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## Graphical Abstract

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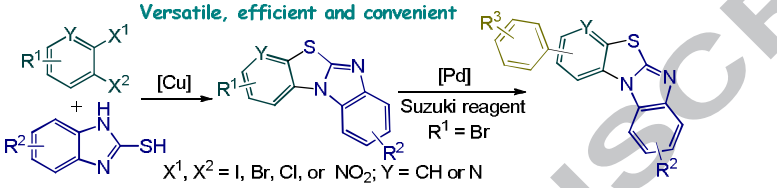

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# Synthesis of benzimidazo[2,1-*b*]benzothiazole derivatives through sequential Cu-catalyzed domino coupling and Pd-catalyzed Suzuki reaction

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ABSTRACT

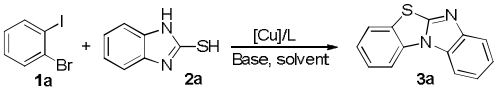
A variety of benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazoles were efficiently and conveniently synthesized from the Cu-catalyzed domino coupling of *o*-dihaloarenes with 2-mercaptobenzimidazoles. The reaction is also applicable to a series of multi-functional substrates, affording the halo-containing products with excellent selectivity. The brominated products can further react with arylboronic acids under Pd catalysis to furnish the aryl-substituted benzimidazo[2,1-*b*]benzothiazole derivatives.

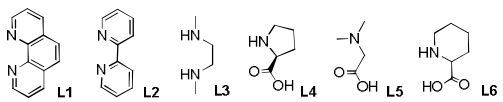


Imidazo[1,2-*b*]thiazoles have attracted considerable attention, since they can be employed as antitumor,[1] antidiabetic,[2] antitubercular[3] and anti-cardiovascular[4] agents. As a subclass of imidazo[2,1-*b*]benzothiazole derivatives,[5] benzo[*d*]benzo[4,5]-imidazo[2,1-*b*]thiazoles, which incorporate benzimidazole and benzothiazole moieties, might possess interesting biological activities and be utilized as drug candidates in therapeutic areas. Although benzimidazo[2,1-*b*]benzothiazole derivatives may play important roles in medicinal chemistry, efficient synthetic routes to them are rarely documented. DeJongh *et al.* found that benzimidazo[2,1-*b*]benzothiazole could be prepared from 1-(2-benzothiazolyl)-benzotriazole using photochemical method.[6] Another method to access such polycyclic molecules is the $S_NAr$ reaction of 2-(2,6-dinitro-4-trifluoromethylphenylthio)benz-imidazole with 2-mercaptobenzimidazole.[7] These methods usually require special starting materials and tedious procedures, and suffer from the low efficiency and narrow scopes. Ma and coworkers developed a one-pot synthesis of benzimidazo[2,1-*b*]thiazoles from the $S_NAr$ reactions of *o*-halonitroarenes/o-dihaloarenes with 2-mercaptoimidazoles.[8] The protocol is efficient and convenient. However, substrates with strong electron-withdrawing groups on the arenes or 2-pyridinyl halorides were required. Such a drawback may restrict the application scope of this domino method.

Transition metal-catalyzed cross-coupling is one of the most useful and efficient strategies in organic synthesis.[9] Because of their low-cost and convenience, Cu-mediated coupling reactions have emerged as powerful tools for C-heteroatom bond formation.[10] And recently, the domino reactions involving Cu-catalyzed coupling as the key steps have aroused increasing interest in modern heterocycle synthesis.[11] However, the reports represent the Cu-mediated one-pot generation of imidazo[2,1-*b*]benzothiazoles are still rare. Recently, Wu *et al.* found that the Cu-catalyzed cascade reaction of 2-iodoaniline and 2-iodobenzothiazole gave benzimidazo[2,1-*b*]benzothiazole,[12] whereas no systematic studies were demonstrated and 2-iodobenzothiazole was synthesized beforehand. Lately, Abele *et al.* reported the synthesis of certain fused imidazo[2,1-*b*]benzothiazoles from *o*-dihaloarenes and 2-mercaptoimidazoles using phase-transfer catalytic system (CuI/KOH/TBAB/phen).[13] Although the transformation could construct the title heterocycles, application of the method would be less attractive due to the harsh conditions required therein (at 140-150 °C and with KOH as the base), the low efficiency (generally in 7-59% yields) and the narrow substrate scope.

**Table 1.** Optimization of the reaction conditions[a]




| Entry | Cat. | L | Base | Sol. | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | CuI | $L_1$ | $K_2CO_3$ | DMF | 85 |

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| | | | | | |
|---|---|---|---|---|---|
| 2 | CuI | $\mathbf{L_2}$ | $K_2CO_3$ | DMF | 75 |
| 3 | CuI | $\mathbf{L_3}$ | $K_2CO_3$ | DMF | 65 |
| 4 | CuI | $\mathbf{L_4}$ | $K_2CO_3$ | DMF | 40 |
| 5 | CuI | $\mathbf{L_5}$ | $K_2CO_3$ | DMF | 73 |
| 6 | CuI | $\mathbf{L_6}$ | $K_2CO_3$ | DMF | 78 |
| 7 | CuI | - | $K_2CO_3$ | DMF | 64 |
| 8 | CuBr | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 78 |
| 9 | CuCl | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 70 |
| 10 | $Cu_2O$ | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 83 |
| 11 | $Cu(OAc)_2$ | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 60 |
| 12 | - | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | trace |
| 13 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 69[c] |
| 14 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 85[d] |
| 15 | CuI | $\mathbf{L_1}$ | $Na_2CO_3$ | DMF | 77 |
| 16 | CuI | $\mathbf{L_1}$ | $Cs_2CO_3$ | DMF | 85 |
| 17 | CuI | $\mathbf{L_1}$ | $K_3PO_4$ | DMF | 75 |
| 18 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 85[e] |
| 19 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMAc | 75[e] |
| 20 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMSO | 61[e] |
| 21 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | NMP | 78[e] |
| 22 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | toluene | 28[e] |
| 23 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 75[e, f] |
| 24 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 86[e, g] |

[a] Reaction conditions: 1-bromo-2-iodobenzene (1.05 mmol), 2-mercaptobenzimidazole (1.0 mmol), Cu catalyst (0.1 mmol, 10 mol%), ligand (0.2 mmol, 20 mol%), base (3 equiv), in dry solvent (3 mL), under $N_2$, at 120 °C for 24 h.

[b] Isolated yield.

[c] CuI (0.05 mmol, 5 mol%) was used as the catalyst.

[d] CuI (0.15 mmol, 15 mol%) was used as the catalyst.

[e] $K_2CO_3$ (2 equiv) was used as the base.

[f] At 110 °C.

[g] At 130 °C.

In continuation of our ongoing efforts to assemble heterocycles using domino transformations,[14] and also to overcome the inherent problems of the previously reported approaches to these useful polycyclic molecules, herein we systematically investigated the Cu-catalyzed domino synthesis of benzimidazo[2,1-*b*]benzothiazoles from various *o*-dihaloarenes and 2-mercaptobenzimidazoles.[14] Comparing with the previous protocols, our method conveniently delivers a wide variety of benzimidazo[2,1-*b*]benzothiazole derivatives with higher efficiency under milder conditions. Furthermore, a series of halo-containing benzimidazo[2,1-*b*]benzothiazoles was selectively prepared from multi-functional substrates, and further derivation of the brominated ones was successfully achieved by Pd-catalyzed Suzuki coupling. In addition, the effect of ligand was also carefully investigated to further enhance the efficiency.

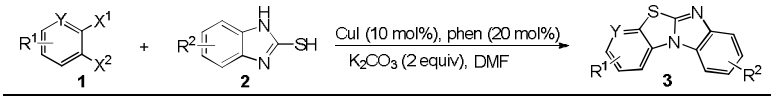
We began our domino synthesis with the reaction between *o*-bromoiodobenzene **1a** and 2-mercaptobenzimidazole **2a**. To our delight, a good yield of desired product **3a** was isolated when the reaction was initially promoted by CuI (10 mol%) and 1,10-phenanthroline (phen, $\mathbf{L_1}$, 20 mol%) with $K_2CO_3$ (3 equiv) as base in DMF at 120 °C (Table 1, entry 1). Different ligands were screened (entries 1-6), and phen was identified as the best. Notably, a moderate yield was obtained in a control experiment without the addition of ligand (entry 7), indicating that binucleophile **2a** itself probably acted as a ligand. We also tested other Cu catalysts such as CuBr, CuCl, $Cu_2O$ and $Cu(OAc)_2$, and CuI performed as the most efficient (compare entry 1 with entries 8-11). Hardly any desired product was detected when the reaction was carried out without any catalyst (entry 12), showing that the Cu catalyst is indispensable for the transformation. The yield decreased when the catalyst loading was decreased to 5 mol% (entry 13). While increasing the amount of the catalyst to 20 mol% did not lead to obvious improvement (entry 14). Various bases were also tested (entries 1 and 15-17). Both $K_2CO_3$ and $Cs_2CO_3$ were suitable, but $K_2CO_3$ was chosen as the preferred base for its low cost. Further investigation found that reducing the amount of $K_2CO_3$ to 2 equiv did not affect the result (entry 18). The effect of solvent was also studied, and DMF was the optimal solvent (compare entry 18 with entries 19-22). Screening on temperature showed that reacting at 120 °C was appropriate for the process (compare entry 18 with entries 23 and 24).

With the optimized conditions in hand, the generality and scope of the domino reaction was evaluated by using various *o*-dihaloarenes and 2-mercaptobenzimidazoles as the materials (Table 2).[15] Initially, we tested *o*-dihalobenzenes bearing different leaving groups ($X^1$, $X^2$) (Table 1, entries 1-6). 1-Bromo-2-iodobenzene acted as the most efficient (entry 1). 1-Chloro-2-iodobenzene and *o*-diiodobenzene also performed well (entries 2-3). Much lower yields were obtained when *o*-dibromobenzene and 1-bromo-2-chlorobenzene were utilized (entries 4-5). Not surprisingly, *o*-dichlorobenzene was ineffective for this domino transformation (entry 6). A variety of 1-bromo-2-iodoarenes with different substituents were then investigated (entries 7-16). In most cases, good to excellent yields of the desired benzimidazo[2,1-*b*]benzothiazoles were delivered within 24 h. Either electron-donating or weak electron-withdrawing groups on the dihalorides could be well tolerated (entries 7-13 and 15-16).[16] However, the strong electron-withdrawing group on the *o*-dihaloride gave a negative effect on the reaction and a moderate yield was obtained (entry 14).[16] Notably, heteroaromatic substrate such as 3-bromo-2-iodopyridine **1o** was also proved applicable, giving the desired benzo[4',5']imidazo[2',1':2,3]-thiazolo[5,4-*b*]pyridine **3j** in 92% yield (entry 15). Pentacyclic benzimidazo[2,1-*b*]benzothiazole **3k** was selectively assembled in an excellent yield from 1-bromo-2-iodonaphthalene **1p** (entry 16). A low yield was isolated when dibromoalkene **1q** was tested, probably due to the special activity of the dibromoalkene and/or the instability of the product in these conditions (entry 17). We also investigated the domino reactions with substituted 2-mercaptobenzimidazoles (Table 2, entries 18-21). Both electron-donating and electron-withdrawing substituents (Me, MeO, Cl, and $NO_2$) on the phenyl ring of the binuclephiles were also compatible with the conditions. 5-Nitro-1*H*-benzo[*d*]imidazole-2-thiol (**2e**) afforded a relatively lower yield, maybe because of its weaker nucleophilicity (entry 21). As expected, in these cases, the substituted 2-mercaptobenzimidazole gave a mixture of two regioisomers, due to the two different tautomerization directions of the binuclephiles.

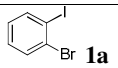
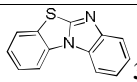
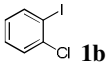
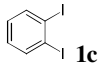
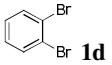
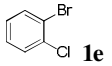
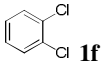
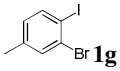
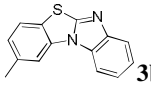
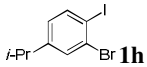
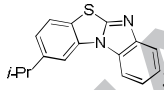
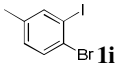
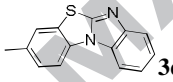
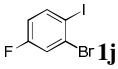
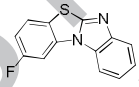
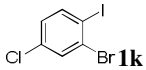
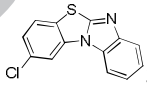
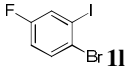
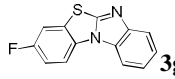
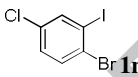
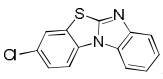
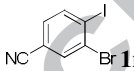
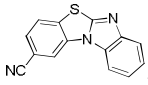
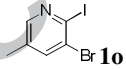
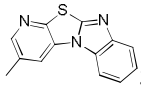
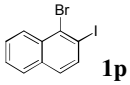
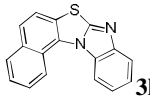
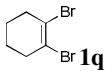
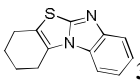
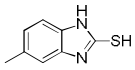
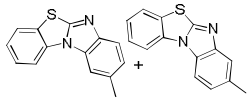
As shown in Scheme 1, the utility of the present method is demonstrated by the scale-up experiment, where running the

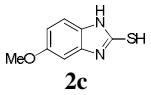
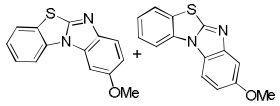
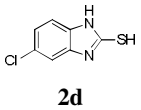
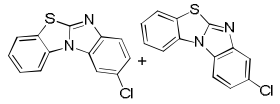
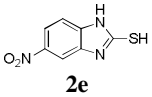
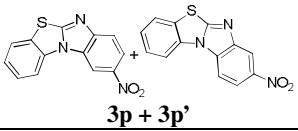
reaction between **1a** and **2a** on 10 mmol scale in a simple two-necked flask delivered the desired product **3a** in good yield.

**Table 2.** Cu-catalyzed one-pot synthesis of benzimidazo[2,1-*b*]benzothiazoles.




1 + 2 → 3

| Entry | Substrate **1** | Nucleophile **2** | Product **3** | Time (h) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 |  **1a** | **2a** |  **3a** | 24 | 85 |
| 2 |  **1b** | **2a** | **3a** | 28 | 80 |
| 3 |  **1c** | **2a** | **3a** | 18 | 78 |
| 4 |  **1d** | **2a** | **3a** | 36 | 45 |
| 5 |  **1e** | **2a** | **3a** | 40 | 25 |
| 6 |  **1f** | **2a** | **3a** | 48 | trace |
| 7 |  **1g** | **2a** |  **3b** | 24 | 82 |
| 8 |  **1h** | **2a** |  **3c** | 24 | 78 |
| 9 |  **1i** | **2a** |  **3d** | 24 | 87 |
| 10 |  **1j** | **2a** |  **3e** | 24 | 77 |
| 11 |  **1k** | **2a** |  **3f** | 24 | 74 |
| 12 |  **1l** | **2a** |  **3g** | 24 | 73 |
| 13 |  **1m** | **2a** |  **3h** | 24 | 70 |
| 14 |  **1n** | **2a** |  **3i** | 25 | 56<br>65[c] |
| 15 |  **1o** | **2a** |  **3j** | 18 | 92 |
| 16 |  **1p** | **2a** |  **3k** | 18 | 95 |
| 17 |  **1q** | **2a** |  **3l** | 24 | 28<br>42[d] |
| 18 | **1a** |  **2b** |  **3m + 3m'** | 24 | 68<br>(51:49)[e] |

| | | | | | |
|---|---|---|---|---|---|
| 19 | **1a** |  **2c** |  **3n + 3n'** | 24 | 74 (63:37)[e] |
| 20 | **1a** |  **2d** |  **3o + 3o'** | 24 | 72 (67:33)[e] |
| 21 | **1a** |  **2e** |  **3p + 3p'** | 36 | 57 (80:20)[e] |

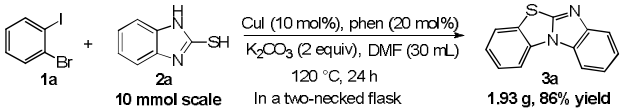
[a] Reaction conditions: substrate **1** (1.05 mmol), 2-mercaptobenzimidazole **2** (1.0 mmol), CuI (0.1 mmol, 10 mol%), phen (0.2 mmol, 20 mol%) and $K_2CO_3$ (2 equiv) in DMF (3 mL) under $N_2$ at 120 °C.

[b] Isolated yield.

[c] 2,9-Dimethyl-1,10-phenanthroline (neocuproine) was utilized as the ligand instead of phen.

[d] 2,2'-Bipyridyl (bipy) was utilized as the ligand instead of phen.

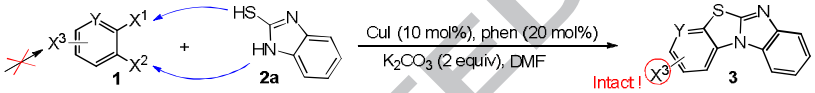
[e] A mixture of two isomers was obtained (the isomeric ratio in parenthesis was approximately determined by $^1$H NMR).

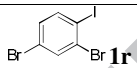
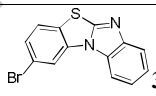
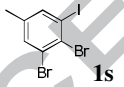
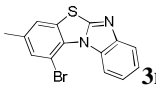
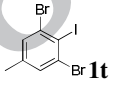
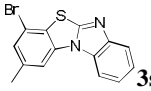
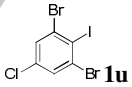
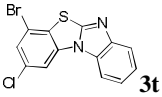
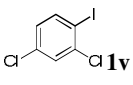
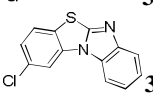
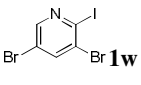
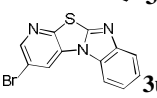
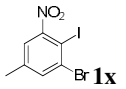
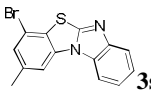


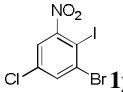
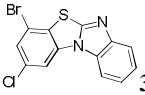

**Scheme 1.** Scale-up experiment for the synthesis of product **3a**

Further studies showed that a range of functional substituents such as Cl, Br and $NO_2$ on the *o*-dihaloarenes were also compatible under our conditions, which might provide an additional handle for further derivation of the products. As shown in Table 3, a variety of tri-functionalized substrates **1s-1y** were utilized to react with **2a**, and the desired halo-containing benzimidazo[2,1-*b*]benzothiazoles were exclusively obtained in moderate to excellent yields. It is noticeable that 1,2-dibromo-3-iodobenzene **1s** presents the highest reactivity and gave 94% yield of the brominated product (Table 3, entry 2). While 1-bromo-2-iodo-3-nitrobenzenes were relatively less reactive and afforded the products in moderate yields (entries 7 and 8).

**Table 3.** Cu-catalyzed selective one-pot synthesis of halo-containing benzimidazo[2,1-*b*]benzothiazoles[a]




| Entry | $R_2$ | Product 3 | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1r** |  **3q** | 22 | 70 |
| 2 |  **1s** |  **3r** | 18 | 94 |
| 3 |  **1t** |  **3s** | 30 | 68 |
| 4 |  **1u** |  **3t** | 36 | 61 |
| 5 |  **1v** |  **3f** | 30 | 69 |
| 6 |  **1w** |  **3u** | 35 | 76 |
| 7 |  **1x** |  **3s** | 30 | 53<br>54[c] |

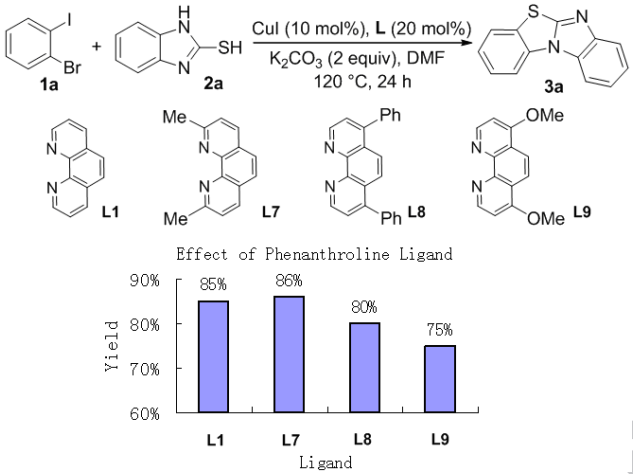
| | | | | |
|---|---|---|---|---|
| 8 |  **1y** |  **3t** | 36 | 41<br>49[c] |

[a] Reaction conditions: substrate **1** (1.05 mmol), 2-mercaptobenzimidazole **2a** (1.0 mmol), CuI (0.1 mmol, 10 mol%), phen (0.2 mmol, 20 mol%), and $K_2CO_3$ (2 mmol, 2 equiv) in DMF (3 mL) under $N_2$ at 120 °C.

[b] Isolated yield.

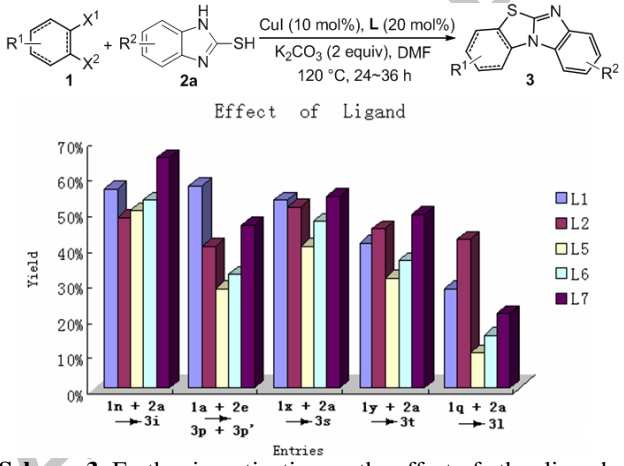
[c] Neocuproine was utilized as the ligand instead of phen.

To further probe the ligand effect on these cascade reactions, structurally modified phenanthroline ligands ($\mathbf{L_7}$-$\mathbf{L_9}$) were also examined for the reaction between **1a** and **2a** (Scheme 2). And it was found that neocuproine ($\mathbf{L_7}$) showed slightly better than phen ($\mathbf{L_1}$), whereas 4,7-diphenyl-1,10-phenanthroline ($\mathbf{L_8}$) and 4,7-dimethoxyl 1,10-phenanthroline ($\mathbf{L_9}$) were inferior to $\mathbf{L_1}$.




**Scheme 2.** The effect of phenanthroline ligand

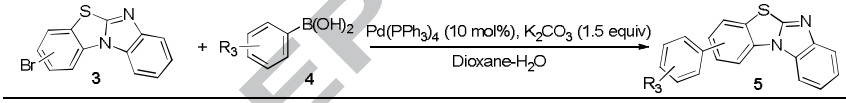
Considering that other types of ligands such as 2,2'-bipyrridyl (Bipy, **L2**), *N,N*-dimethylglycine (DMG, **L5**) and pipecolinic acid (**L6**) afforded comparable level of efficiency (Table 1), the effects of these ligands (including $\mathbf{L_7}$) for the unsatisfactory entries under the promotion of phen (Table 2, entries 14, 17 and 21; Table 3, entries 7 and 8) were also investigated (Scheme 3).

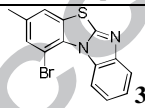
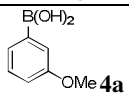
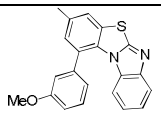
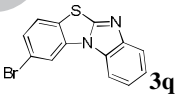
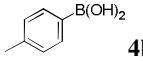
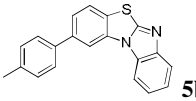
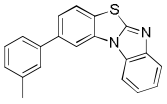
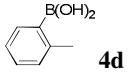
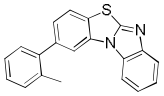


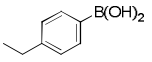
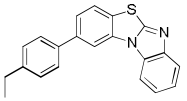
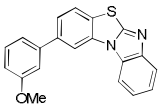
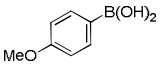
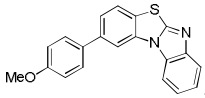

**Scheme 3.** Further investigation on the effect of other ligands

As shown in Scheme 3, for the reactions of electron-poor substrates **1** (**1n**, **1x** and **1y**) with **2a**, neocuproine ($\mathbf{L_7}$) was the most efficient ligand (phen also acted as a good candidate for these reactions). However, phen appeared to be the optimal promoter for the reaction with electron-deficient binucleophile 5-nitro-1*H*-benzo[*d*]imidazole-2-thiol (**2e**). And the domino reactions of **1q** indicated that bipy $\mathbf{L_2}$ was the best ligand when dibromoalkene was utilized as the substrate.

**Table 4.** Pd-catalyzed reactions of bromo-containing benzimidazo[2,1-*b*]benzothiazoles with arylboronic acids[a]




| Entry | Compound **3** | Reagent **4** | Product **5** | Time (h) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 |  **3r** |  **4a** |  **5a** | 15 | 72 |
| 2 |  **3q** |  **4b** |  **5b** | 10 | 83 |
| 3 | **3q** |  **4c** |  **5c** | 10 | 85 |
| 4 | **3q** |  **4d** |  **5d** | 18 | 82 |

| | | | | | |
|---|---|---|---|---|---|
| 5 | **3q** |  **4e** |  **5e** | 12 | 79 |
| 6 | **3q** | **4a** |  **5f** | 10 | 80 |
| 7 | **3q** |  **4f** |  **5g** | 15 | 88 |

[a] Reaction conditions: benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (0.3 mmol, 1 equiv), arylboronic acid (0.45 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.1 mmol, 10 mol%), and $K_2CO_3$ (0.45 mmol, 1.5 equiv) in dioxane/$H_2O$ (6 mL, 5:1, v:v) under $N_2$ at 100 °C.

[b] Isolated yield.

The derivation of the halo benzimidazo[2,1-*b*]benzothiazoles is also feasible. We found that under proper Pd catalysis, several bromo-containing products could smoothly react with arylboronic acids to afford the corresponding arylated benzimidazo[2,1- *b*]benzothiazole derivatives (Table 4, entries 1-7).[17] As a novel class of imidazo[2,1-*b*]benzothiazole derivatives, these polycyclic molecules possess unprecedented structural features and might be of particular biological interest.

In summary, we have described an efficient and convenient approach to benzimidazo[2,1-*b*]benzothiazoles through Cu-catalyzed domino reactions. A variety of *o*-dihaloarenes and 2-mercaptobenzimidazoles with electron-donating and electron-withdrawing substituents smoothly gave the desired products. Moreover, tri-functionalized substrates selectively delivered the halo-containing benzimidazo[2,1-*b*]benzothiazoles, and the brominated ones successfully reacted with arylboronic acids under Pd catalysis to give the corresponding aryl benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole derivatives. The methodology may be practical and useful for the synthesis of related heterocyclic compounds of biological and medicinal interests.

## Acknowledgments

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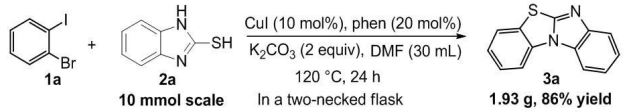
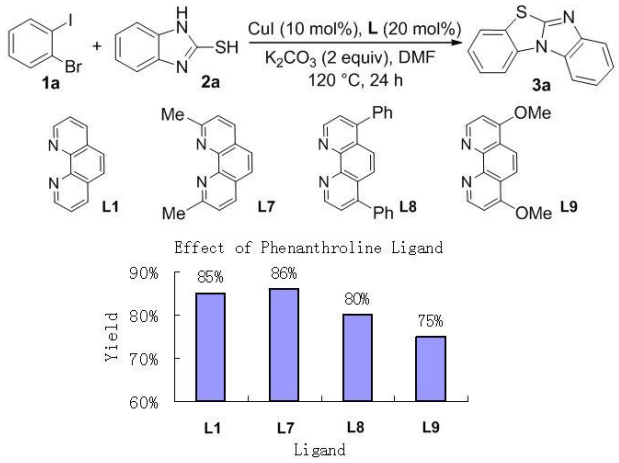
## References and notes

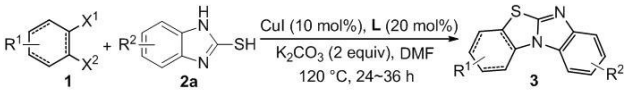
1. (a) Park, J. –H.; El-Gamal, M. I.; Lee, Y. S.; Oh, C. –H. *Eur. J. Med. Chem.* **2011**, *46*, 5769-5777. (b) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N. S.; Shoemaker, R. H. *J. Med. Chem.* **2008**, *51*, 809-816. (c) Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Bossa, R.; Fraccari, A.; Galatulas, I.; Salvatore, G. *J. Med. Chem.* **1996**, *39*, 2852-2855. (d) Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Fraccari, A.; Galatulas, I.; *J. Med. Chem.* **1992**, *35*, 4634-4637.
2. Vu, C. B.; Bemis, J. E.; Disch, J. S.; Ng, P. Y.; Nunes, J. J.; Milne, J. C.; Carney, D. P.; Lynch, A. V.; Smith, J. J.; Lavu, S.; Lambert, P. D.; Gagne, D. J.; Jirousek, M. R.; Schenk, S.; Olefsky, J. M.; Perni, R. B. *J. Med. Chem.* **2009**, *52*, 1275-1283.
3. Moraski, G. C.; Markley, L. D.; Chang, M.; Cho, S.; Franzblau, S. G.; Hwang, C. H.; Boshoff, H.; Miller, M. J. *Boorg. Med. Chem.* **2012**, *20*, 2214-2220.
4. (a) Locatelli, A.; Cosconati, S.; Micucci, M.; Leoni, A.; Marinelli, L.; Bedini, A.; Loan, P.; Spampinato, S. M.; Novellino, E.; Chiarini, A.; Budriesi, R. *J. Med. Chem.* **2013**, *56*, 3866-3877. (b) Budriesi, R.; Ioan, P.; Locatelli, A.; Cosconati, S.; Leoni, A.; Ugenti, M. P.; Andreani, A.; Toro, R. D.; Bedini, A.; Spampinato, S.; Marinelli, L.; Novellino, E.; Chiarini, A. *J. Med. Chem.* **2008**, *51*, 1592-1600.
5. Several imidazo[2,1-*b*]benzothiazoles have been reported as potential drugs with antineuropathic, antimicrobial, and anticancer activities. For examples, see: (a) Yousefi, B. H.; Manook, A.; Drzezga, A.; Reutern, B.; Schwaiger, M.; Wester, H. J.; Henriksen, G. *J. Med. Chem.* **2011**, *54*, 949-956. (b) Malik, J. K.; Noolvi, M. N.; Manvi, F. V.; Nanjwade, B. K.; Patel, H. M.; Manjula, S. N.; Rao, C. M.; Barve, A. *Lett. Drug Des. Discov.* **2011**, *8*, 717-724. (c) Al-Tel, T. H.; Al-Qawasmeh, R. A.; Zaarour, R. *Eur. J. Org. Chem.* **2011**, *46*, 1874-1881. (d) Palkar, M.; Noolvi, M.; Sankangoud, R.; Maddi, V.; Gadad, A.; Nargund, L. V. G. *Arch. Pharm.* **2010**, *343*, 353-359.
6. Lin, D. C. K.; DeJongh, D. C. *J. Org. Chem.* **1974**, *39*, 1780-1782.
7. D'Amico, J. J.; Tung, C. C.; Dahl, W. E. *J. Org. Chem.* **1977**, *42*, 600-602.
8. Zhang, X. H.; Jia, J.; Ma, C. *Org. Biomol. Chem.* **2012**, *10*, 7944-7948.
9. For selected reviews, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596-1636. (b) Carril, M.; SanMartin, R.; Dominguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639-647. (c) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd. Wiley-VCH: Weinheim, Germany, 2004.
10. For selected recent reviews, see: (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13-31. (b) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971. (c) Ma, D. W.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450-1460. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054-3131.
11. For reviews, see: (a) Liu, Y.; Wan, J. –P. *Chem. Asian J.* **2012**, *7*, 1488-1501. (b) Liu, Y.; Wan, J. –P. *Org. Biomol. Chem.* **2011**, *9*, 6873-6894.
12. Wu, Z. Q.; Huang, Q.; Zhou, X. G.; Yu, L. T.; Li, Z. K.; Wu, D. *Eur. J. Org. Chem.* **2011**, 5242-5245.
13. During the preparation of this manuscript, Abele *et al.* reported the synthesis of the fused imidazo[2,1-*b*]benzothiazoles from *o*-dihaloarenes and 2-mercaptoimidazoles using phase-transfer catalytic system: (a) Abele, E.; Beresneva, T. *Heterocycl. Lett.* **2013**, *3*, 397-401. (b) Beresneva, T.; Abele, E. *Chem. Heterocycl. Comp.* **2013**, *49*, 345-347.
14. (a) Yuan, G.; Liu, H.; Gao, J.; Yang, K.; Niu, Q.; Mao, H.; Wang, X.; Lv, X.; *J. Org. Chem.* **2014**, *79*, 1749-1757. (b) Niu, Q.; Mao, H.; Yuan, G.; Gao, J.; Liu, H.; Tu, Y.; Wang, X.; Lv, X. *Adv. Synth. Catal.* **2013**, *355*, 1185-1192. (c) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. *Org. Biomol. Chem.* **2012**, *10*, 1602-1611.
15. *General procedure for Cu-catalyzed one-pot synthesis of benzimidazo[2,1-b]benzothiazoles.* An oven-dried Schlenk tube was charged with a magnetic stir bar, binucleophile 2-mercaptobenzimidazole **2** (1.0 mmol, 1.0 equiv), CuI (0.1 mmol, 10 mol %), phen (0.2 mmol, 20 mol %), and $K_2CO_3$ (2.0 mmol, 2 equiv). The tube was capped and then evacuated and backfilled with nitrogen (3 times). Under a positive pressure of nitrogen, a solution of *o*-dihaloarene **1** (1.05 mmol, 1.05 equiv) in DMF (3 mL) was added *via* syringe. The tube was sealed and allowed to stir at 120 °C (monitored by TLC). After being cooled to room temperature, EtOAc (40 mL) was added and the mixture was washed with brine (20 mL × 3). The organic phase was dried over $Na_2SO_4$ and concentrated. The residue was purified by column

chromatography on silica gel using petrol/EtOAc (10:1 → 3:1, v:v) as eluent to give product **3**.

16. The phenomenon is different from Ma's report, indicating that the present reaction may undergo a different pathway instead of the $S_NAr$ process.
17. *General procedure for Pd-catalyzed coupling of brominated benzimidazo[2,1-b]benzothiazoles with benzoboric acids.* An oven-dried Schlenk tube was charged with a magnetic stir bar, brominated benzimidazo[2,1-*b*]benzothiazole **3** (0.3 mmol, 1 equiv), arylboronic acid **4** (0.45 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.03 mmol, 10 mol %), and $K_2CO_3$ (0.45 mmol, 1.5 equiv). The tube was capped and then evacuated and backfilled with nitrogen (3 times). Under a positive pressure of nitrogen, $H_2O$ (1 mL) and 1,4-dioxane (5 mL) was then added subsequently. The tube was sealed and allowed to stir at 100 °C (monitored by TLC). After being cooled to room temperature, $CH_2Cl_2$ (20 mL) was added and the mixture was washed with brine (10 mL × 3). The organic phase was dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography on silica gel using petrol/EtOAc (15:1 → 8:1, v:v) as eluent to give product **5**.







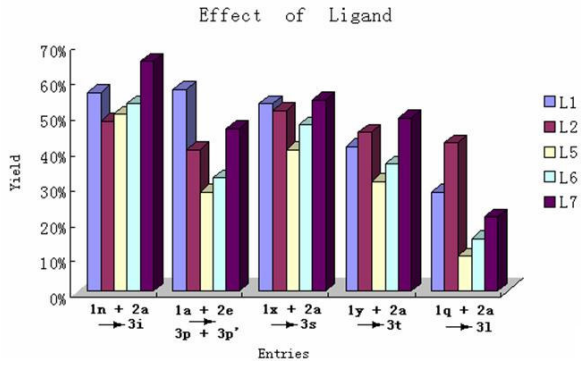
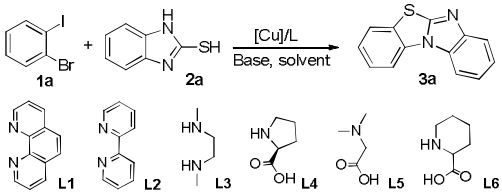



**Table 1.** Optimization of the reaction conditions[a]




| Entry | Cat. | L | Base | Sol. | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 85 |
| 2 | CuI | $\mathbf{L_2}$ | $K_2CO_3$ | DMF | 75 |
| 3 | CuI | $\mathbf{L_3}$ | $K_2CO_3$ | DMF | 65 |
| 4 | CuI | $\mathbf{L_4}$ | $K_2CO_3$ | DMF | 40 |
| 5 | CuI | $\mathbf{L_5}$ | $K_2CO_3$ | DMF | 73 |
| 6 | CuI | $\mathbf{L_6}$ | $K_2CO_3$ | DMF | 78 |
| 7 | CuI | - | $K_2CO_3$ | DMF | 64 |
| 8 | CuBr | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 78 |
| 9 | CuCl | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 70 |
| 10 | $Cu_2O$ | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 83 |
| 11 | $Cu(OAc)_2$ | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 60 |
| 12 | - | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | trace |
| 13 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 69[c] |
| 14 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 85[d] |
| 15 | CuI | $\mathbf{L_1}$ | $Na_2CO_3$ | DMF | 77 |
| 16 | CuI | $\mathbf{L_1}$ | $Cs_2CO_3$ | DMF | 85 |
| 17 | CuI | $\mathbf{L_1}$ | $K_3PO_4$ | DMF | 75 |
| 18 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 85[e] |
| 19 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMAc | 75[e] |
| 20 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMSO | 61[e] |
| 21 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | NMP | 78[e] |
| 22 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | toluene | 28[e] |
| 23 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 75[e, f] |
| 24 | CuI | $\mathbf{L_1}$ | $K_2CO_3$ | DMF | 86[e, g] |

[a] Reaction conditions: 1-bromo-2-iodobenzene (1.05 mmol), 2-mercaptobenzimidazole (1.0 mmol), Cu catalyst (0.1 mmol, 10 mol%), ligand (0.2 mmol, 20 mol%), base (3 equiv), in dry solvent (3 mL), under $N_2$, at 120 °C for 24 h.

[b] Isolated yield.

[c] CuI (0.05 mmol, 5 mol%) was used as the catalyst.

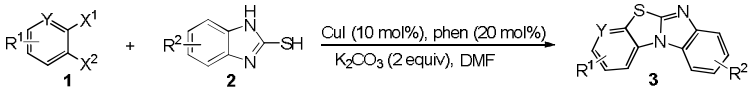
[d] CuI (0.15 mmol, 15 mol%) was used as the catalyst.

[e] $K_2CO_3$ (2 equiv) was used as the base.

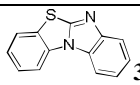
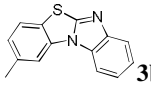
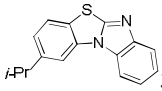
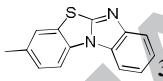
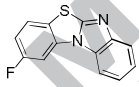
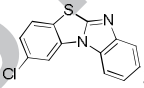
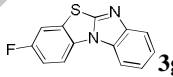
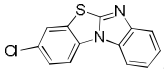
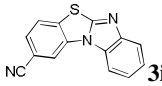
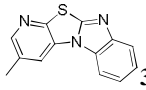
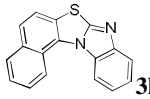
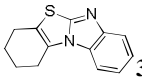
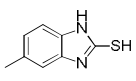
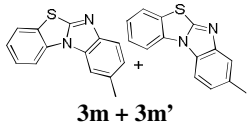
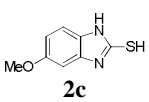
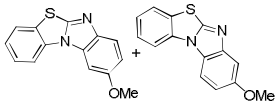
[f] At 110 °C.

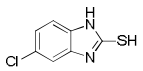
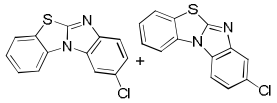
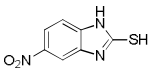
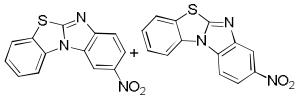
[g] At 130 °C.

**Table 2.** Cu-catalyzed one-pot synthesis of benzimidazo[2,1-*b*]benzothiazoles.




1 + 2 → 3

| Entry | Substrate **1** | Nucleophile **2** | Product **3** | Time (h) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 |  **1a** | **2a** |  **3a** | 24 | 85 |
| 2 |  **1b** | **2a** | **3a** | 28 | 80 |
| 3 |  **1c** | **2a** | **3a** | 18 | 78 |
| 4 |  **1d** | **2a** | **3a** | 36 | 45 |
| 5 |  **1e** | **2a** | **3a** | 40 | 25 |
| 6 |  **1f** | **2a** | **3a** | 48 | trace |
| 7 |  **1g** | **2a** |  **3b** | 24 | 82 |
| 8 |  **1h** | **2a** |  **3c** | 24 | 78 |
| 9 |  **1i** | **2a** |  **3d** | 24 | 87 |
| 10 |  **1j** | **2a** |  **3e** | 24 | 77 |
| 11 |  **1k** | **2a** |  **3f** | 24 | 74 |
| 12 |  **1l** | **2a** |  **3g** | 24 | 73 |
| 13 |  **1m** | **2a** |  **3h** | 24 | 70 |
| 14 |  **1n** | **2a** |  **3i** | 25 | 56<br>65[c] |
| 15 |  **1o** | **2a** |  **3j** | 18 | 92 |
| 16 |  **1p** | **2a** |  **3k** | 18 | 95 |
| 17 |  **1q** | **2a** |  **3l** | 24 | 28<br>42[d] |
| 18 | **1a** |  **2b** |  **3m + 3m'** | 24 | 68<br>(51:49)[e] |
| 19 | **1a** |  **2c** |  | 24 | 74<br>(63:37)[e] |

| | | | | | |
|---|---|---|---|---|---|
| | | | **3n + 3n'** | | |
| 20 | **1a** |  **2d** |  | 24 | 72 (67:33)[e] |
| | | | **3o + 3o'** | | |
| 21 | **1a** |  **2e** |  | 36 | 57 (80:20)[e] |
| | | | **3p + 3p'** | | |

[a] Reaction conditions: substrate **1** (1.05 mmol), 2-mercaptobenzimidazole **2** (1.0 mmol), CuI (0.1 mmol, 10 mol%), phen (0.2 mmol, 20 mol%) and $K_2CO_3$ (2 equiv) in DMF (3 mL) under $N_2$ at 120 °C.

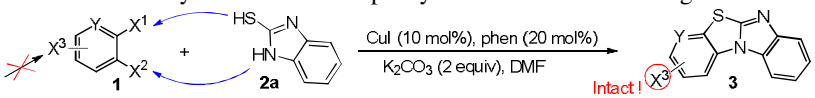
[b] Isolated yield.

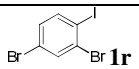
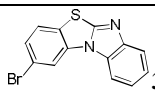
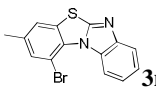
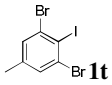
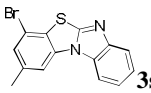
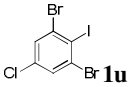
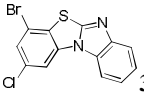
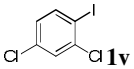
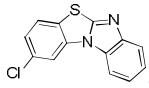
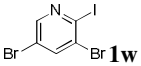
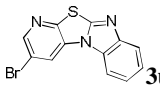
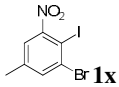
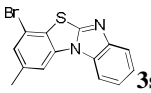
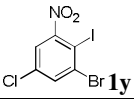
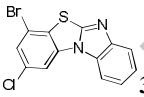
[c] 2,9-Dimethyl-1,10-phenanthroline (neocuproine) was utilized as the ligand instead of phen.

[d] 2,2'-Bipyridyl (bipy) was utilized as the ligand instead of phen.

[e] A mixture of two isomers was obtained (the isomeric ratio in parenthesis was approximately determined by $^1$H NMR).

**Table 3.** Cu-catalyzed selective one-pot synthesis of halo-containing benzimidazo[2,1-*b*]benzothiazoles[a]



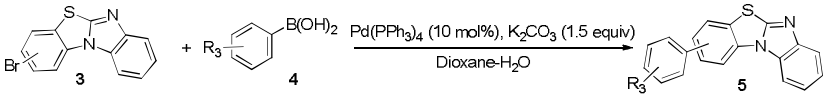

| Entry | $R_2$ | Product 3 | Time (h) | Yield (%) [b] |
|---|---|---|---|---|
| 1 |  **1r** |  **3q** | 22 | 70 |
| 2 |  **1s** |  **3r** | 18 | 94 |
| 3 |  **1t** |  **3s** | 30 | 68 |
| 4 |  **1u** |  **3t** | 36 | 61 |
| 5 |  **1v** |  **3f** | 30 | 69 |
| 6 |  **1w** |  **3u** | 35 | 76 |
| 7 |  **1x** |  **3s** | 30 | 53<br>54[c] |
| 8 |  **1y** |  **3t** | 36 | 41<br>49[c] |

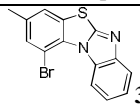
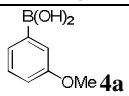
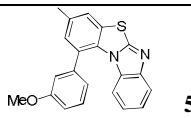
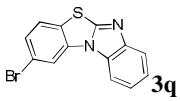
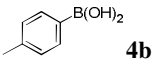
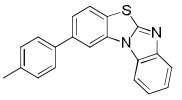
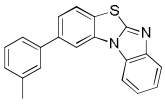
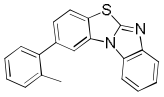
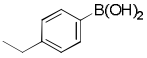
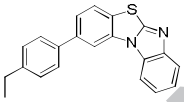
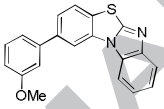
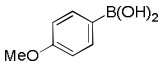
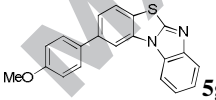
[a] Reaction conditions: substrate **1** (1.05 mmol), 2-mercaptobenzimidazole **2a** (1.0 mmol), CuI (0.1 mmol, 10 mol%), phen (0.2 mmol, 20 mol%), and $K_2CO_3$ (2 mmol, 2 equiv) in DMF (3 mL) under $N_2$ at 120 °C.

[b] Isolated yield.

[c] Neocuproine was utilized as the ligand instead of phen.

**Table 4.** Pd-catalyzed reactions of bromo-containing benzimidazo[2,1-*b*]benzothiazoles with arylboronic acids[a]




| Entry | Compound **3** | Reagent **4** | Product **5** | Time (h) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 |  **3r** |  **4a** |  **5a** | 15 | 72 |
| 2 |  **3q** |  **4b** |  **5b** | 10 | 83 |
| 3 | **3q** |  **4c** |  **5c** | 10 | 85 |
| 4 | **3q** |  **4d** |  **5d** | 18 | 82 |
| 5 | **3q** |  **4e** |  **5e** | 12 | 79 |
| 6 | **3q** | **4a** |  **5f** | 10 | 80 |
| 7 | **3q** |  **4f** |  **5g** | 15 | 88 |

[a] Reaction conditions: benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (0.3 mmol, 1 equiv), arylboronic acid (0.45 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.1 mmol, 10 mol%), and $K_2CO_3$ (0.45 mmol, 1.5 equiv) in dioxane/$H_2O$ (6 mL, 5:1, v:v) under $N_2$ at 100 °C.

[b] Isolated yield.

## *Graphical Abstract*

**Synthesis of benzimidazo[2,1-*b*]benzothiazole derivatives through sequential Cu-catalyzed domino coupling and Pd-catalyzed Suzuki reaction**

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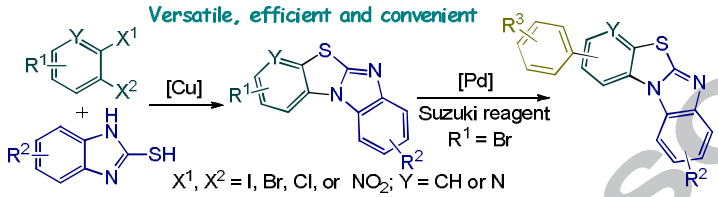


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