

Letter

MOF-derived metal oxide clusters in porous aluminosilicates: a new catalyst design for the synthesis of bioactive aza-heterocycles

Nuria Martin, Michiel Dusselier, Dirk E. De Vos, and Francisco G Cirujano

ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.8b03908 • Publication Date (Web): 20 Nov 2018 Downloaded from http://pubs.acs.org on November 21, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7

8 9 10

11 12

13 14 15

16 17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

58 59

60

MOF-derived metal oxide clusters in porous aluminosilicates: a new catalyst design for the synthesis of bioactive aza-heterocycles

Nuria Martín, Michiel Dusselier, Dirk E. De Vos and Francisco G. Cirujano*

Centre for Surface Chemistry and Catalysis, KU Leuven Celestijnenlaan 200F, 3001 Leuven, Belgium.

Supporting Information Placeholder

ABSTRACT: Simple solid-state mixing and calcination of catalytic amounts of MOFs in the presence of aluminosilicates allows for the generation of active and robust supported metal oxide nanoparticles that catalyze C-C and C-N bond formations. The proposed Cu and Zn containing aluminosilicates outperform state-of-the-art solid catalysts for the synthesis of various azaheterocycles under mild and heterogeneous conditions, exhibiting the highest TOFs ever reported for cost-efficient and reusable CuO and ZnO active sites.

KEYWORDS: *metal oxides, MOFs, organic synthesis, Nheterocycles, heterogeneous catalysis, aluminosilicates.*

New strategies are needed to improve the activity and selectivity of MOF catalysts in industrial synthesis of organic molecules. In our group, we have recently designed reusable and heterogeneous catalytically active metal sites in MOFs as an eco-friendly alternative to traditional homogeneous organic catalysts.¹ Full coordination of the metal sites and/or poor accessibility of the inner active sites in the crystal are the main challenges to improve its catalytic activity in comparison with homogeneous catalysts. Although the generation of active defects in highly stable frameworks, like UiO-66 with its normally 8-coordinated Zr⁴⁺, partially solves the problem,^{1b,c} an excessive amount of defects compromises the stability of the framework, especially for more labile MOFs with tetrahedrally coordinated Zn²⁺ or Cu²⁺ metals.²

39 Alternatively, it is possible to thermally decompose these bulk 40 MOFs into high performance carbons³ or metal catalysts.⁴ With 41 the aim of decreasing the cost of such MOF derived catalysts, 42 lower amounts of MOF are proposed here as precursor of metal 43 oxide catalytic species on inexpensive and robust aluminosilicates (~1 wt.% MOF with respect to the aluminosilicate). The excellent 44 dispersion of the metal-oxo clusters in the MOF precursor (spaced 45 by the organic linker in the extended framework) and the very low 46 MOF loading, produce well-dispersed nanoparticles after thermal 47 decomposition of the linker with respect to the use of discrete molecular species, such as acetate salts or preformed metal nano-48 particles in a porous zeolite support (Fig. 1, top).⁵ Despite the 49 widespread use of supported metal oxide nanoparticles in the 50 synthesis of bulk chemicals and petrochemicals (selective oxida-51 tions, NH₃ and MeOH synthesis, etc.), their application in the 52 production of fine chemicals and pharmaceuticals has been large-53 ly overlooked, due to their smaller production scale.⁶ However, it 54 is necessary to develop alternative strategies to selectively modify important bio-active scaffolds in a clean and efficient manner, 55 avoiding the waste generated during the steps of purification of 56 pharmaceutically interesting compounds. 57



Figure 1. Pharmaceutically interesting scaffolds obtained using well-dispersed MOF derived metal oxides within porous H-USY.

The new general methodology presented here is based on the solvent-free grounding and co-calcination of catalytic amounts of MOFs (HKUST-1 or MOF-5) with aluminosilicates (USY or MCM-41). This solid-state synthesis allows to generate MOF derived non-precious metal oxide nanoparticles as catalysts in C-C (alkynylation, alkylation, aldol condensation, hetero-Diels-Alder) and C-N (amination) bond formations to make propargylamine, (spiro)(ox)indole and quinoline derivatives (Fig. 1, bottom),⁷ with the highest TOFs ever reported for simple H⁺/Zn/CuO active sites. The MOF derived metal oxide MO in the H-USY zeolite used as support is abbreviated in this work as " $MO_{MOF}Y_w$ ", where M is Zn or Cu and w indicates the weight percentage (A, B, C) of metal in each sample (see Tables S1-S2). For comparison purposes, zinc or copper acetates as precursors of metal oxides "MOAcYw" were employed, following a similar synthetic procedure (see supporting information for details).

On the one hand, X-ray diffraction (XRD) patterns of the CuO_{MOF}Y_C and ZnO_{MOF}Y_C catalysts, which contain the higher metal loading, indicate that the zeolite structure is maintained after its co-calcination with the MOF (at 550 °C in air for 4 h). Diffraction peaks of the MOF precursor vanish; new peaks appear corresponding to the CuO or ZnO phases around $2\theta \sim 30-40$ degrees (see Fig. 2a). N₂ physisorption suggests some decrease of the H-USY porosity due to MOF derived metal oxide species since the microporous volume (obtained by *t*-plot) of the starting zeolite decreases from 0.28 cm³g⁻¹ to 0.25 cm³g⁻¹ after calcining the MOFs in the presence of the H-USY support, as well as its surface area (see Fig. 2b and Table S3). Temperature



Figure 2. (a) XRD, (b) N_2 physisorption, (c) NH₃-TPD (left) and XAS (right) of the MOF derived metal oxide on H-USY support.

programmed NH₃ desorption (NH₃-TPD) experiments show the higher strength of the acid sites in the H-USY support with respect to those in the acid mesoporous silica H-MCM-41(Al). The incorporation of MOF derived metal oxide slightly decreases the number of acid sites (H⁺) and affects their strength distribution (see left part of Fig. 2c). Finally, X-ray Absorption Spectroscopy (XAS) indicates that the Cu active sites are in the form of CuO (see right part of Fig. 2c).

The supported CuO_{MOF}Y metal oxide samples were employed as catalysts in C-C (alkynylation) and C-N (amination) bond forming reactions involving a multicomponent reaction between alkyne, aldehyde and amine groups, a green process for the synthesis of bio-active propargylamines.⁸ Copper catalysts have been traditionally employed due to their low cost and toxicity, especially when immobilized in a solid support.9 The CuO_{MOF}Y_A proposed here (having only 0.9 wt.% Cu) compares very favorably to literature data of benchmark copper oxide or Cu-MOFs,9a,b copper on mesoporous silica,9c,d or copper nanoparticles on zeolite NaY (see Table S5).9e Other amines, such as morpholine and pyrrolidine, also produce the corresponding propargylamines 1a-c in good vields using the novel CuO_{MOF}Y_A catalytic system (see Table S9). In our hands, the turnover frequency (TOF) of the well-dispersed copper active sites in CuO_{MOF}Y, is one order of magnitude higher than those present in bulk copper oxide derived from the MOF (CuO_{MOF}) and starting Cu-MOF material (see Fig. 3a). Moreover, using the calcined MOF instead of the intact one facilitates the regeneration of the spent CuO_{MOF}Y catalyst after reaction, by a simple thermal treatment in order to remove the reactants that otherwise remain adsorbed in the microporous zeolite for subsequent reuses (see Fig. 2b and Fig. S4-S6). On the contrary, the limited thermal stability of MOF powders only allows regeneration by washing, which is associated with large volumes of organic solvents and compromises the stability of the MOF.



Figure 3. Catalytic performance of CuO containing aluminosilicates and MOFs in the synthesis of propargylamine 1 (a) and quinoline 2 (b). Left: MOF derived CuO on different supports. Right: MOF (blue) *vs.* Cu(OAc)₂ (red) derived CuO at increasing metal loadings (A < B < C) on H-USY (see Table S1).

The higher TOFs obtained using the H-USY zeolite with strong acidity (CBV 720) as support of the CuO active sites with respect to lower Si/Al ratio (from 15 to 2.5, named as CBV 400 in Fig. 3) alludes to the fact that the acidity of the support favors the A3 reaction (see left part of Fig. 4).¹⁰ An important role of the acidity is to promote a very high dispersion of the CuO clusters, maybe due to some re-protonation of the MOF linkers (during the catalyst preparation in the presence of acidic supports) and relocation of the Cu²⁺ cations partially compensated by the oxide anions of the CuO clusters and zeolite. The catalytic activity of the bifunctional CuO/H⁺ sites on the microporous H-USY zeolite or mesoporous H-MCM-41(Al) is higher than that obtained when using non-acidic mesoporous or amorphous silica supports (see Fig. 3a). The same trend is observed for reactions where the acidity of the support plays a major role, such as the Friedländer condensation of 2-aminobenzophenone with acetylacetone (see Fig. 3b and Fig. S7).¹¹ In this case, the TOFs obtained with copper oxide containing MCM-41 catalyst, bulk Cu₃(BTC)₂ or pure CuO derived from this MOF (by calcining it in bulk) are far below from those obtained when CuO is dispersed via co-calcination in acid supports such as H-USY or H-MCM-41(Al). For both reactions, the use of the CuBTC as precursor of CuO active species instead of traditional Cu(OAc)₂ remarkably improves the catalytic activity of the copper containing zeolite.

Faujasite zeolites were also described as acid catalysts in the Friedel-Crafts alkylation at the C-3 of the electron rich indole, using alcohols or electron deficient alkenes such as

60

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34



Figure 4. Proposed mechanism for the synthesis of propargylamines 1 and substituted indoles 3 using the bifunctional MO/H⁺ CuO_{MOF}Y and ZnO_{MOF}Y heterogeneous catalysts.

 β -nitrostyrene.^{1d, 12} For the last reaction, we have observed that commercial H-USY zeolite with Si/Al =15 shows a higher initial reaction rate ($r_0 = 0.40 \text{ h}^{-1}$) with respect to lower Si/Al = 2.5, i.e. weaker acid sites, $r_0 = 0.28 \text{ h}^{-1}$, (see CBV720 and CBV400 in Fig. S8 and Table S7). With CuO_{MOF}Y_A, the initial reaction rate increases twofold with respect to the pure Faujasite acid support and the TOF_{Cu} is two orders of magnitude higher with respect to CuBTC: 104 vs. 5 h⁻¹ (see Fig. S8 and Table S7).^{1a, 13} Those findings indicate that the novel method of creating CuO active sites in acidic supports could be unique and generic for different catalytic reactions. To broaden the scope of this concept, we have also employed zinc MOFs as precursor of inexpensive and non-toxic ZnO acid-base sites on H-USY. This bifunctional system is an optimal catalyst for the Michael addition of indole to βnitrostyrene (see right part of Fig. 4). The catalytic activity of the Zn sites is boosted when they are dispersed on the HY porous zeolite, especially for low metal loadings (1.4 wt.%), obtaining a TOF_{Zn} of 204 with respect to the 104 mol of indole converted per mol of copper sites and per hour in the CuO_{MOF}Y_A. Moreover, the ZnO_{MOF}Y_A MOF derived heterogeneous catalytic approach remarkably outperform reported homogeneous Zn(OAc)₂ catalysts.14 The acid sites associated to Al in the H-USY or H-MCM-41(Al) supports (see NH₃-TPD in Fig. 2c), cooperatively interact with the supported and well-dispersed (~1 wt.%) CuO or ZnO nanoparticles and promote the nitro, carbonyl and alkyne activations involved in the C-C and C-N couplings shown in Figure 4.

35 Apart from propargylamines and indoles, oxindoles are interesting 36 compounds that exhibit antitumor activity by inhibiting tyrosine 37 kinase receptors, as occurs with the C-3 substituted indolin-2-one Sunitinib.15 This type of substituted oxindoles are currently pre-38 pared using harsh conditions and/or toxic reagents, i.e. KF/Al₂O₃ 39 or piperidine, piperazine, NaOH in ethanol under reflux.¹⁶ When 40 using the 1.2 wt.% loaded ZnOMOFYA it is possible to obtain the 41 3-benzyliden-2-oxindole 4 in high yields (90%) after only two 42 hours of aldol condensation of benzaldehyde with oxindole, prov-43 ing the good performance of these novel Zn containing zeolites in C-C bond forming Michael additions (see Fig. 4) and aldol con-44 densations (see Fig. 5a). Other aliphatic aldehydes such as 45 heptanaldehyde or the biomass derived furfural were successfully 46 employed to functionalize the oxindole substrate (see Table S9). 47 The use of H-MCM-41(Al) acid mesoporous support increases the 48 Zn TOFs with respect to the use of microporous H-USY 49 (CBV720) zeolite, non-acidic MCM-41 or amorphous silica. This indicates the importance of H+/ZnO acid-base sites, as well as a 50 good dispersion and accessibility to the active sites.¹⁷ Finally, the 51 aldol condensation/oxa-Diels-Alder reaction of isatin (1H-indole-52 2,3-dione) with an hetero diene such as an α , β -unsaturated ketone, 53 was also studied in order to obtain pharmaceutically interesting 54 spirooxoindoles.¹⁸ A clear improvement in the final turnover 55 number (TON_{Zn}) or moles of isatin converted to 5 per mol of Zn 56 is obtained with the lowest loaded sample ZnOMOFYA (see Fig. 5b). As observed previously for the Cu containing catalysts, high-57

er Zn MOF loadings, or the use of $Zn(OAc)_2$ precursor, pure or calcined MOF, results in the decrease of TOF_{Zn} and TON_{Zn} by 1-2 orders of magnitude (see Figure 5 and Table S10).



Figure 5. Catalytic performance of ZnO containing aluminosilicates and MOFs in the synthesis of substituted oxindoles **4** (a) or spirooxindoles **5** (b). Left: MOF derived ZnO on different supports. Right: MOF (blue) vs. Zn(OAc)₂ (red) derived ZnO at increasing metal loadings (A < B < C) on H-USY (see Table S2).

In conclusion, the methodology proposed allows for the ecoefficient solid-state synthesis of metal containing porous catalysts. producing more mechanically and chemically resistant materials in comparison with the starting MOFs, with a very low metal content (below 2 wt.%). No solvent is employed during the procedure; thus the solid-to-solid (MOF-zeolite) co-calcination synthesis can be easily scaled up without requiring filtration or washing steps. The solids were used as active and stable heterogeneous catalysts for a range of C-C (compounds 1-5) and C-N (compounds 1 and 2) bond formations in N-heterocyclic scaffolds, resulting in substituted propargylamines (1), quinolines (2), indoles (3), oxoindoles (4) and spirooxoindoles (5), outperforming state-of-the-art Cu and Zn supported catalysts and MOF benchmarks. The higher availability of this metal oxide sites when they are dispersed within the porous matrix with respect to bulk metaloxide or metal-organic framework, results in a better activity (TOFs up to two orders of magnitude higher) and reusability (by simple calcination), compared to the pure MOF.

ASSOCIATED CONTENT

Supporting Information

58 59

60

The Supporting Information is available free of charge on the ACS Publications website.

Kinetic experiments, characterization of the catalysts and reaction products.

AUTHOR INFORMATION

Corresponding Author

*E-mail: francisco.garcia@kuleuven.be

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

F.G.C. and N.M. acknowledge the European Commission-Horizon 2020 for funding through Marie Sklodowska Curie Individual Fellowships under the grant agreements numbers: 750391 (SINMOF) and 792943 (ZEOCO2). The XAS experiments were performed on beamline BM26A at the European Synchrotron Radiation Facility (ESRF), Grenoble, France. We are grateful to D. Banerjee at the ESRF for providing assistance in using beamline and also to Cristina Almansa for performing the TEM analysis of the samples at the research technical services of the University of Alicante in Spain.

REFERENCES

- (a) Cirujano, F. G.; Lopez-Maya, E.; Rodriguez-Albelo, M.; Bar-1. ea, E.; Navarro, J. A. R.; De Vos, D. E. Selective One-Pot Two-Step C-C Bond Formation using Metal-Organic Frameworks with Mild Basicity as Heterogeneous Catalysts. Chem-CatChem. 2017, 9, 4019-4023. (b) Cirujano, F. G. MOFs vs. zeolites: carbonyl activation with M (IV) catalytic sites. Catal. Sci. & Technol. 2017, 7, 5482-5494. (c) Cirujano, F. G.; Luz, I.; Soukri, M.; Van Goethem, C.; Vankelecom, I. F. J.; Lail, M.; De Vos, D. E. Boosting the Catalytic Performance of Metal-Organic Frameworks for Steroid Transformations by Confinement within a Mesoporous Scaffold. Angew. Chem., Int. Ed. 2017, 56, 13302-13306. (d) Cirujano, F. G.; Stalpaert, M.; Vos, D. E. De Vos. Ionic liquids vs. microporous solids as reusable reaction media for the catalytic C-H functionalization of indoles with alcohols. Green Chem. 2018, 20, 2481-2485. (e) Cirujano, F. G.; Leo, P.; Vercammen, J.; Smolders, S.; Orcajo, G.; De Vos, D. MOFs Extend the Lifetime of Pd(II) Catalyst for Room Temperature Alkenylation of Enamine Like Arenes. Adv. Synth. Catal. 2018, 360, 3872-3876. (f) Cirujano, F. G.; Lopez-Maya, E.; Navarro, J. A. R.; De Vos, D. E. Pd(II)-Ni(II) Pyrazolate Framework as Active and Recyclable Catalyst for the Hydroamination of Terminal Alkynes. Top. Catal. 2018, 61, 1414-1423.
- (a) Chui, S.-Y.; Lo, S. M.; Charmant, J. P.; Orpen, A. G.; Williams, I. D. A chemically functionalizable nanoporous material. *Science* 1999, 283, 1148-1150. (b) Eddaoudi, M.; Kim, J.; Rosi, N.; Vodak, D.; Wachter, J.; O'Keeffe, M.; Yaghi, O. M. Systematic Design of Pore Size and Functionality in Isoreticular MOFs and Their Application in Methane Storage. *Science* 2002, 295, 469-472. (c) Huang, L.; Wang, H.; Chen, J.; Wang, Z.; Sun, J.; Zhao, D.; Yan, Y. Synthesis, morphology control, and properties of porous metal–organic coordination polymers. *Microporous Mesoporous Mater*. 2003, 58, 105-114.
- (a) Tang, J.; Yamauchi, Y. Carbon materials: MOF morphologies in control. *Nat. Chem.* 2016, *8*, 638-639. (b) Salunkhe, R. R.; Young, C.; Tang, J.; Takei, T.; Ide, Y.; Kobayashi, N.; Yamauchi Y. A high-performance supercapacitor cell based on ZIF-8derived nanoporous carbon using an organic electrolyte. *Chem. Commun.* 2016, *52*, 4764-4767. (c) Carrasco, J. A.; Romero, J.; Abellán, G.; Hernández-Saz, J.;Molina, S. I.; Martí-Gastaldo, C.; Coronado, E. Small-pore driven high capacitance in a hierarchical carbon via carbonization of Ni-MOF-74 at low temperatures, *Chem. Commun.* 2016, *52*, 9141-9144. (d) Zhang, W.; Jiang, X.;

dimensional porous or hollow carbon-based nanofibers for energy

storage and conversión. Mater. Horiz. 2018, 5, 394-407.

- 4 (a) Santos, V. P.; Wezendonk, T. A.; Delgado Jaén, J. J.; Iulian Dugulan, A.; Nasalevich, M. A.; Islam, H. U.; Chojecki, A.; Sartipi, S.; Sun, X.; Hakeem, A. A.; Koeken, A. C. J.; Ruitenbeek, M.; Davidian, T.; Meima, G. R.; Sankar, G.; Kapteijn, F.; Makkee, M.; Gascon, J. Metal organic frameworkmediated synthesis of highly active and stable Fischer-Tropsch catalysts. Nat. Commun. 2015, 6, 6451. (e) Sun, X.; Olivos Suarez, A. I.; Meijerink, M.; van Deelen, T.; Ould-Chikh, S.; Zečević, J.; de Jong, K. P.; Kapteijn, F., Gascon, J. Manufacture of highly loaded silica-supported cobalt Fischer-Tropsch catalysts from a metal organic framework. Nat. Commun. 2017, 8, 680. (f) Ronda-Lloret, M.; Rico-Francés, S.; Sepúlveda-Escribano, A.; Ramos-Fernandez, E. V. CuOx/CeO2 catalyst derived from metal organic framework for reverse water-gas shift reaction. Appl. Catal. A 2018, 562, 28-36. (g) Luz, I.; Soukri, M.; Lail, M. Transformation of single MOF nanocrystals into single nanostructured catalysts within mesoporous supports: a platform for pioneer fluidized-nanoreactor hydrogen carriers. Chem. Commun. 2018. 54. 8462-8465.
- (a) Alonso, F.; Arroyo, A.; Martín-García, I.; Moglie, Y. Cross-Dehydrogenative Coupling of Tertiary Amines and Terminal Alkynes Catalyzed by Copper Nanoparticles on Zeolite. *Adv. Synth. Catal.* 2015, *357*, 3549-3561. (b) Mitrofanov, A. Y.; Murashkina, A. V.; Martín-García, I.; Alonso, F.; Beletskaya, I. P. Formation of C–C, C–S and C–N bonds catalysed by supported copper nanoparticles. *Catal. Sci. Technol.* 2017, *7*, 4401-4412.
- (a) Hattori, H. Heterogeneous Basic Catalysis. Chem. Rev. 1995, 6. 95, 537-558. (b) Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. CuO Nanoparticles Catalyzed C-N, C-O, and C-S Cross-Coupling Reactions: Scope and Mechanism. J. Org. Chem. 2009, 74, 5, 1971-1976. (c) Son, S. I; Lee, W. K.; Choi, J.; Ha, H. J. Atom economical synthesis of oxindoles by metal-catalyzed intramolecular C-C bond formation under solvent-free and aerobic conditions. Green Chem. 2015, 17, 3306-3309. (d) Ojha, N. K.; Zyryanov, G. V.; Majee, A.; Charushin, V. N.; Chupakhin, O. N.; Santra, S. Copper nanoparticles as inexpensive and efficient catalyst: A valuable contribution in organic synthesis. Coord. Chem. Rev. 2017, 353, 1-57.(e) Rai, B.; Shuklaa, R. D.; Kumar, A. Zinc oxide-NP catalyzed direct indolation of in situ generated bioactive tryptanthrin. Green Chem. 2018, 20, 822-826.
- 7. (a) Langston, J. W.; Irwin, I.; Langston, E. B.; Forno, L. S. Pargyline prevents MPTP-induced parkinsonism in primates. Science 1984, 225, 1480-1482. (b) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J. Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. Discovery of 5-[5-Fluoro-2-oxo-1,2- dihydroindol-(3Z)ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase. J. Med. Chem. 2003, 46, 1116-1119. (c) Zhao, Y; Aguilar, A.; Bernard, D.; Wang, S. Small-Molecule Inhibitors of the MDM2-p53 Protein-Protein Interaction (MDM2 Inhibitors) in Clinical Trials for Cancer Treatment. J. Med. Chem. 2015, 58, 1038-1052. (d) Rechac, V. L.; Cirujano, F. G.; Corma, A.; Llabrés i Xamena, F. X. Diastereoselective synthesis of pyranoquinolines over Zr-containing UiO-66 Metal Organic Frameworks. Eur. J. Inorg. Chem. 2016, 2016, 4512-5416.
- (a) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. Synthesis and Reactivity of Propargylamines in Organic Chemistry. *Chem. Rev.* 2017, *117*, 14091-14200; (b) Zindo, F. T.; Joubert, J.; Malan, S. F. Propargylamine as functional moiety in the design of

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60

multifunctional drugs for neurodegenerative disorders: MAO inhibition and beyond. *Future Med. Chem.* **2015**, *7*, 609-629.

- 9 (a) Lakshmi Kantam, M.; Laha, S.; Yadav, J.; Bhargava, S. An efficient synthesis of propargylamines via three-component coupling of aldehydes, amines and alkynes catalyzed by nanocrystalline copper(II) oxide. Tetrahedron Lett. 2008, 49, 3083-3086. (b) Luz, I.; Llabrés i Xamena, F.X.; Corma, A. Bridging homogeneous and heterogeneous catalysis with MOFs: Cu-MOFs as solid catalysts for three-component coupling and cyclization reactions for the synthesis of propargylamines, indoles and imidazopyridines. J. Catal. 2012, 285, 285-291. (c) Srinivas, M.; Srinivasua, P.; Bhargava, S. K.; Kantama, M. L. Direct synthesis of two-dimensional mesoporous copper silicate as an efficient catalyst for synthesis of propargylamines. Catal. Today 2013, 208, 66-71. (d) Abdollahi-Alibeik, M.; Moaddeli, A. Copper modified spherical MCM-41 nano particles: an efficient catalyst for the three-component coupling of aldehydes, amines and alkynes in solvent-free conditions. RSC Adv. 2014, 4, 39759-39766. (e) Albaladejo, M. J.; Alonso, F.; Moglie, Y.; Yus, M. Three-Component Coupling of Aldehydes, Amines, and Alkynes Catalyzed by Oxidized Copper Nanoparticles on Titania. Eur. J. Org. Chem. 2012, 3093-3104.
- Marquez, C.; Cirujano, F. G.; Van Goethem, C.; Vankelecom, I.; De Vos, D.; De Baerdemaeker, D. Tunable Prussian blue analogues for the selective synthesis of propargylamines through A3 coupling. *Catal. Sci. Technol.* **2018**, *8*, 2061-2065.
- (a) Lopez-Sanz, J.; Perez-Mayoral, E.; Prochazkova, D.; Martin-Aranda, R. M.; Lopez-Peinado, A. J. Zeolites Promoting Quinoline Synthesis via Friedländer Reaction. *Top Catal* 2010, 53,1430-1437; (b) Pérez-Mayoral, E.; Musilová, Z.; Gil, B.; Marszalek, B.; Položij, M.; Nachtigalld, P.; Čejka, J. Synthesis of quinolines via Friedländer reaction catalyzed by CuBTC metal– organic-framework. *Dalton Trans.* 2012, *41*, 4036-4044.
- Jeganathan, M; Kanagaraj, K; Dhakshinamoorthy, A.; Pitchumani, K. Michael addition of indoles to β-nitrostyrenes catalyzed by HY zeolite under solvent-free conditions. *Tetrahedron Lett.* 2014, 55, 2061-2064.
- Anbu, N.; Dhakshinamoorthy, A. Cu₃(BTC)₂ as a viable heterogeneous solid catalyst for Friedel-Crafts alkylation of indoles with nitroalkenes. *J. Colloid Interface Sci.* 2017, 494, 282-289.
- 14. Ji, X; Tong, H.; Yuan, Y. Facile and Efficient Michael Addition of Indole to Nitroolefins Catalyzed by Zn(OAc)₂·2H₂O. *Synth. Commun.* **2011**, *41*, 372-379.
- Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J. Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. Discovery of 5-[5-Fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4dimethyl-1H-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase. J. Med. Chem. 2003, 46, 1116-1119.
- (a) Ribeiro, C. J.A.; Amaral, J. D.; Rodrigues, C. M. P.; Moreira, R.; Santos, M. M. M. Synthesis and evaluation of spiroisoxazoline oxindoles as anticancer agents. *Bioorg. Med. Chem.* 2014, 22, 577-584. (b) Suthar, S. K.; Bansal, S.; Alam, M. M.; Jaiswal, V.; Tiwari, A.; Chaudhary, A.; Alex, A. T.; Joseph, A. Design, synthesis, and biological evaluation of oxindole derivatives as antidepressive agents. *Bioorg. Med. Chem. Lett.* 2015, 25, 5281-5285. (c) Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S. Synthesis of spirooxindoles via asymmetric 1,3-dipolar cycloaddition. *Tetrahedron Lett.* 2005, 46, 5949-5951. (d) Zhang, W.; Go, M. L. Functionalized 3-benzylidene-indolin-2-ones: inducers of NAD(P)H-quinone oxidoreductase 1 (NQO1) with antiproliferative activity. *Bioorg. Med. Chem.* 2009, 17, 2077-2090.
- (a) Ito, S.; Tanuma, K.; Matsuda, K.; Hayashi, A.; Komai, H.; Kubota, Y; Asami, M. Mesoporous aluminosilicate-catalyzed Mukaiyama aldol reaction of aldehydes and acetals. *Tetrahedron*, **2014**, 70, 8498-8504. (b) Luque, R.; Campelo, J. M.; Luna, D.; Marinas, J. M.; Romero, A. A. Catalytic performance of Al-MCM-41 materials in the *N*-alkylation of aniline. *J. Mol. Catal. A* **2007**, 269, 190-196.
- (a) Liu, J. J.; Zhang, Z. Spiroindolinone derivatives. WO2008055812. (b) Liu, J. J. Spiroindolinone derivatives.

WO2009115425. (c) Zhang, J.; Zhang, Z. 3, 3' -Spiroindolinone derivatives as anticancer. WO2010094622.

SYNOPSIS TOC "Co-calcining MOFs with aluminosilicate hosts as a new path to uniquely active metal-oxide catalysts for eco-friendly C-C and C-N bond formations in *N*-heterocyclic scaffolds"

