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Synergic effect of copper-based metal–organic frameworks for highly efficient C–H activation of amidines†

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A Cu–MOF-catalyzed C–H functionalization of substituted amidines was developed for the facile and efficient synthesis of benzimidazoles. More importantly, this transformation is compatible with various substrates derived from aryl nitriles without *ortho* substituents. Under reaction conditions devoid of O_2 atmosphere or specific groups, **537-MOF** has been revealed as a key parameter for expanding the reaction scope and increasing the yield up to 96%. Importantly, this strategy also provides numerous opportunities for further utilization of MOFs as catalysts for challenging organic reactions.
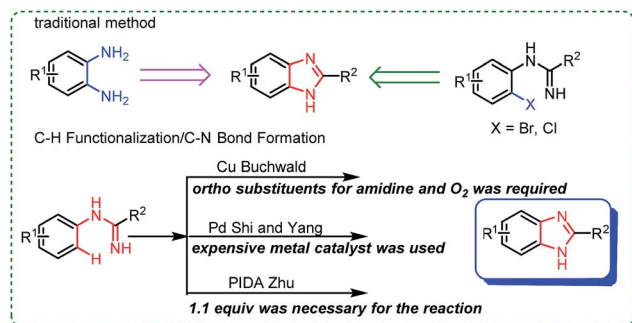
Activation of C–H bonds has been identified as a straightforward and untraditional strategy for the decoration of unreactive hydrocarbon skeletons in terms of its broad application in synthesis of pharmacological active agents, natural products, and functional materials.[1] Given the prevalence and relevance of heteroatoms in molecules of interest, C–Het bond formation *via* direct functionalization of C–H bonds has received considerable attention. In this context, numerous transition metal complexes, especially of Rh,[2] Ir,[3] Co,[4] Ru,[5] Pd[6] and others,[7] have exhibited outstanding catalytic efficiency towards C–H bond functionalization reactions.

Benzimidazoles have been deemed to be valuable intermediates and significant building blocks for the construction of
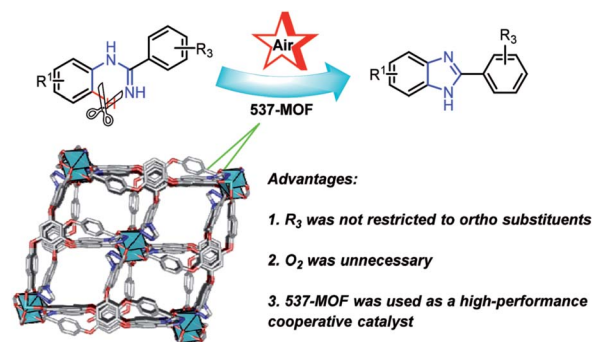
natural products and for achieving the extension of molecule complexity.[8] Conventional synthetic routes to this scaffold rely predominantly on condensation of carbonyl derivatives with 1,2-phenylenediamines.[9] Nevertheless, this strategy was impeded because of the limited availability of 1,2-phenylenediamines and the disadvantage of further derivations. Several other approaches toward the synthesis of benzimidazoles have also been reported, though the use of stoichiometric amounts of reagents and limited substrate scope were formidable obstacles.[10] Chemists have attempted to fabricate benzimidazole derivates by replacement of a C–H bond from amidines,[11] refraining from utilization of halogenated and pseudohalogenated substrates to abbreviate or avoid waste byproducts (Scheme 1).[12] In general, high temperature, inert atmosphere or high loading of oxidants was required.[13] Besides noble transition-metal catalysts, there have been reports on low-cost and low-toxic copper-catalyze C–H derivation of amidines to deliver benzimidazoles, whereas there remained several issues

Scheme 1 Catalytic strategies for the formation of benzimidazoles.

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Scheme 2 Synthesis of benzimidazoles from amidines *via* C–H functionalization reaction catalyzed by **537-MOF**.
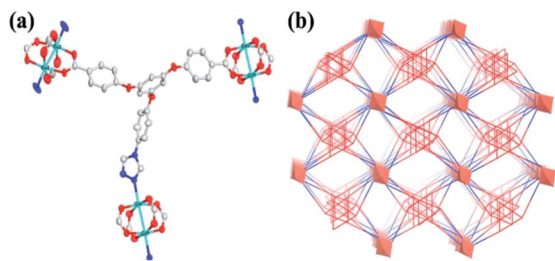
Fig. 1 (a) Illustrations of the coordination mode of TPPB^{2-} ligand. (b) View of (3,6)-connected **rtl** topology of **537-MOF**.

to be resolved. Representatively, Buchwald *et al.* developed an C–H functionalization/C–N bond formation reaction to afford benzimidazoles under an oxygen atmosphere.[14] However, amidines derived from aryl nitriles without *ortho* substituents demonstrated frustrating conversion due to the decomposition of substrates, which mainly retard the catalytic cycle. In addition, 2-phenyl-1*H*-benzo[*d*]imidazole was obtained in only 44% yield under an air atmosphere. Thus, the development of effective and low-cost catalytic system under reaction conditions devoid of O$_2$ atmosphere and specific groups was highly demanded.

Metal–organic frameworks (MOFs), assembled from metal cluster secondary building units (SBUs) and organic linkers, have emerged as a class of highly promising porous materials with the advantages of high porosity, tunable compositions, and decorative pore surface,[15] as evidenced by wide potential for various applications in drug deliver[16] and separation,[17] gas storage,[18] chemical sensing.[19] Furthermore, using crystalline MOFs as heterogeneous catalyst provides opportunities for sustainable chemistry, thereby reducing waste and costs as well as boosting the overall efficiency of a catalyst.[20] For example, Cohen *et al.*[21] discovered that UiO-66-PdTCAT with site-isolated Pd can be applied to C–H derivation and high catalytic activity of UiO-66-PdTCAT can be attributed to the strong covalent metalthiocatecholato binding. Recently, a heterogeneous nanoscaled [Cu$_3$(BTC)$_2$] catalyst was furnished and applied to the aerobic oxidation of aromatic alcohols with excellent catalytic reactivity originated from the aromatic carboxylate ligand.[22] Inspired by the above work, combined with the advantages of shape and size selectivity,[23] and lower activity comparing with homogeneous catalysts to decrease the side reaction, we devote to develop a new effective MOFs catalyst to control the selectivity and catalytic activity in C–H functionalization of amidines. Herein, we described successful fabrication of a highly porous MOF, Cu$_2$N$_2$(CO$_2$)$_4$ (**537-MOF**), that shows remarkably high efficiency on catalytic synthesis of benzimidazoles *via* C–H functionalization under air atmosphere with broad substrates scope (Scheme 2).

Single-crystal X-ray diffraction analysis reveals that **537-MOF** {[Cu$_2$(TPPB)$_2$](DMF)$_6$} crystallizes in the triclinic space group $\bar{P}1$. The Cu1 and Cu2 atoms are bridged by four bridging carboxylate groups from TPPB^{2-} ligands, forming a {Cu$_2$(O$_2$C)$_4$} secondary building unit (SBU) with a short Cu–Cu distance of 2.70 Å. As a result, each TPPB^{2-} ligand binding to three 6-

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Additive	Yield^b
1^{c,d}	**537-MOF**	HOAc	64
2^d	**537-MOF**	HOAc	59
3^{d,e}	**537-MOF**	HOAc	54
4	HKUST-1	HOAc	40
5	**537-MOF**	HOAc	73
6	**537-MOF**	HCOOH	21
7	**537-MOF**	MBSA	Trace
8	**537-MOF**	Benzoic acid	96
9	**537-MOF**	2-Fluorobenzoic acid	62
10	**537-MOF**	2-Bromobenzoic acid	13
11	**537-MOF**	2,3,4-Trifluorobenzoic acid	26
12	**537-MOF**	2,3,4,5-Tetrafluorobenzoic acid	11

^{a} Reaction conditions: *N*-phenylbenzimidamide **1a** (0.25 mmol), acid (5 equiv.), **537-MOF** (10 mg), DMSO/DMF (2 mL, 1/1) at 100 °C under air atmosphere for 24 h. ^{b} HPLC yield. ^{c} O$_2$. ^{d} DMSO as solvent. ^{e} Without 4 Å MS.

connected paddlewheel dimers leads to the assembly of a (3,6)-connected **rtl** network displaying 1D atactic channels along *b* axis with the pore diameter of 5.1 Å and the available void of 1579.9 Å^3, corresponding to 43.5% of the crystal volume (3629.0 Å^3) (Fig. 1).

Our initial discovery of C–H functionalization of amidines in the presence of **537-MOF** and the subsequent screening investigations for the optimization are detailed in Table 1. The initial discovery utilized a mixture of **537-MOF**, 5 equiv. of HOAc and 4 Å MS (molecular sieve) as additive in (methylsulfinyl)methane (DMSO) at 100 °C under O$_2$ atmosphere to deliver 2-phenyl-1*H*-benzo[*d*]imidazole **2a** in 64% HPLC yield (entry 1). To our delight, treatment of the transformation under air atmosphere also gave satisfactory result (entry 2). The catalytic efficiency was decreased when 4 Å MS was absent (entry 3). Further optimization using typical HKUST-1 failed to give superior result (entry 4). We next turned our attention to enhancing the yield of **2a** by extensively screening solvents. The yield of **2a** was indeed improved when a mixed solvent (DMSO/DMF = 1/1) was used (entry 5). Of note, when benzoic acid was employed as an acidic additive, the targeted product was detected in 96% HPLC yield. The reason for this phenomena is probably due to the suppression of decomposition products under this condition (entry 8).

With the optimized reaction conditions in hand, we investigated the scope of the various substituted amidines (Table 2). Functionalized amidines derived from aryl nitriles with electron-neutral, electron-withdrawing, and electron-donating substituents in *ortho*, *para* or *meta* positions, were smoothly transformed into corresponding benzimidazoles **2a–2p** in moderate to excellent yields under air atmosphere. Among these transformations, decomposition of amidines was
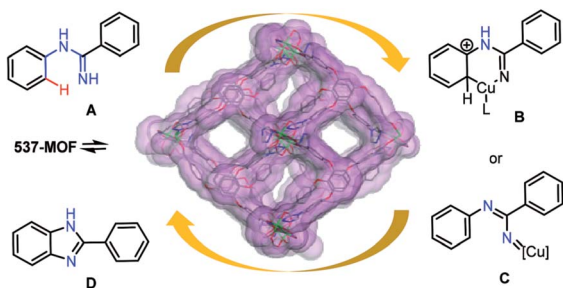
Table 2 Formation of benzimidazoles from different amidines[a]

Entry	R^1	R^2	Product	Yield[b] (%)
1	H	C_6H_5		96 (**2a**)
2	H	$4\text{-}ClC_6H_4$		84 (**2b**)
3	H	$4\text{-}MeC_6H_5$		90 (**2c**)
4	H	$3\text{-}MeC_6H_4$		87 (**2d**)
5	H	$2\text{-}CH_3C_6H_4$		89 (**2e**)
6	H	$2\text{-}CF_3C_6H_4$		85 (**2f**)
7	H	$2\text{-}MeOC_6H_4$		70 (**2g**)
8	H	$5\text{-}F\text{-}2\text{-}MeC_6H_5$		83 (**2h**)
9	4-Cl	3-Me		85 (**2i**)
10	4-Br	$2\text{-}MeC_6H_5$		94 (**2j**)
11	4-F	$2\text{-}CF_3C_6H_5$		85 (**2k**)
12	4-I	$2\text{-}MeC_6H_5$		89 (**2l**)
13	3-MeO	$4\text{-}ClC_6H_4$		75 (**2m**)
14	4-MeO	$4\text{-}CF_3C_6H_5$		70 (**2n**)
15	3-F-4-MeO	C_6H_5		73 (**2o**)
16	Br	$2\text{-}Me,5\text{-}ClC_6H_5$		87 (**2p**)

[a] Reaction conditions: N-phenylbenzimidamide **1a** (0.25 mmol), benzoic acid (5 equiv.), **537-MOF** (10 mg), DMSO/DMF (2 mL, 1/1) at 100 °C under air atmosphere for 24 h. [b] Isolated yield.

Scheme 3 Proposed mechanism for **537-MOF**-catalyzed C–H functionalization of amidine.

inhibited effectively with **537-MOF** as the catalyst (entries 1–16). Regardless of their positions (*ortho*, *para* or *meta*), electron-donating substituents for the starting nitriles, exerted no apparently negative effect on the reaction efficiency and provided the expected products **2c–2e** in high yields (entries 3–5). The amidine with *ortho*-MeO group was also found to be compatible with the reaction conditions, while **2g** was obtained in 70% yield (entry 7). Using the disubstituted amidines **2h–2o**, the corresponding products could be isolated in admirable yields (entries 8–15). 6-Bromo-2-(*o*-tolyl)-1*H*-benzo[*d*]imidazole **1j**, benefiting from *ortho* substituent (–Me), demonstrated preferable reactivity than **1i**, provided **2j** in 94% yield (entries 10–11). *Para*-Substituted electron-withdrawing (*p*-F, Cl, Br, I) on the *N*-aryl ring of the substituted *N*-phenylbenzimidamide gave superior yields than the one with electron-donating group (*p*-MeO), which presumably ascribed to the partial decomposition of **2m–2o** (entries 10–15). Notably, we were pleased to find *N*-(4-bromophenyl)-5-chloro-2-methylbenzimidamide **1p** could deliver the desired benzimidazole derivative in an excellent yield of 87% (entry 16).

The catalyst was retrieved after reaction of **1a** and characterized by powder X-ray diffraction (PXRD), which evidently confirmed that the catalyst maintained excellent crystallinity and was not damaged during the catalytic process (Fig. S4†). After three cycles, the high yields and high selectivity of the reactions were maintained (93% HPLC yield). Although it was failed to isolate the intermediate to illustrate the accurate mechanism, on the basis of the preliminary mechanistic studies for related processes,[14] two possible paths of the C–H functionalization of amidines were proposed in Scheme 3. Path 1: coordination of **537-MOF**[24] and amidines is followed by electrophilic addition of copper center to *N*-phenyl ring to afford the metallacycle B.[25] B is proposed to undergo reductive elimination of the metal and rearomatization to provide target product D. Alternatively, path 2: the amidines reacts with **537-MOF** to generate copper nitrene C.[26] Insertion of the nitrogen into a C–H bond of amidine, electrocyclic ring closure and subsequent [1,3]-shift of a hydrogen lead to the formation of D.

Taken together, the experiment shows that propeller type copper-catalyst has a positive catalytic activity, wherein {$Cu_2(O_2C)_4$} secondary building unit (SBU) with a short Cu–Cu distance and four bridging carboxylate groups from TPPB^{2-} ligands were crucial to the reaction. Compared with Cu(OAc)₂,

TPPB ligand was probably deemed to be the really key parameter for enhancement of coordination ability of **537-MOF** as well as stabilizing intermediates B or C. Therefore, **537-MOF** comprised of metal catalytic site and auxiliary ligand was utilized as a synergic catalyst, providing benzimidazoles in moderate to high yields from amidines without the requirement of *ortho* substituents for the staring nitriles under the atmosphere of air.

Conclusions

In summary, we have developed an efficient, practical and reliable route for **537-MOF**-catalyzed C–H functionalization of amidines to the synthesis of diverse benzimidazoles. This new process features not only air condition instead of O₂ atmosphere, but also extremely broad substrate scope and good functional-group compatibility, wherein challenging amidines derived from aryl nitriles without *ortho*-substituent afforded products in excellent yields. The synergic effect of **537-MOF** was proposed to be the critical factor of high efficiency and selectivity. We anticipate that Cu–MOF will be utilized in other challenging reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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