FULL PAPER DOI: 10.1002/adsc.202001365

Advanced Synthesis & Catalysis

Transition-Metal-Free Base-Controlled C–N Coupling Reactions: Selective Mono *Versus* Diarylation of Primary Amines with 2-Chlorobenzimidazoles

Wei Sang,[a, b] Yan-Yan Gong,[c] Hua Cheng,[d] Rui Zhang,[d] Ye Yuan,[a] Guang-Gao Fan,[a] Zhi-Qin Wang,[a] Cheng Chen,[a,*] and Francis Verpoort[a, e, f,*]

[a] State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan University of Technology, 122 Luoshi Road, Wuhan 430070, People's Republic of China
phone: (+86)-27-88016035
fax: (+86)-27-87879468
E-mail: chengchen@whut.edu.cn; francis.verpoort@ghent.ac.kr
[b] School of Materials Science and Engineering, Wuhan University of Technology, 122 Luoshi Road, Wuhan 430070, People's Republic of China
[c] State Key Laboratory of Biobased Material and Green Papermaking, Qilu University of Technology, Shandong Academy of Sciences, Jinan, People's Republic of China
[d] Department of Chemical Engineering and Food Science, Hubei University of Arts and Science, 296 Longzhong Road, Xiangyang 441053, People's Republic of China
[e] National Research Tomsk Polytechnic University, Lenin Avenue 30, Tomsk 634050, Russian Federation
[f] Ghent University - Global Campus, 119 Songdomunhwa-Ro, Yeonsu-Gu, Incheon 21985, Korea

Manuscript received: November 3, 2020; Revised manuscript received: January 9, 2021;
Version of record online: January 27, 2021

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001365

Abstract: Herein, a base-controlled protocol was developed for the C–N coupling of primary amines and 2-chlorobenzimidazoles, affording a handful of secondary or tertiary amines in a selective fashion. Moreover, this protocol was realized under transition-metal-free conditions, and the variation of the base from *i*Pr_2NH to LiO*t*Bu completely switched the selectivity from monoarylation to diarylation. Further investigations elucidated that the variety, intrinsic basicity and amount of the utilized bases considerably affected these reactions.

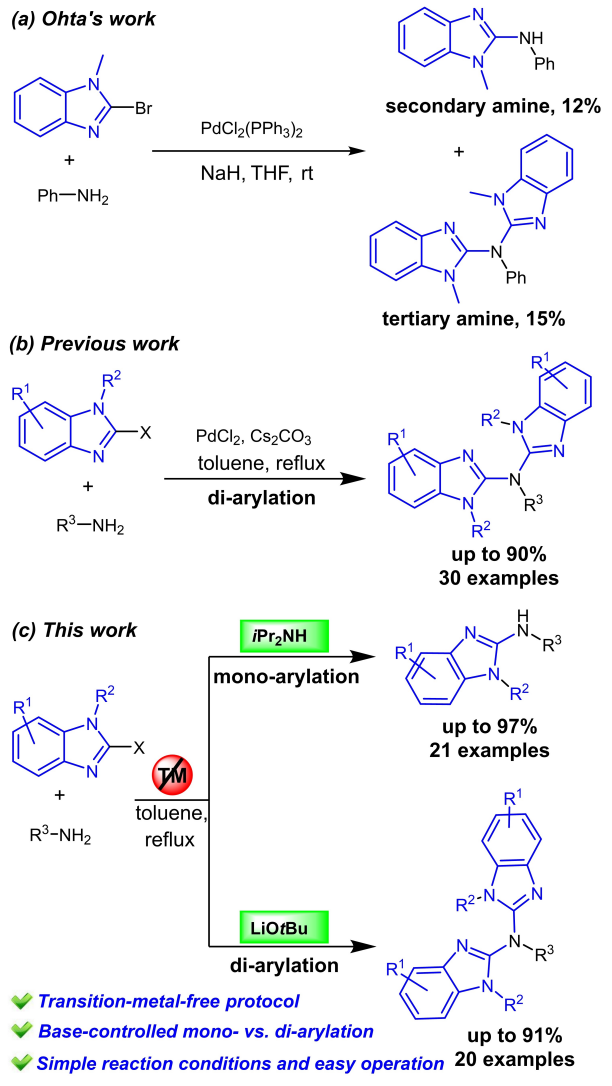
Keywords: transition-metal-free; base-controlled; C–N coupling; diarylation; monoarylation; 2-aminobenzimidazoles

Introduction

Benzimidazole and its derivatives are an important class of N-heterocyclic compounds which are widely distributed in pharmaceuticals, metal ligands, polymers and materials.[1] More specifically, 2-aminobenzimidazoles such as astemizole,[2] mizolastine[3] and oxbendazole[4] are vital structural units which demonstrate versatile biological and pharmaceutical activity.[5] In addition, these compounds have been used as ligands for organometallic compounds or materials. For instance, Aleksandra Bocian et al. prepared several iron complexes comprising 2-aminobenzimidazole ligands and evaluated their potential as artificial biomimetic enzyme analogues.[6] 2-Aminobenzimidazole was also utilized as a ligand to modify the structures of zeolitic imidazolate frameworks (ZIFs), thereby adjusting the properties of the corresponding materials.[7] Besides, the 2-aminobenzimidazole skeleton is prevailing in chemical sensors for the detection of anions[8] as well as in corrosion inhibitors.[9]

In view of the widespread applications, expedient synthetic approaches were described for accessing 2-aminobenzimidazoles. In particular, direct functionalization of the benzimidazole framework via representative C–N coupling strategies such as Buchwald-Hartwig amination[10] and Chan-Lam coupling[11] reveals an attractive pathway for the 2-aminobenzimidazole synthesis, which includes Pd-catalyzed monoarylation of 2-aminobenzimidazole with aryl halides,[12]

the cross-coupling of 2-aminobenzimidazoles with arylboronic acids via Cu or Ni catalysis,[13] and treatment of 2-halobenzimidazoles with amines.[14] It was noted that the above-mentioned methods went through one amination sequence to give the aminated products, while rare examples were reported for the direct formation of tertiary amines from primary amines (as outlined in Scheme 1). As the first example, Ohta et al. reported a Pd-catalyzed protocol to generate the tertiary amine in 15% yield, with the concurrent formation of the secondary amine in 12% yield (Scheme 1a).[15] In our previous work, selective diarylation was accomplished via a ligandless Pd-catalyzed strategy (Scheme 1b).[16] During the investigations, secondary amines were occasionally provided. Inspired by this work, we envisaged that adjusting various reaction parameters may allow for controlling the mono *vs.* diselectivity. Gratifyingly, a transition-metal-free protocol was discovered to exclusively deliver secondary or tertiary amines (Scheme 1c). At the outset, plenty of inorganic bases were screened. Interestingly, LiO*t*Bu efficiently promoted two consecutive C–N coupling processes, delivering tertiary amines in a highly selective manner. In addition to inorganic bases, organic bases were also attempted. To our delight, diisopropylamine (iPr$_2$NH) was identified as an optimum base to selectively give secondary amines. Furthermore, additional experiments implied that the types, strength and equivalents of the bases were pivotal factors for regulating the selectivity of mono *vs.* diarylation.

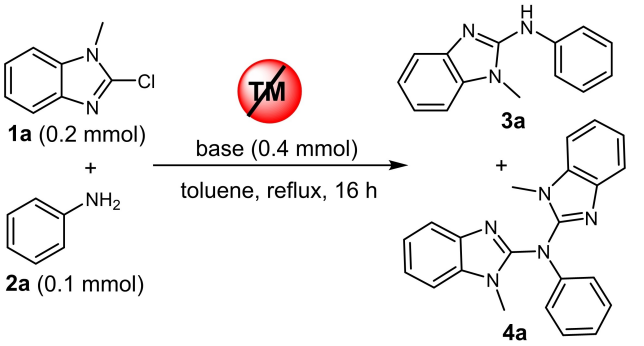


Scheme 1. The design strategy of this work.

Results and Discussion

2-Chloro-1-methyl-benzimidazole (**1 a**) and aniline (**2 a**), the two coupling partners, were chosen to optimize the reaction conditions (as listed in Table 1). It was anticipated that either secondary amine **3 a** or tertiary amine **4 a** was obtained with high yield and

Table 1. The effect of various bases on the reaction of **1 a** and **2 a**.[a]



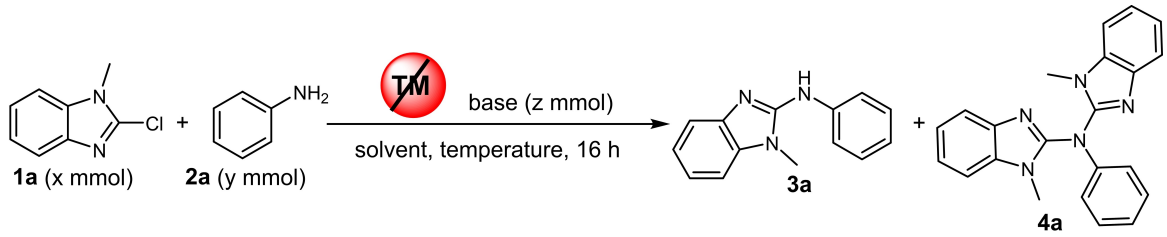
Entry	Base	Yield (%)[b] 3 a	4 a	Unreacted **1 a** (mmol)
1	Cs_2CO_3	4	–	0.144
2	K_2CO_3	3	–	0.170
3	LiOH	47	–	0.110
4	NaOH	–	30	0.084
5	KOH	52	16	–
6	**LiO*t*Bu**	–	**73**	**0.030**
7	NaO*t*Bu	65	28	–
8	KO*t*Bu	78	6	–
9	LDA	51	25	–
10	NaH	30	35	–
11	TMEDA	5	–	0.170
12	Pyridine	40	–	0.070
13	Et_3N	65	–	0.084
14	***i*Pr$_2$NH**	**95**	**–**	**0.090**
15	–	–	–	0.108

[a] **1 a** (0.2 mmol), **2 a** (0.1 mmol), base (0.4 mmol) and toluene (0.5 mL) were heated at reflux under argon for 16 h;
[b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard (average of two consistent runs).

excellent selectivity. In our previous paper, an unsatisfactory result was obtained for Cs_2CO_3 without a Pd catalyst (entry 1).[16] In order to develop an efficient and transition-metal-free synthetic approach, a number of other inorganic bases were screened without a transition metal catalyst (entries 2–10). It appeared that K_2CO_3 did not effectively navigate the C–N coupling process, with the detection of **3a** in only 3% yield (entry 2). In addition, different hydroxides were attempted (entries 3–5). LiOH selectively provided **3a** in moderate yield (entry 3), while NaOH delivered **4a** as the major product (entry 4). With regard to the stronger base (KOH), 52% of **3a** and 16% of **4a** were observed (entry 5). Next, alkoxides including LiO*t*Bu, NaO*t*Bu and KO*t*Bu were also employed (entries 6–8). Interestingly, LiO*t*Bu selectively provided disubstituted product **4a** with high yield and superb selectivity (entry 6), while NaO*t*Bu and KO*t*Bu gave rise to a mixture of both products, with **3a** as the major product (entries 7–8). In terms of even stronger bases such as lithium diisopropylamide (LDA) and NaH, complicated reaction mixtures were obtained (entries 9–10). Furthermore, several organic bases were screened (entries 11–14). N,N,N′,N′-Tetramethylethylenediamine (TMEDA) was not effective for this transformation, with only 5% of **3a** being observed (entry 11). Pyridine produced the formation of **3a** in moderate yield, with 35% of **1a** remaining (entry 12). To our delight, Et_3N and diisopropylamine (iPr_2NH) resulted in the secondary amine (**3a**) as the major product (entries 13–14). Especially, iPr_2NH selectively provided **3a** in excellent yield (entry 14). As a comparative study, neither **3a** or **4a** was detected for the reaction of **1a** and **2a** under base-free conditions (entry 15).

To gain better results for both conditions, further screening of other parameters was carried out (as listed in Tables 2, S1 and S2). At the outset, adjustment of the base amounts and substrate ratios resulted in improved results, which gave rise to 88% of **4a** and 95% of **3a**, respectively (as listed in entries 1–4 of Table 2 and detailed in Tables S1 and S2 of the

Table 2. Further screening of reaction conditions.[a]



Entry	x	y	Base (z)	solvent	Temperature	Yield (%)[a] **3a**	**4a**	Unreacted **1a** (mmol)
1	0.200	0.100	iPr_2NH (0.400)	toluene	120 °C	95	–	0.090
2	0.200	0.100	LiO*t*Bu (0.400)	toluene	120 °C	–	73	0.170
3	**0.125**	**0.100**	**iPr_2NH (0.400)**	**toluene**	**120 °C**	**95 (93[b])**	–	**0.019**
4	**0.200**	**0.150**	**LiO*t*Bu (0.400)**	**toluene**	**120 °C**	–	**88 (85[b])**	–
5[c]	0.125	0.100	iPr_2NH (0.400)	THF	120 °C	–	–	0.085
6[c]	0.200	0.150	LiO*t*Bu (0.400)	THF	120 °C	28	30	0.050
7	0.125	0.100	iPr_2NH (0.400)	DMF	120 °C	68	–	0.028
8	0.200	0.150	LiO*t*Bu (0.400)	DMF	120 °C	12	35	0.026
9	0.125	0.100	iPr_2NH (0.400)	dioxane	120 °C	90	–	–
10	0.200	0.150	LiO*t*Bu (0.400)	dioxane	120 °C	–	65	0.030
11	0.125	0.100	iPr_2NH (0.400)	toluene	100 °C	12	–	0.106
12	0.200	0.150	LiO*t*Bu (0.400)	toluene	100 °C	–	14	0.156
13	0.125	0.100	iPr_2NH (0.400)	toluene	80 °C	–	–	0.112
14	0.200	0.150	LiO*t*Bu (0.400)	toluene	80 °C	–	–	0.178
15[d]	1.25	1.00	iPr_2NH (4.00)	toluene	120 °C	86 (82[b])	–	0.113
16[d]	2.00	1.50	LiO*t*Bu (4.00)	toluene	120 °C	–	80 (76[b])	0.160
17[e]	6.25	5.00	iPr_2NH (20.0)	toluene	120 °C	48 (45[b])	–	2.81
18[e]	10.0	7.50	LiO*t*Bu (20.0)	toluene	120 °C	–	56 (51[b])	3.80

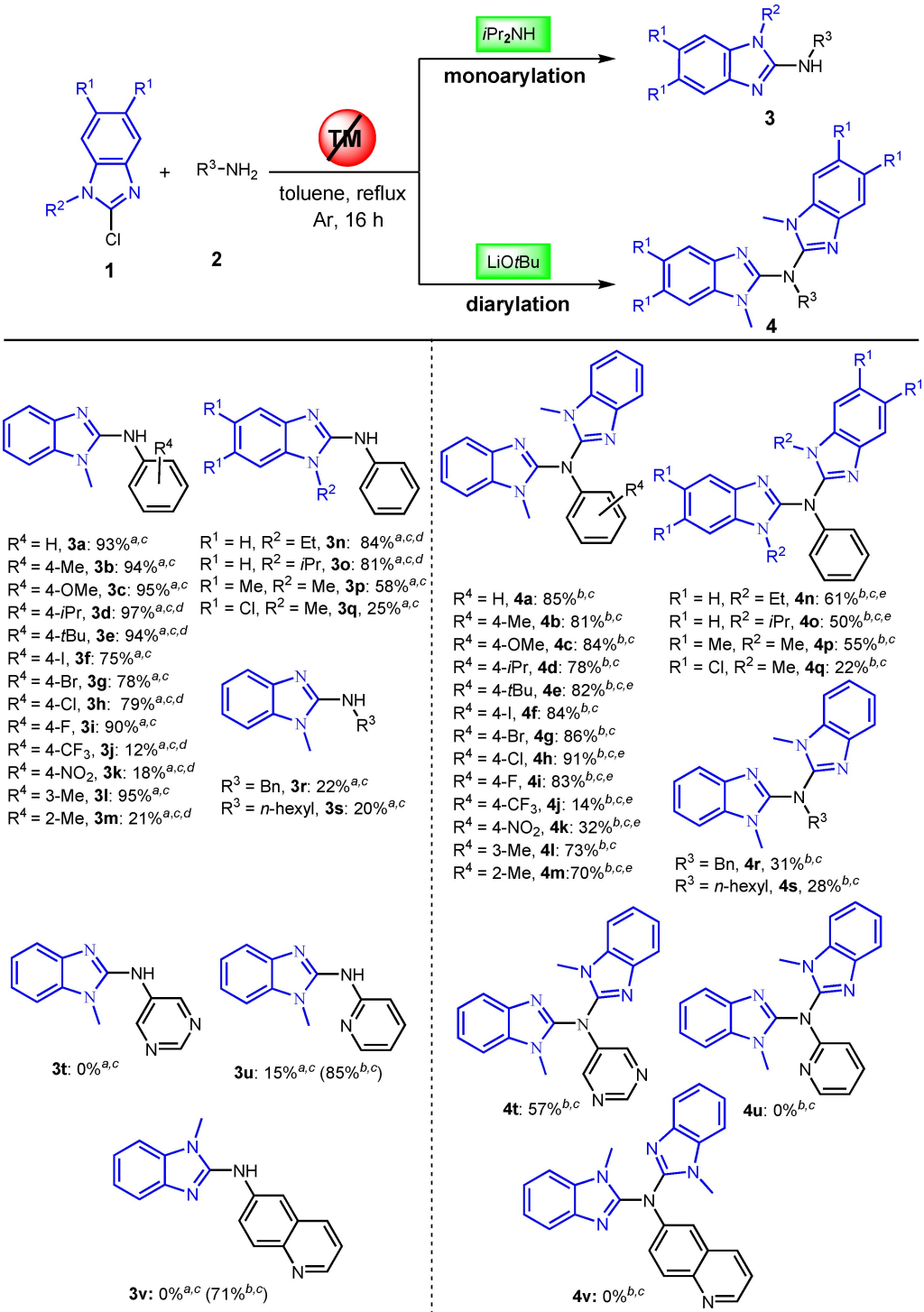
[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard (average of two consistent runs);
[b] Isolated yield;
[c] A sealed tube was used;
[d] 1 mmol-scale reactions;
[e] 5 mmol-scale reactions.

supporting information). Moreover, different solvents were attempted under the same temperature (entries 5–10). The results indicated that THF and DMF did not provide good results (entries 5–8). In contrast, dioxane led to moderate to high yield of the desired products with excellent selectivity (entries 9–10), but it exhibited lower performance in comparison with toluene (entry 9 *vs.* entry 3, entry 10 *vs.* entry 4). Next, the influence of the reaction temperatures on this reaction was also explored (entries 11–14). Lowering the temperature from 120 °C to 100 °C led to significantly reduced yield of **3a** or **4a** (entries 11–12), while almost no reaction occurred if a further decreased temperature of 80 °C was used (entries 13–14). Furthermore, the protocol was applicable for 1 mmol-scale reactions, with the selective formation of **3a** (or **4a**) in high yield under the *i*Pr_2NH-promoted (or LiO*t*Bu-based) conditions (entries 15–16). Excellent selectivity remained for each base at an even larger scale of 5 mmol, despite moderate yield of **3a** or **4a** was obtained (entries 17–18). From the above observations, it was noteworthy that switchable mono and diarylation were realized simply by altering the base from *i*Pr_2NH to LiO*t*Bu under transition-metal-free conditions.

After the reaction conditions were optimized, the substrate scope of this protocol was expanded (as depicted in Scheme 2). Initially, the coupling of **1a** with different anilines were attempted. For the *i*Pr_2NH-promoted reactions, electron-rich anilines **2b–2e** yielded products **3b–3e** in excellent yield, while electron-deficient counterparts **2f–2i** afforded the corresponding secondary amines (**3f–3i**) in slightly lower yield (75–90%). Unfortunately, highly electron-deficient amines **2j** and **2k** provided the desired products (**3j** and **3k**) in merely 12–18% yield. Similarly, desired products **4b–4i** were furnished in 78–91% yield for the LiO*t*Bu-promoted reactions, whereas highly electron-poor products **4j** and **4k** were isolated in only 14–32% yield. Afterwards, the effects of the substituent positions on the phenyl ring were then evaluated. Under the monoarylation conditions, 4-methylaniline (**2b**) and 3-methylaniline (**2l**) exhibited similar reactivity, whereas 2-methylaniline (**2m**) provided product **3m** in merely 21% yield even if a smaller amount of **1a** was used. As for the diarylation conditions, **2l** and **2m** generated the desired products in marginally lower yield than **2b**. Moreover, the suitability of the current protocol was examined for the reactions of **2a** with 1-substituted 2-chlorobenzimidazoles. If R^2 was changed from Me to more hindered Et and *i*Pr groups, 0.4 mmol of *i*Pr_2NH promoted the formation of products **3n** and **3o** in 84% and 81% yield, respectively. Under the diarylation conditions, product **4n** (or **4o**) was delivered in 61% (or 50%) yield, albeit an elevated temperature was required. Furthermore, different R^1 substituents were introduced on the backbone of the benzimidazole framework. If a Me group was applied as R^1, 58% of product **3p** and 55% of **4p** were provided, respectively. When a Cl group was incorporated into the R^1 position, the corresponding products **3q** and **4q** were isolated in 25% and 22%, respectively. Apart from aromatic primary amines, benzyl amine (**2r**) and *n*-hexylamine (**2s**) were also tolerated, providing the respective products **3r–3s** or **4r–4s** in 20–31% yield. Finally, heteroaromatic primary amines **2t–2v** were explored. Very limited reactivity was observed under the *i*Pr_2NH-promoted conditions, whereas higher reactivity was detected in terms of the LiO*t*Bu-mediated conditions. Under the diarylation conditions, tertiary amine **4t** was selectively yielded in 57% yield, while only secondary amines **3u–3v** (without the observation of tertiary amines **4u–4v**) were isolated in good yield. Probably, the weak nucleophilicity of heteroaromatic amines **2u–2v** could not promote the second amination.

To provide the rational for the base-controlled switch between mono and diarylation, the relationship between the intrinsic basicity of our selected bases and the product selectivity was investigated (as listed in Table 3). The pKa values of the corresponding conjugate acids were used to indicate the intrinsic basicity of these bases. At the beginning, inorganic bases were studied (entries 1–10). It appeared that weak bases including the carbonates (pKa = 10.3) could not efficiently promote this C–N coupling reaction (entries 1–2). For stronger bases such as the hydroxides (pKa = 15.7), the cross-coupling reactions could take place, but with moderate conversion or selectivity (entries 3–5). In terms of the *tert*-butoxides (pKa = 17.0) as even stronger bases, C–N coupling efficiently occurred with good conversion (entries 6–8), with LiO*t*Bu as the ideal base for the diarylation (entry 6) and the other two *tert*-butoxides leading to a mixture of **3a** and **4a** (entries 7–8). It was found that very strong bases such as LDA (pKa = 35.7) and NaH (pKa = ~36) resulted in relatively complicated reaction mixtures with poor product selectivity (entries 9–10). Apart from inorganic bases, organic bases having good solubility in toluene were also examined (entries 11–14). Pyridine (pKa = 5.21) and TMEDA (pKa = 8.97) were not efficient coupling promoters, resulting in **3a** in 5–40% yield (entries 11–12). However, stronger bases including Et_3N (pKa = 10.75) and *i*Pr_2NH (pKa = 11.05) were better promoters (entries 13–14), with *i*Pr_2NH being identified as the optimized base for the monoarylation (entry 14).

Further exploration using **1a** and **2a** as the reactants was also carried out (as depicted in Figure 1). At the outset, product distribution was explored at different amounts of *i*Pr_2NH (Figure 1a). As the base usage gradually increased from 0.1 mmol to 0.5 mmol, the yield of **3a** was steadily improved from 20% to

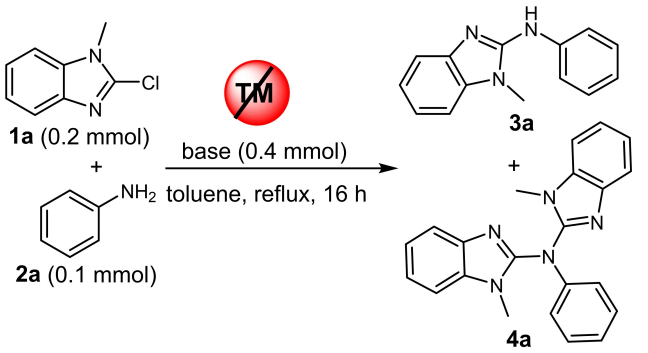


[a] **1** (0.125 mmol), **2** (0.1 mmol), iPr_2NH (0.4 mmol), and toluene (0.5 mL) were heated at reflux; [b] **1** (0.2 mmol), **2** (0.15 mmol), LiO*t*Bu (0.4 mmol), and toluene (0.5 mL) were heated at reflux; [c] Isolated yield; [d] **1** (0.063 mmol); [e] at refluxing *m*-xylene.

Scheme 2. The substrate exploration.

96%, with no formation of **4a** under all the circumstances. This result indicated that the weak organic base (iPr_2NH) could effectively promote the C–N coupling of **1a** and **2a** to afford **3a**, but was unable to accomplish the subsequent coupling of **3a** and **1a**. Subsequently, the amounts of LiO*t*Bu were also evaluated for the coupling of **1a** and **2a** (Figure 1b and Table S3). If 0.1 mmol of LiO*t*Bu was used, 15%

Table 3. The relationship between the intrinsic basicity of our selected bases and the product selectivity.



Entry	Base	pKa of the conjugate acid	Yield (%)[a] 3a	4a
1	K_2CO_3	10.3[b]	3	–
2	Cs_2CO_3	10.3[b]	4	–
3	LiOH	15.7[b]	47	–
4	NaOH	15.7[b]	–	30
5	KOH	15.7[b]	52	16
6	**LiO*t*Bu**	**17.0**[b]	–	**73**
7	NaO*t*Bu	17.0[b]	65	28
8	KO*t*Bu	17.0[b]	78	6
9	LDA	35.7[c]	51	25
10	NaH	~36[b]	30	35
11	Pyridine	5.21[b]	40	–
12	TMEDA	8.97[b]	5	–
13	Et_3N	10.75[b]	65	–
14	**iPr_2NH**	**11.05**[b]	**95**	–

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard (average of two consistent runs);
[b] in water;
[c] in THF.

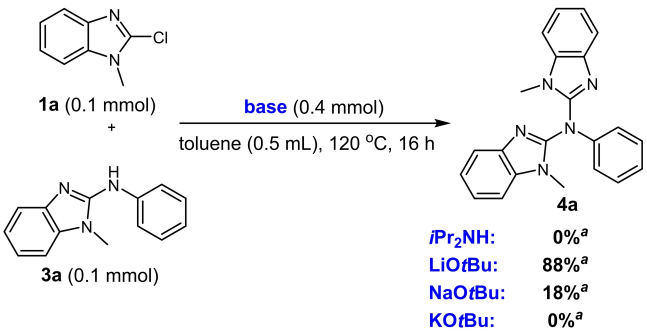
of **3a**, 20% of **4a** and 64% of unreacted **1a** were observed. Enhancement of the base amount triggered higher selectivity of **4a** *vs.* **3a**, with 0.4 mmol as the optimal result. To have a clearer understanding about the counter-ion effect in the three *tert*-butoxides, NaO*t*Bu and KO*t*Bu were also examined (Figure 1c-d and Table S3). In the case of NaO*t*Bu, fewer amounts (0.1–0.2 mmol) triggered **4a** as the major product. In contrast, higher amounts (0.3–0.5 mmol) gradually switched the main product from **4a** to **3a**, affording 81% of **3a** with 0.5 mmol of NaO*t*Bu. An even stronger base, KO*t*Bu, led to a mixture of **3a** and **4a** when the base amounts were 0.1–0.2 mmol. Similar with NaO*t*Bu, 0.3–0.5 mmol of KO*t*Bu also delivered **3a** as the major product. Even though the three bases contain the same anion, the distinct radii of their counter ions make their basicity follow the trend of LiO*t*Bu < NaO*t*Bu < KO*t*Bu,[17] which should be a crucial factor for the selectivity of **3a** and **4a** in this coupling. It was concluded that 0.4 mmol of iPr_2NH effectively promoted one amination sequence to selectively give **3a**, while 0.4 mmol of LiO*t*Bu facilitated two consecutive amination sequences to exclusively provide **4a**. On the other hand, the regulation of the base types, basicity and concentration is pivotal for the product selectivity between **3a** and **4a**.

Furthermore, the coupling of **1a** and secondary amine **3a** under a few selected bases was performed (as shown in Scheme 3). Expectedly, no diarylation product **4a** was detected in the presence of iPr_2NH, while 88% of **4a** was observed applying LiO*t*Bu. Besides, NaO*t*Bu and KO*t*Bu were also utilized. However, both bases could not efficiently promote this cross-coupling reaction, with only 18% of **4a** for NaO*t*Bu and 0% of **4a** for KO*t*Bu, respectively. This result clearly indicated that NaO*t*Bu and KO*t*Bu, two stronger bases than LiO*t*Bu (especially with excess amounts), could not effectively mediate the second amination (the C–N coupling of **1a** and **3a**) to give **4a**, which clarified the essential role of the base types and basicity in this coupling.

Based on the above results, we proposed the possible pathways for this protocol (as illustrated in Scheme S1). By screening a variety of bases, iPr_2NH and LiO*t*Bu were identified as the optimized bases for the selective mono and diarylation, respectively. It was found that both iPr_2NH and LiO*t*Bu facilitated the first amination (the coupling of **1** and **2**) to give secondary amines **3**. In addition, iPr_2NH was not capable of promoting the second amination (the C–N coupling of **3** with **1**), whereas LiO*t*Bu was proven as the optimal base for the diarylation. Except the types and basicity of the bases, their quantities also accounted for the yield and selectivity of either secondary or tertiary amines.

Conclusion

In summary, a transition-metal-free base-controlled protocol was developed for the C–N coupling of 2-chlorobenzimidazoles and primary amines. Through a



[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard (average of two consistent runs).

Scheme 3. The reactions of **1a** and **3a** applying different bases.

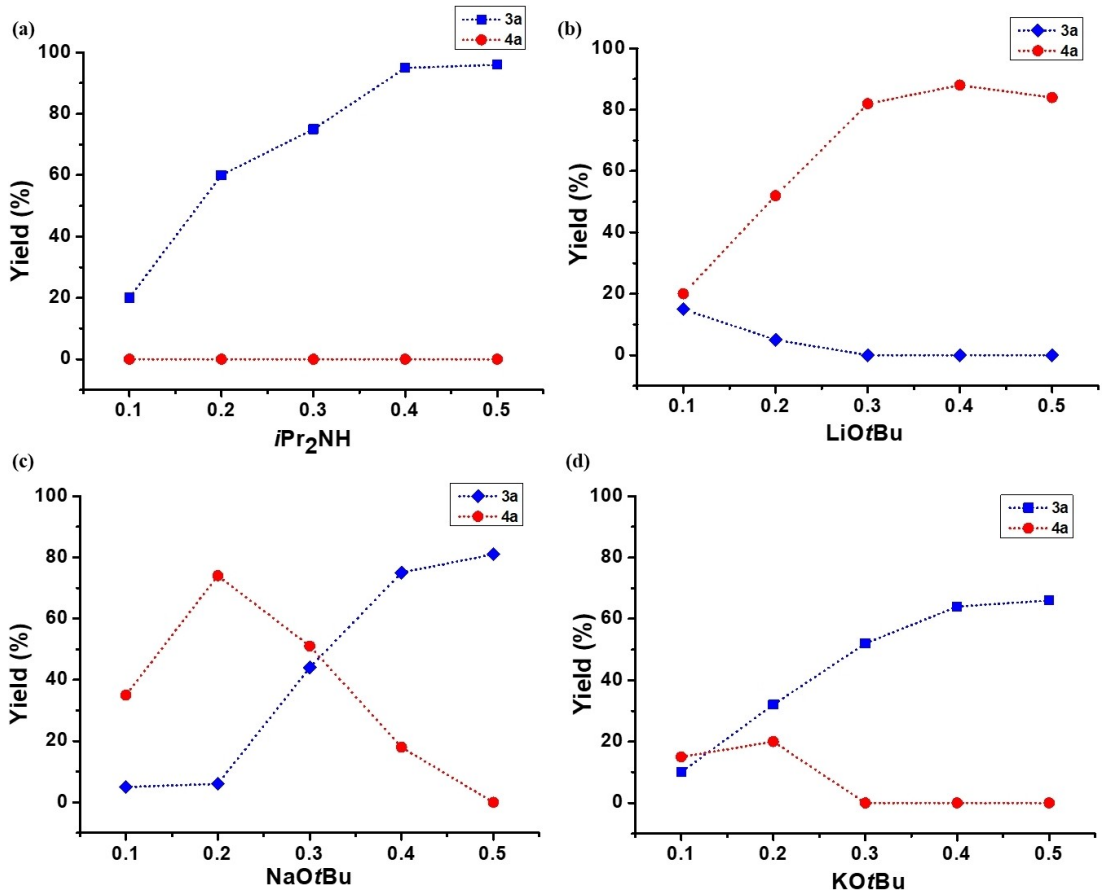


Figure 1. Selectivity of **3 a** *vs.* **4 a** at different amounts of (a) *i*Pr$_2$NH, (b) LiO*t*Bu, (c) NaO*t*Bu, (d) KO*t*Bu.

systematic investigation of various bases, *i*Pr$_2$NH and LiO*t*Bu were identified to exclusively afford a series of secondary and tertiary amines, respectively. Originally, plenty of substituted anilines were smoothly converted into the corresponding products. With regard to the reactions of aniline (**2 a**) and different 2-chlorobenzimidazoles, the desired products were selectively yielded under both conditions. Besides, aliphatic/heteroaromatic primary amines were also compatible. Furthermore, additional experiments were carried out to rationalize this base-controlled protocol, which indicated that an appropriate base and a suitable amount were equally paramount for the superb selectivity and excellent yield of cross-coupled products **3** or **4**.

Experimental Section

General Considerations

The reactions were carried out using standard Schlenk techniques or in an argon-filled glovebox unless otherwise mentioned. ^{1}H-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer, and ^{13}C-NMR spectra were measured on a Bruker Avance 500 (126 MHz) spectrometer. For the NMR analyses, $CDCl_3$, DMSO-d_6 or acetone-d_6 was used as the deuterated solvent, and tetramethylsilane (TMS) was utilized as the internal reference. Melting points were taken on a Buchi M-560 melting point apparatus without calibration. High resolution mass spectrometry (HRMS) analyses were done with a Bruker Daltonics microTOF-QII or a Thermo Fisher Q Exactive™ UHMR Orbitrap™ instrument. All the common reagents, solvents and primary amines **2 a**–**2 v** were purchased from commercial suppliers and directly used. Besides, 2-chloro-1-methyl-1*H*-benzo[*d*]imidazole (**1 a**),[18] 2-chloro-1-ethyl-1*H*-benzo[*d*]imidazole (**1 n**),[19] 2-chloro-1-isopropyl-1*H*-benzo[*d*]imidazole (**1 o**),[19] 2-chloro-1,5,6-trimethyl-1*H*-benzo[*d*]imidazole (**1 p**),[20] 2,5,6-trichloro-1- methyl-1*H*-benzo[*d*]imidazole (**1 q**)[16] were synthesized using the previously reported procedures. The pKa values of LDA[21] and TMEDA[22] were obtained from the literature sources, while those of the other bases could be found via https://organicchemistrydata.org/hansreich/resources/pka/#pka_general.

General Procedures for the Base-Controled C–N Coupling of Substituted 2-Chlorobenzimidazoles with Primary Amines

The *i*Pr$_2$NH-promoted reactions: Inside an argon-filled glovebox, *i*Pr$_2$NH (56 µL, 0.4 mmol), a 2-chlorobenzimidazole derivative (0.125 mmol), a primary amine (0.1 mmol) and

toluene (0.5 mL) were added to a 25 mL Schlenk flask, which was then taken out of the glovebox. Subsequently, the mixture was refluxed under argon atmosphere for 16 h. For the 1 mmol-scale reaction, a mixture of iPr$_2$NH (0.56 mL, 4.0 mmol), **1a** (208.3 mg, 1.25 mmol), **2a** (91 μL, 1.0 mmol) and toluene (2.5 mL) were refluxed under argon for 48 h, and pure **3a** (183.1 mg) was isolated in 82% yield. For the 5 mmol-scale reaction, a mixture of iPr$_2$NH (2.8 mL, 20.0 mmol), **1a** (1.04 g, 6.25 mmol), **2a** (457 μL, 5.00 mmol) and toluene (6.0 mL) were refluxed under argon for 48 h, and pure **3a** (502.4 mg) was isolated in 45% yield.

The LiO*t*Bu-promoted reactions: To a 25 mL Schlenk flask were added LiO*t*Bu (32.0 mg, 0.4 mmol), a 2-chlorobenzimidazole derivative (0.2 mmol), a primary amine (0.15 mmol) and toluene (0.5 mL) in the glovebox. The Schlenk tube was capped and subjected to three cycles of evacuation-backfilling with argon. Subsequently, the mixture was stirred at reflux under argon for 16 h. For the 1 mmol-scale reaction, a mixture of LiO*t*Bu (0.32 g, 4.0 mmol), **1a** (333.2 mg, 2.00 mmol), **2a** (137 μL, 1.50 mmol) and toluene (2.5 mL) were heated at reflux under argon for 48 h, affording pure **4a** (268.6 mg) in 76% yield. For the 5 mmol-scale reaction, a mixture of LiO*t*Bu (1.60 g, 20.0 mmol), **1a** (1.67 g, 10.0 mmol), **2a** (685 μL, 7.50 mmol) and toluene (6.0 mL) were heated at reflux under argon for 48 h, affording pure **4a** (901.2 mg) in 51% yield.

General Procedure for the Calculations of NMR Yield

After the indicated time, the reaction mixture was cooled down to room temperature and concentrated by a vacuum pump (for the reactions utilizing LiO*t*Bu, NaO*t*Bu, KO*t*Bu or NaH, a few drops of water were added to quench the reactions). Afterwards, 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol) and $CDCl_3$ (1.0 mL) were added. The insoluble solid was filtered off, and 0.5 mL of the filtrate was added to an NMR tube. The NMR yield was obtained based on the exact amount of 1,3,5-trimethoxybenzene.

General Procedure for the Isolation of the Products and Their Isolated Yield

The reaction mixture was cooled down and the solvent was removed under reduced pressure. Subsequently, silica-gel column chromatography was utilized to obtain the pure products **3** or **4**. Petroleum ether was used as the starting eluent and solvent systems containing petroleum ether/ethyl acetate (from 10:1 to 1:1) was then applied. After the solvent was removed, the pure products were obtained. By this way, the yield of the products can be obtained.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (No. 21502062), and the Fundamental Research Funds for the Central Universities (No. 205201026), the National Natural Science Foundation Cultivation Project of Hubei University of Arts and Science (No. 2019kypygp003), Scientific Research Program Guiding Project of Hubei Provincial Department of Education (B2019135), the Foundation of Hubei University of Arts and Science (Grant No. 2059057), The Open Foundation of Discipline of Hubei University of Arts and Science (Grant No. XK2019038).

References

[1] a) M. Ali, S. Ali, M. Khan, U. Rashid, M. Ahmad, A. Khan, A. Al-Harrasi, F. Ullah, A. Latif, *Bioorg. Chem.* **2018**, *80*, 472–479; b) A. Bocian, A. Gorczyński, D. Marcinkowski, G. Dutkiewicz, V. Patroniak, M. Kubicki, *Acta Crystallogr. Sect. C: Struct. Chem.* **2020**, *76*, 367–374; c) S. R. Chaudhari, P. N. Patil, U. K. Patil, H. M. Patel, J. D. Rajput, N. S. Pawar, D. B. Patil, *Chem. Data. Collect.* **2020**, *25, 100344*; d) M. Faheem, A. Rathaur, A. Pandey, V. Kumar Singh, A. K. Tiwari, *ChemistrySelect* **2020**, *5*, 3981–3994; e) J. Jang, D. H. Kim, C. M. Min, C. Pak, J. S. Lee, *J. Membr. Sci.* **2020**, *605*; f) M. Maruthapandi, L. Eswaran, R. Cohen, N. Perkas, J. H. T. Luong, A. Gedanken, *Langmuir* **2020**, *36*, 4280–4288; g) W. K. Kwok, M. C. Tang, S. L. Lai, W. L. Cheung, L. K. Li, M. Ng, M. Y. Chan, V. W. W. Yam, *Angew. Chem. Int. Ed.* **2020**, *59*, 9684–9692.

[2] L. Su, J. Feng, T. Peng, J. Wan, J. Fan, J. Li, J. O'Connell, D. R. Lancia Jr., G. J. Franklin, G. Liu, *Org. Lett.* **2020**, *22*, 1290–1294.

[3] K. Lavrador-Erb, S. B. Ravula, J. Yu, S. Zamani-Kord, W. J. Moree, R. E. Petroski, J. Wen, S. Malany, S. R. Hoare, A. Madan, P. D. Crowe, G. Beaton, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2916–2919.

[4] H. Park, W. Lim, S. You, G. Song, *Comp. Biochem. Physiol. C: Toxicol. Pharmacol.* **2019**, *220*, 9–19.

[5] M. Gergely, A. Bényei, L. Kollár, *Tetrahedron* **2020**, *76*, 131079.

[6] A. Bocian, M. Szymanska, D. Brykczynska, M. Kubicki, M. Walesa-Chorab, G. N. Roviello, M. A. Fik- Jaskółka, A. Gorczyński, V. Patroniak, *Molecules* **2019**, *24*, 3173.

[7] a) K. Eum, M. Hayashi, M. D. D. Mello, F. Xue, H. T. Kwon, M. Tsapatsis, *Angew. Chem. Int. Ed.* **2019**, *58*, 16390–16394; b) R. Ding, W. Zheng, K. Yang, Y. Dai, X. Ruan, X. Yan, G. He, *Sep. Purif. Technol.* **2020**, *236*, 116209; c) M. Zhang, E. Zhang, C. Hu, Y. Zhao, H. M. Zhang, Y. Zhang, M. Ji, J. Yu, G. Cong, H. Liu, J. Zhang, C. Zhu, J. Xu, *ACS Appl. Mater. Interfaces* **2020**, *12*, 11693–11701.

[8] M. Atar, Ö. Taspinar, S. Hanft, B. Goldfuss, H. G. Schmalz, A. G. Griesbeck, *J. Org. Chem.* **2019**, *84*, 15972–15977.

[9] H. Zhu, X. Chen, X. Li, J. Wang, Z. Hu, X. Ma, *J. Mol. Liq.* **2020**, *297*, 111720.

[10] a) K. Ogawa, K. R. Radke, S. D. Rothstein, S. C. Rasmussen, *J. Org. Chem.* **2001**, *66*, 9067–9070; b) M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965–3968; c) K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843–845; d) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180–190; e) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649;

f) M. A. Topchiy, P. B. Dzhevakov, M. S. Rubina, O. S. Morozov, A. F. Asachenko, M. S. Nechaev, *Eur. J. Org. Chem.* **2016**, 1908–1914; g) K. Mitsudo, K. Shigemori, H. Mandai, A. Wakamiya, S. Suga, *Org. Lett.* **2018**, *20*, 7336–7340; h) J. M. Dennis, N. A. White, R. Y. Liu, S. L. Buchwald, *ACS Catal.* **2019**, *9*, 3822–3830; i) Y. Q. Zhu, R. Zhang, W. Sang, H. J. Wang, Y. Wu, B. Y. Yu, J. C. Zhang, H. Cheng, C. Chen, *Org. Chem. Front.* **2020**, *7*, 1981–1990.

[11] P. Y. Lam, *Synth. Methods Drug Discov.* **2016**, *1*, 242–273.

[12] a) J. Yin, M. M. Zhao M A Huffman, J. M. McNamara, *Org. Lett.* **2002**, *4*, 3481–3484; b) M. A. McGowan, J. L. Henderson, S. L. Buchwald, *Org. Lett.* **2012**, *14*, 1432–1435; c) S. Ueda, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 10364–10367.

[13] a) K. A. Kumar, P. Kannaboina, D. N. Rao, P. Das, *Org. Biomol. Chem.* **2016**, *14*, 8989–8997; b) D. N. Rao, S. Rasheed, K. A. Kumar, A. S. Reddy, P. Das, *Adv. Synth. Catal.* **2016**, *358*, 2126–2133.

[14] a) I. C. Barrett, M. A. Kerr, *Tetrahedron Lett.* **1999**, *40*, 2439–2442; b) M. W. Martin, J. Newcomb, J. J. Nunes, C. Boucher, L. Chai, L. F. Epstein, T. Faust, S. Flores, P. Gallant, A. Gore, Y. Gu, F. Hsieh, X. Huang, J. L. Kim, S. Middleton, K. Morgenstern, A. Oliveira-dos-Santos, V. F. Patel, D. Powers, P. Rose, Y. Tudor, S. M. Turci, A. A. Welcher, D. Zack, H. Zhao, L. Zhu, X. Zhu, C. Ghiron, M. Ermann, D. Johnston, C.-G. P. Saluste, *J. Med. Chem.* **2008**, *51*, 1637–1648; c) L. Benavent, F. Puccetti, A. Baeza, M. Gómez-Martínez, *Molecules* **2017**, *22*,1333; d) S. H. Sharma, J. L. Pablo, M. S. Montesinos, A. Greka, C. R. Hopkins, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 155–159.

[15] I. Kawasaki, N. Taguchi, Y. Yoneda, M. Yamashita, S. Ohta, *Heterocycles* **1996**, *43*, 1375–1379.

[16] W. Sang, A. J. Gavi, B. Y. Yu, H. Cheng, Y. Yuan, Y. Wu, P. Lommens, C. Chen, F. Verpoort, *Chem. Asian J.* **2020**, *15*, 129–135.

[17] E. Shirakawa, K. I. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539.

[18] D. Zornik, R. M. Meudtner, T. El Malah, C. M. Thiele, S. Hecht, *Chem. Eur. J.* **2011**, *17*, 1473–1484.

[19] Y. Luo, F. Xiao, S. Qian, W. Lu, B. Yang, *Eur. J. Med. Chem.* **2011**, *46*, 417–422.

[20] B. Shao, J. Huang, Q. Sun, K. J. Valenzano, L. Schmid, S. Nolan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 719–723.

[21] R. R. Fraser, T. S. Mansour, *J. Org. Chem.* **1984**, *49*, 3442–3443.

[22] L. Spialter, R. W. Moshier, *J. Am. Chem. Soc.* **1957**, *79*, 5955–5957.

