RSC Advances



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Cite this: RSC Adv., 2017, 7, 51658

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 O₂ 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.

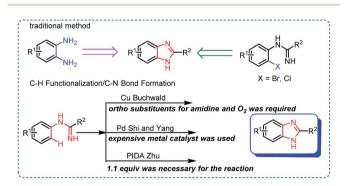
Received 27th September 2017 Accepted 23rd October 2017

DOI: 10.1039/c7ra10682c

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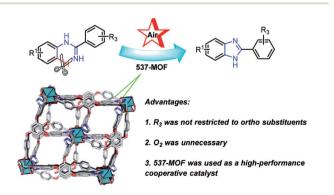
Activation of C–H bonds has been identified as a straightforward and untraditional strategy for the decoration of unreactive hydrocarbon skeletons in terms of its broad application in synthesis of pharmacological active agents, natural products, and functional materials.¹ Given the prevalence and relevance 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 Pd⁶ 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



Scheme 1 Catalytic strategies for the formation of benzimidazoles.

Department of Material and Chemical Engineering, Zhengzhou University of Light Industry, Zhengzhou 450002, P. R. China. E-mail: fenxu_zzuli@163.com 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 2 Synthesis of benzimidazoles from amidines *via* C–H functionalization reaction catalyzed by **537-MOF**.

[†] Electronic supplementary information (ESI) available: Experimental details, crystal data and structural figures, gas adsorption, and characterization data. CCDC 1547691. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra10682c

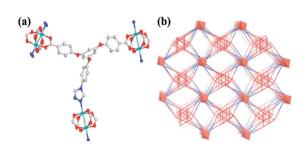


Fig. 1 (a) Illustrations of the coordination mode of TPPB^{2-} ligand. (b) View of (3,6)-connected rtl topology of 537-MOF.

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 O₂ 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 deliver¹⁶ 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 [Cu₃(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, $Cu_2N_2(CO_2)_4$ (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 $\overline{P1}$. The Cu1 and Cu2 atoms are bridged by four bridging carboxylate groups from TPPB²⁻ ligands, forming a $\{Cu_2(O_2C)_4\}$ secondary building unit (SBU) with a short Cu–Cu distance of 2.70 Å. As a result, each TPPB²⁻ ligand binding to three 6-

Table 1 Optimization of the reaction conditions^a

	H NH	Cu-catalyst/additive	
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

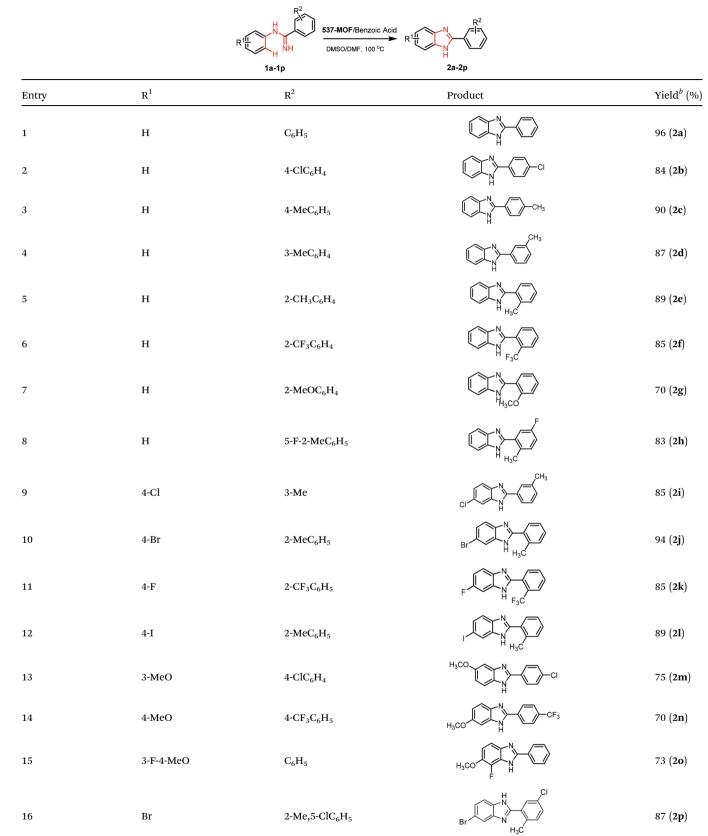
^{*a*} Reaction conditions: *N*-phenylbenzimidamide **1a** (0.25 mmol), acid (5 equiv.), **537-MOF** (10 mg), DMSO/DMF (2 mL, 1/1) at 100 °C under air atmosphere for 24 h. ^{*b*} HPLC yield. ^{*c*} O₂. ^{*d*} DMSO as solvent. ^{*e*} Without 4 Å MS.

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 Å³, corresponding to 43.5% of the crystal volume (3629.0 Å³) (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 A MS (molecular sieve) as additive in (methylsulfinyl)methane (DMSO) at 100 °C under O2 atmosphere to deliver 2-phenyl-1Hbenzo[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

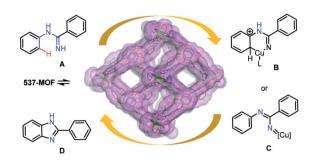
Table 2 Formation of benzimidazoles from different amidines^a



^{*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.

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 $\label{eq:scheme 3} \begin{array}{l} \mbox{Proposed mechanism for $537-MOF-catalyzed C-H functionalization of amidine.} \end{array}$

inhibited effectively with 537-MOF as the catalyst (entries 1-16). Regardless of their positions (ortho, para or meta), electrondonating 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)-1H-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-(4bromophenyl)-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-MOF²⁴ 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 TPPB²⁻ 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 O_2 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

We are grateful to the support from the National Natural Science Foundation of China (21471134, 21571158, and 21701148), Program for Science & Technology Innovative Research Team in University of Henan Province (15IRTSTHN002), Innovation Scientists and Technicians Troop Construction Projects of Henan Province (15-2101510003), Plan for Scientific Innovation Talent of Henan Province (154200510011), and Universities in Henan Province (17A150053).

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