl-Amination Chemistry. *J. Org. Chem.* **2003**, *68*, 6814–6816. DOI: 10.1021/jo034824l.

[37] Evindar, G.; Batey, R. A. Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation: An Efficient Method for the Synthesis of 2-Aminobenzimidazoles. *Org. Lett.* **2003**, *5*, 133–136. DOI: 10.1021/ol027061h.

[38] Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. A Palladium-Catalyzed Regiospecific Synthesis of *N*-Aryl Benzimidazoles. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 7509–7512. DOI: 10.1002/anie.200702542.

[39] Zheng, N.; Buchwald, S. L. Copper-Catalyzed Regiospecific Synthesis of *N*-Alkylbenzimidazoles. *Org. Lett.* **2007**, *9*, 4749–4751. DOI: 10.1021/ol7020737.

[40] Liu, X.; Cao, H.; Bie, F.; Yan P.; Han, Y. C-N Bond Formation and Cyclization: A Straightforward and Metal-Free Synthesis of *N*-1-Alkyl-2-Unsubstituted Benzimidazoles. *Tetrahedron Lett.* **2019**, *60*, 1057–1059. DOI: 10.1016/j.tetlet.2019.03.028.

[41] Liu, C.; Achtenhagen, M.; Szostak, M. Chemoselective Ketone Synthesis by the Addition of Organometallics to *N*-Acylazetidines. *Org. Lett.* **2016**, *18*, 2375–2378. DOI: 10.1021/acs.orglett.6b00842.

[42] Ohno, K.; Ishida, W.; Kamata, K.; Oda, K.; Machida, M. Synthesis of 2-Dimethylaminobenzazoles via a Guanidine Intermediate: Reaction of 2-Substituted Aniline Derivatives with 2-Chloro-1,1,3,3-Tetramethylformamidinium Chloride. *Heterocycles.* **2003**, *59*, 317. DOI: 10.3987/COM-02-S39.

[43] Denise, A. C.; Robert, G. B.; Jonathan, A. E. Rhodium-Catalyzed C–C Bond Formation via Heteroatom-Directed C–H Bond Activation. *Chem. Rev.* **2010**, *110*, 624.

[44] Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Direct Functionalization of Nitrogen Heterocycles via Rh-Catalyzed C–H bond Activation. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. DOI: 10.1021/ar800042p.

[45] Wang, B. B.; Smith, P. J. Synthesis of a Terbenzimidazole Topoisomerase I Poison via Iterative Borinate Ester Couplings. *Tetrahedron Lett.* **2003**, *44*, 8967–8969. DOI: 10.1016/j.tetlet.2003.10.007.

[46] HanCai, Y. L. An Efficient and Convenient Synthesis of Formamidines. *Tetrahedron Lett.* **1997**, *38*, 5423–5426. DOI: 10.1016/S0040-4039(97)01206-9.