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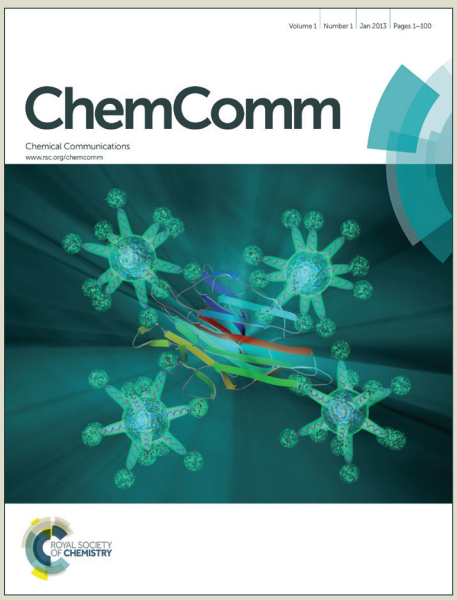

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Investigation of Prototypal MOFs Consisting of Polyhedral Cages with Accessible Lewis-Acid Sites for Quinoline Synthesis

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A series of prototypal metal-organic frameworks (MOFs) consisting of polyhedral cages with accessible Lewis-acid sites, have been systematically investigated for Friedlander annulation reaction, a straightforward approach to synthesizing quinoline and its derivatives. Amongst them MMCF-2 demonstrates significantly enhanced catalytic activity compared with the benchmark MOFs, HKUST-1 and MOF-505, as a result of a high-density of accessible Cu(II) Lewis acid sites and large window size in the cuboctahedral cage-based nanoreactor of MMCF-2.

Quinoline derivatives attract great interest as a major class of nitrogen heterocyclic compounds because of various important pharmacological and biological applications including antimalarial, antiasthmatic, antihypertensive, antibacterial and tyrosine kinase inhibiting agents.[1] They have also been applied for hierarchical self-assembly of nano- and meso-structures endowed with enhanced electronic and photonic properties.[2] The advancement of new and efficient catalysts for quinoline synthesis via Friedlander annulation reaction has been a long-sought goal in the last decades because this reaction is considered to be one of the most efficient and straightforward approaches for the synthesis of poly-substituted quinolines.[3] It's been documented from existing studies that a strong Lewis-acid catalyst plays an integral role for the Friedlander reaction between 2-aminobenzoketones and ketones. A number of catalysts have been employed for the Friedlander condensation reaction, including $SnCl_2/ZnCl_2$, Al_2O_3, H_2SO_4/SiO_2, $NaHSO_4/SiO_2$, $HClO_4/SiO_2$, silica gel-supported phosphomolybdic acid, MCM-41(mesoporous silica) and HKUST-1(MOFs).[4] However, earlier methods suffer from a number of disadvantages including harsh reaction conditions, poor yields, long reaction times and tedious workup procedures. Therefore, there is still a need to develop new types of catalysts for efficiently catalysing the Friedlander reaction.

Metal-organic frameworks (MOFs)[5], emerging as a new type of functional porous materials, have captivated tremendous attention from both academia and industrial research over the past decades. One of the most striking features of MOFs lies in their amenability and modularity,[6] which result from custom-design of functional organic ligands and judicious selection of secondary building units (SBUs).[7] The tubable pore sizes, controllable surface areas, and functionalizable pore walls render MOFs the potential for a plethora of applications, including gas adsorption,[8] gas separation,[9] sensor,[10] catalysis[11] amongst others.[12] Recently, the benchmark MOF, HKUST-1[13] was explored for the synthesis of quinoline and its derivatives via Friedlander annulation reaction.[4h-k] However, its catalytic performance is limited by the low density of accessible Lewis-acid sites, and a large loading amount of catalyst is needed to achieve high conversion. This prompts us to explore alternative MOF catalysts for the Friedlander reaction. In continuation of our efforts on developing polyhedral-cage containing MOFs as nanoreactors for catalysis application,[14] in this contribution, we report the systematic investigation of a series of prototypal MOFs consisting of polyhedral cages with accessible Lewis-acid sites for the synthesis of quinoline derivatives.

It's well-known that first-row transition metal ions exhibit Lewis acidity, and we select three prototypal polyhedral cage containing MOFs, HKUST-1, MOF-505[15] and MMCF-2,[16] which feature accessible Cu(II) sites, as Lewis-acid catalysts for the synthesis of quinoline derivatives. MMCF-2[16] is assembled from the custom-designed azamacrocyclic tetracarboxylate ligand, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra-*p*-methylbenzoic acid (tactmb)[17] and $Cu(NO_3)_2$ under solvothermal conditions. Single-crystal X-ray diffraction reveals that the **nbo**-topology network generates

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from two types of square planar nodes served by tactmb ligands and $Cu_2(CO_2)_4$ SBUs. Every six tactmb ligands link twelve copper paddlewheel SBUs to form a nanoscopic cuboctahedral cage (Fig. 1(a)) with six Cu(II) metallated azamacrocycles residing on the six square faces. Compared to MOF-505 built from 3,3',5,5'-biphenyltetracarboxylate (bptc) ligand (Fig. S4, ESI), the addition of six center-oriented copper sites per cuboctahedral cage can afford extra catalytically active centers accessible by substrates. The **nbo** network of MOF-505 and MMCF-2 can also be regarded as the close packing of nanoscopic cuboctahedral cages, illustrated in Fig. 1(b). In comparison, HKUST is comprised of octahedral and cuboctahedral cages, as shown in Fig. S5, ESI. The cuboctahedral cages in HKUST-1, MOF-505 and MMCF-2 are systematically investigated as Lewis-acid nanoreactors for the synthesis of poly-substituted quinolines via Friedlander condensation reaction.

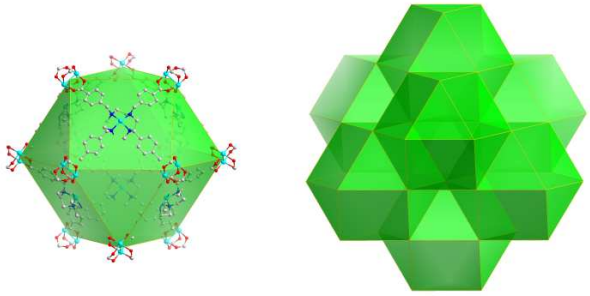
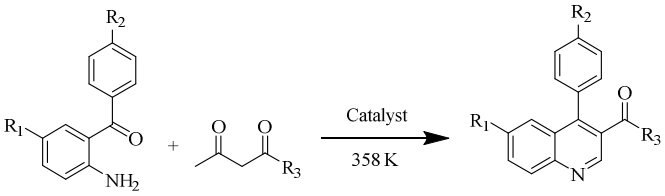


Fig. 1. (a) the cuboctahedral cage in MMCF-2 composed of six tactmb ligands and twelve copper paddlewheel SBUs; (b) the nbo-topology MMCF-2 closely packed by nanoscopic cuboctahedral cages.

The Friedlander condensation reactions were conducted using different 2-aminoaryl ketones with different carbonyl compounds under solvent-free environment at 358K via loading the same amount (0.01mmol) of $Cu_2(CO_2)_4$ SBUs from HKUST-1, MOF-505 and MMCF-2, as shown in Scheme 1 and Table 1. The control experiment was conducted in absence of catalyst. Fig. 2 depicts a time dependence of conversion for condensation between 2-aminobenzophenone and acetylacetone catalysed by MMCF-2, MOF-505, and HKUST-1, and non-catalyst test under the solvent-free conditions at 358K. As shown in Fig. 2 and Table 1, MMCF-2 demonstrates highly efficient catalytic activity for quinoline synthesis via Friedlander condensation reaction with a yield of 93.1% (Table 1, entry 4) over 24 hours. This compares favourably to the corresponding value for the benchmarked polyhedral cage-containing copper MOF, HKUST-1 (58.2%, Table 1, entry 2). MMCF-2 also remarkably outperforms the prototypal **nbo**-topology copper MOF, MOF-505 (20.3%, Table 1, entry 3), which possesses the similar cuboctahedral cages-derived network with MMCF-2. We attribute the high catalytic activity of MMCF-2 for quinoline synthesis via Friedlander condensation reaction to the high density of active sites with some of them well-oriented in the cuboctahedral cage, promoting substrates and active sites interactions. Moreover, though the number of active copper centers in the cuboctahedral cage of MMCF-2 is 1.5 times that in the cuboctahedral cage of MOF-505 (18 for MMCF-2 v.s. 12 for MOF-505), the yield of quinoline synthesis of MMCF-2 increases by 3.6 times when compared to that of MOF-505 (93.1% for MMCF-2 v.s. 20.3% for MOF-505). The dramatic enhancement of catalytic activity from MOF-505 to MMCF-2 for quinoline synthesis via Friedlander reaction can be tentatively ascribed to the synergetic effect of these active copper centers coupled with their high density within the confined nanospace, as well as the larger window size of the cuboctahedral cage in MMCF-2 facilitating the ingress of reactants and the egress of products. The catalyst loading, closely related to turnover number (TON) or turnover frequency (TOF), is an important parameter to assess catalytic behaviour. HKUST-1 as investigated by Cejka *et al.* for quinolone synthesis, showed an optimum loading amount as high as *ca.* 4 mol%.[4i] The high catalytic activity of MMCF-2 reduces the loading amount to as low as 1 mol%. In this regard, the turnover number (TON) improves from 15 of HKUST-1 to 90 of MMCF-2. These results thus highlight the Cu(II)-azamacrocycle decorated cuboctahedral cage in MMCF-2 as a highly efficient nanoreactor for quinoline synthesis via Friedlander condensation reaction.



Scheme 1. Illustrative representation of Friedlander reaction between 2-aminoaryl ketones and ketones under solvent free conditions and at 358 K.

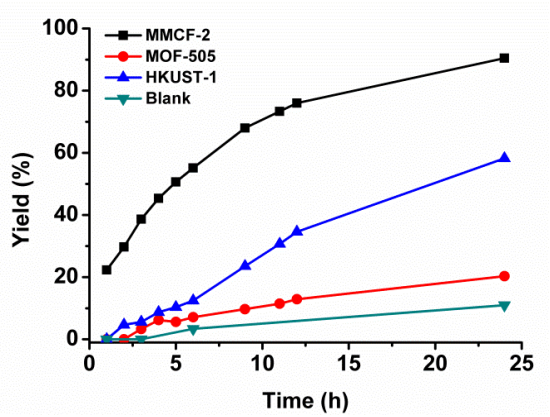


Fig. 2. Kinetic traces of Friedlander condensation reaction between 2-aminobenzophenone and acetylacetone under solvent-free conditions at 358 K catalysed by MMCF-2, MOF-505, HKUST-1, and in absence of catalyst.

In order to generalize the results of this study, we carried out the Friedlander condensation reaction with different 2-aminoaryl ketones and different carbonyl compounds, illustrated in Table 1. MMCF-2 also demonstrates high catalytic activity for the synthesis of other poly-substituted quinolines via Friedlander condensation reaction, as indicated by the 96.8% yield between 2-aminobenzophenone and ethyl acetoacetate (Table 1, entry 5), the 90.2% yield between 2-amino-5-chlorobenzophenone and acetylacetone (Table 1, entry 6), the 92.5% yield between 2-amino-5-chlorobenzophenone and ethyl acetoacetate (Table 1, entry 7), and the 89.0% yield between 2-amino-4'-chlorobenzophenone and acetylacetone

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(Table 1, entry 8). However, a very low yield of 25.8% is observed for 2-amino-5-nitrobenzophenone with acetylacetone due to the strong electron-withdrawing nitro group. These data therefore further highlight MMCF-2 as a highly efficient Lewis-acid catalyst for Friedlander condensation reactions between different substrates.

Table 1. Friedlander reaction between different 2-aminoaryl ketones and different ketones under solvent-free conditions and at 358 K.[a]

Entry	Catalyst	R_1/R_2	R_3	Yield (%)[b]
1	N/A	H/H	CH_3	10.9
2	HKUST-1	H/H	CH_3	58.2
3	MOF-505	H/H	CH_3	20.3
4	MMCF-2	H/H	CH_3	93.1
5	MMCF-2	H/H	OCH_2CH_3	96.8
6	MMCF-2	Cl/H	CH_3	90.2
7	MMCF-2	Cl/H	OCH_2CH_3	92.5
8	MMCF-2	H/Cl	CH_3	89.0
9	MMCF-2	NO_2/H	CH_3	25.8

[a] All the reaction were carried out using 1 mmol 2-aminoaryl ketone in the presence of 2.0 mL ketone; [b] the reagents were stirred at 358 K for 24 hours and monitored by GC-MS carefully.

The enhanced activity of MMCF-2 over HKUST-1 and MOF-505 prompts us to examine the Lewis acidity strength in those MOFs, which was estimated by NH_3-temeprature programmed desorption (NH_3-TPD) studies. As indicated by the temperature range of desorption peaks in Fig. S6, MMCF-2 exhibits relatively higher Lewis acidity than HKUST-1 followed by MOF-505, which follows the trend of catalytic activities observed for the three MOFs. Therefore, the improved catalytic efficiency of MMCF-2 should be attributed to the combination of the high density of Lewis acid Cu(II) sites and the stronger Lewis acidity of those Cu(II) sites within MMCF-2.

In summary, several prototypal MOFs consisting of polyhedral cages have been systematically investigated as Lewis acid catalysts in the context of Friedlander annulation reaction for quinoline synthesis. Amongst them MMCF-2 demonstrates very high catalytic activity, surpassing that of HKUST-1 and MOF-505. The superior catalytic performance of MMCF-2 stems from the high density of accessible yet stronger Lewis acidic copper sites and large window size of its polyhedral cages. Our studies support that creating a high density of active sites within polyhedral cages by the use of custom-designed metallorganic ligands can be a plausible approach to achieving high catalytic activity in MOF-based nanoreactors. Ongoing research in our laboratory focuses on developing other types of highly efficient MOF-based nanoreactors for practically applicable reactions, as well as the systematic investigation of prototypal MOF platforms as heterogeneous catalysts for various types of reactions.

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Electronic Supplementary Information (ESI) available: [The synthesis procedure of MOFs, powder X-ray diffraction patterns, catalytic details and pictures of MOFs]. See DOI: 10.1039/c000000x/

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