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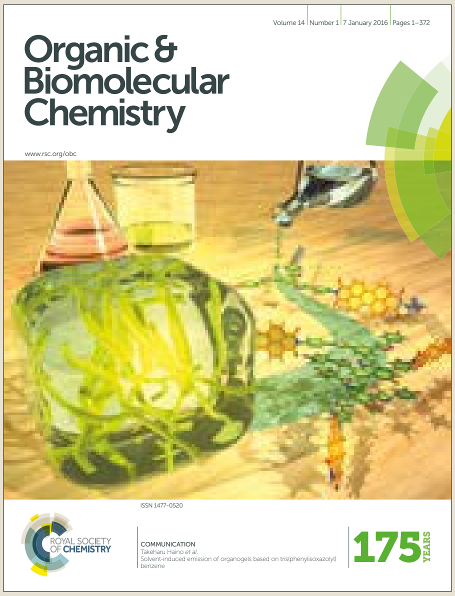

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ARTICLE

Efficient and recyclable copper-based MOF-catalyzed N-arylation of *N*-containing heterocycles with aryliodides

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Copper-based MOF-199 was used as an efficient heterogeneous catalyst to catalyze the crossing-coupling reactions between *N*-containing heterocycles and aryliodides with high yields. The catalyst can be easily separated from the reaction mixture, and be reused at least 5 times without significantly decreasing activity. The XRD results showed that the crystallinity and structure of MOF-199 can be kept well during the coupling reaction.

Introduction

Copper-catalyzed Ullmann-type C-N bond-forming reactions are widely used in industry and academic for the synthesis of pharmaceuticals, materials, natural products and other biologically active molecules.[1] To date, the development, in these field, continues to progress dramatically by the discovery of various of efficient monodentate and bidentate ligands.[2] Despite the extensive investigations on homogeneous copper/ligand catalytic system for N-arylation reactions, they inherently suffer from non-reusability, difficulty in separating from the reaction media, as well as difficulty in the removal of residual copper impurities from the final products. Thereafter, several heterogeneous copper-based catalysts have been developed to overcome these drawbacks mentioned above. For example, supported copper or copper nanoparticles (such as CELL-Cu(0)[3], CuO nanoparticles (NPs)[4], Cu_2O coated Cu NPs[5], CuO NPs[6], Cu^0 or Cu^{2+}/4Å[7], RGO/Cu NPs[8], electrospun CuO NPs[9], Cu NPs/Zeolite[10], Cu@Cu_2O NPs-RGO[11], CuO NPs/MWCNT[12], activated Cu powder[13] and Cu^+-montmorillonite[14]) have been used successfully as the heterogeneous catalyst for C-N coupling reactions with the advantages of simplified isolation of the product, easy recovery and recyclability of the catalysts. Meanwhile, immobilized copper-ligand complexes such as $[Cu(Im_{12})]_2CuCl_2$[15], MCM-41-2N-CuI[16], polystyrene-supported-N,N-dimethylethylenediamine Cu(II)[17] complex, polymer-supported-β-alanine Cu(I)[18] and Fe_3O_4-EDTA–Cu(II)[19] were also been applied for these reactions due to their thermal stability, reusability and high catalytic activities.

Metal-organic frameworks (MOFs) are a unique class of porous and crystalline materials composed of metal cations (or metal clusters) and organic linkers, and are receiving extensive attention for their specific applications in the areas of gas separation and storage, drug delivery and chemical sensor.[20] Since several MOFs possess large surface areas, good thermal stability and potentially metal active sites, their application in heterogeneous catalytic reactions is another important field.[21] Among them, MOF-199 [copper(II))-benzene-1,3,5-tricarboxylate] is one of the well-studied MOFs, which was firstly reported in 1999 by Chui et al., who denominated the structure as ‘‘HKUST-1”.[22] After then, MOF-199 has been employed widely as heterogeneous catalyst for various transformations.[23] However, to the best of our knowledge, there is no example using MOF-199 as catalyst for Ullmann-tpye C-N coupling reactions. As part of our studies on the homogeneous copper-catalyzed coupling reactions,[24] in this paper, we wish to report the direct N-arylation of heterocycles with aryl iodides by using MOF-199 as the efficient and recyclable heterogeneous catalyst.

Results and discussion

Initially, 4-iodotoluene and 1*H*-pyrrole were chosen as the model substrates to optimize the reaction conditions, including catalyst, bases and solvents. The results are listed in Table 1. High value of yield toward the cross-coupling product (96%) was obtained, when the reaction was carried out in DMSO using 10 mol% of MOF-199 catalyst, in the presence of NaOH (2 equiv.) as a base at 120 °C for 12 h (entry 1). $Cu(NO_3)_2$ or the mixture of $Cu(NO_3)_2$ and trimesic acid, which were used as the catalyst under the same reaction conditions, both results in obviously decrease yields (entries 2 and 3). Control experiment was carried out in the absence of catalyst, and no product was afforded (entry 4). The catalytic efficiency was observed to be reduced when the catalyst loading was decreased to 5 mol% or 2.5 mol% (entries 5 and 6). Several bases, including KOH, K_2CO_3, Cs_2CO_3 and K_3PO_4, were assayed,

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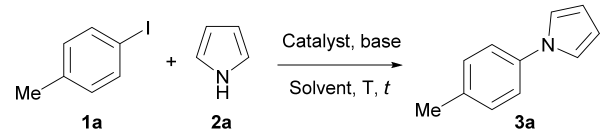
Table 1 Optimization of the reaction conditions[a]



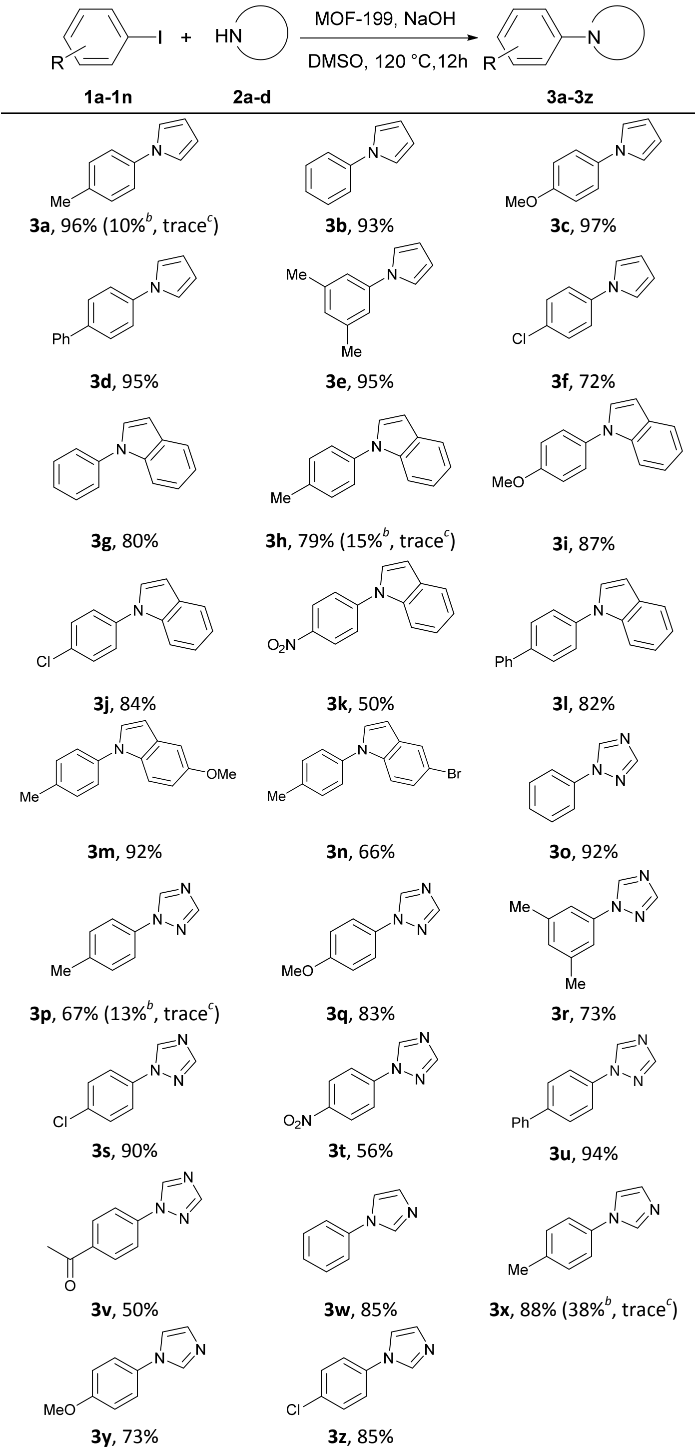
Entry	Catalyst (mol%)	Base	Solvent	Yield[b] (%)
1	MOF-199 (10)	NaOH	DMSO	96
2	$Cu(NO_3)_3$ (10) + trimesic acid (20)	NaOH	DMSO	68
3	$Cu(NO_3)_3$ (10)	NaOH	DMSO	50
4	-	NaOH	DMSO	0
5	MOF-199 (5)	NaOH	DMSO	89
6	MOF-199 (2.5)	NaOH	DMSO	83
7	MOF-199 (10)	KOH	DMSO	81
8	MOF-199 (10)	K_2CO_3	DMSO	15
9	MOF-199 (10)	Cs_2CO_3	DMSO	75
10	MOF-199 (10)	K_3PO_4	DMSO	78
11	MOF-199 (10)	NaOH	DMF	15
12	MOF-199 (10)	NaOH	DMAC	51
13	MOF-199 (10)	NaOH	Dioxane	0
14	MOF-199 (10)	NaOH	DMSO	72[c]
15	MOF-199 (10)	NaOH	DMSO	75[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst, base (1.0 mmol), solvent (1 mL), 120 °C, 12 h. [b] Isolated yield. [c] 100 °C. [d] 8 h.

and NaOH provided the highest yield (entries 7-10). The reaction conducted in DMSO were found faster than those conducted in DMF, dimethylacetamide (DMAC) or 1,4-dioxane (entries 11-13). Moreover, lowering the reaction temperature from 120 °C to 100 °C led to a dramatic decrease in the yield (entry 14), and the same result also appeared in shorting reaction time from 12 to 8 h (entry 15). In summary, the combination of 10 mol% MOF-199 and 2 equiv. NaOH in DMSO at 120 ^{o}C for 12 h was the optimal condition.

Under the optimal conditions, the scope of the MOF-199 catalyst system was explored between various aryl iodides and *N*-containing heterocycles. As shown in Table 2, the coupling reactions were performed well for most of aryl iodides with electron-rich, electron-neutral and electron-deficient groups with 1*H*-pyrrole to afford corresponding 1-aryl-1*H*-pyrrole in good to excellent yields (**3a**-**3f**). In general, the electron-deficient aryl iodides gave the coupling products in lower yields. Indoles could also be reacted well with 50-92% yields (**3g**-**3n**), and the electron-rich indole exhibited a higher activity than the electron-deficient one (**3m** vs **3n**). For 1*H*-1,2,4-triazole, this catalyst system also applied to react, however, the reactions of the 1-iodo-4-nitrobenzene and the 1-(4-iodophenyl)ethanone gave the *N*-arylated products in 56% and 50% yields (**3t** and **3v**) due to incomplete conversion of aryl iodides and formation of dehalogenated by-products. Additionally, other reactions of aryl iodides with 1*H*-1,2,4-triazole provided 73%-94% yields (**3o**-**3u**). Furthermore, we were pleased to find that the crossing-coupling reactions proceeded well to give the respective products in good to excellent yields, when the 1*H*-imidazole was used as the nucleophile (**3w**-**3z**). Because of less reactivity, extension of

Table 2 Reaction of aryl iodides with nitrogen-containing heterocycles[a]



3a, 96% (10%[b], trace[c])
3b, 93%
3c, 97%
3d, 95%
3e, 95%
3f, 72%
3g, 80%
3h, 79% (15%[b], trace[c])
3i, 87%
3j, 84%
3k, 50%
3l, 82%
3m, 92%
3n, 66%
3o, 92%
3p, 67% (13%[b], trace[c])
3q, 83%
3r, 73%
3s, 90%
3t, 56%
3u, 94%
3v, 50%
3w, 85%
3x, 88% (38%[b], trace[c])
3y, 73%
3z, 85%

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), MOF-199 (10 mol%), NaOH (1.0 mmol), DMSO (1 mL), 120 °C, 12 h; isolated yield. [b] 4-Bromotoluene as the substrate. [c] Chlorobenzene as the substrate.

this process to 4-bromotoluene gave lower yields. Unfortunately, the reaction did not occur when chlorobenzene was used as the substrate under the standard reactions (**3a**, **3h**, **3p** and **3x**). Table 3 provides a comparison of the results obtained for our present MOF-199 catalyst with other reported copper heterogeneous catalytic systems[3,7,27-29] in

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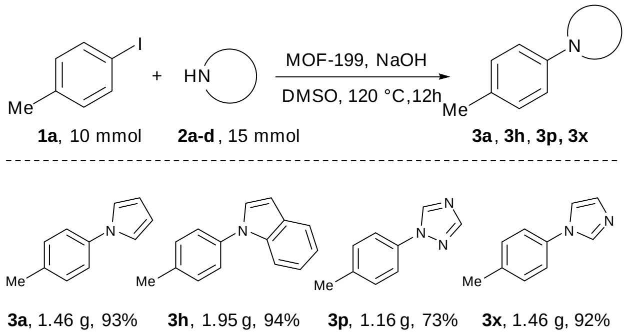
Ullmann-type C-N cross-coupling reactions of aryl iodides with *N*-containing heterocycles. And we can see that the present catalyst exhibited higher efficiency compared to other reported system, with higher yields, relatively milder conditions and broader functional groups tolerate.

On the basis of the optimal reaction conditions, we also carried out for each type of reaction in a large scale by taking 10 mmol of 4-iodotoluene in 10 mL DMSO at 120 °C for 12 h. As shown in the Scheme 1, the reactions proceeded without any difficulty to obtain 93% yield of **3a** (1.46 g), 94% yield of **3h** (1.95 g), 73% yield of **3p** (1.16 g) and 92% yield of **3x** (1.46 g), respectively.

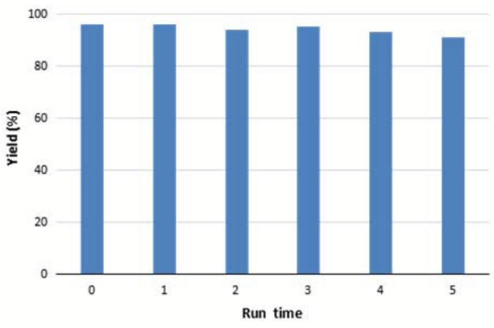
As a solid catalyst in organic transformation, issues that should be addressed are the ease of separation as well as the deactivation and reusability of the catalyst. The MOF-199 was therefore investigated for the recoverability and reusability, by repeatedly separating from the reaction mixture *via* centrifugation, washing it and then reusing it (Scheme 2). The coupling reaction was carried out in DMSO at 120 ^{o}C for 12 h, using 4-iodotoluene (0.5 mmol), pyrrole (0.75 mmol), in the presence of 10 mol% MOF-199 catalyst. After completion of the first run, the catalyst was separated from the reaction mixture by simple centrifugation, washed with H_2O, ethyl acetate and ethyl alcohol, and dried 100 ^{o}C under vacuum in 6 h. The recovered MOF-199 was then reused as catalyst in further transformation under the standard conditions. Experimental results indicated that the MOF-199 catalyst could be recovered and reused without a significant deactivation in catalytic activity, and the yield of **3a** always maintains above 90% after 5 runs. By comparing the XRD of MOF-199 before and after 5 runs' reaction, we can find that there are no obvious differences, which indicate that the crystallinity and structure of MOF-199 can be kept well during the course of the reaction. Furthermore, we have investigated the metal leaching of catalyst MOF-199 by atomic absorption spectroscopy (AAS) analysis. And low than 0.18% of the initial copper content was detected in reaction solution, which indicated that MOF-199 was an excellent heterogeneous catalyst for this type reaction.

Table 3 The comparison of efficiency of different heterogeneous copper catalyst in Ullmann-typle C-N coupling reactions of aryl iodides with *N*-containing heterocycles

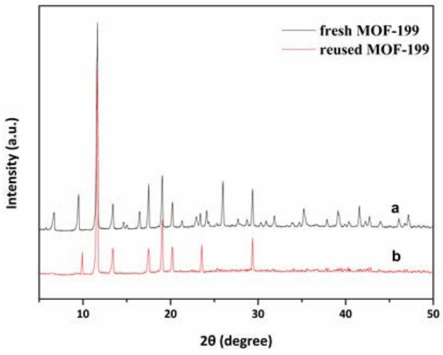
Catalyst (Cu mol%)	Condition and yield (%)	Ref.
MOF-199 (10)	NaOH, DMSO, 120 °C; 50-97%	This work
CELL-Cu(0) (0.9)	K_2CO_3, DMSO, 130 °C; 40-95%	3
Cu^0/4Å (8.7)	Cs_2CO_3, pyrrole, 135 °C; 25-100%	7
$Cu_2(BDC)_2(DABCO)$ (5)	KO^{t}Bu, DMF, 120 °C; 0-84%	27
CuI/meso-N-C-1 (15)	KOH, DMSO, 125 °C; 88%	28
CuO/AB (5)	KO^{t}Bu, toluene, 180 °C; 26-100%	29



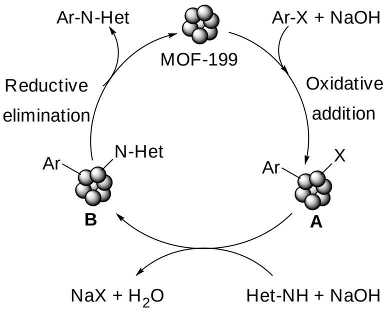
Scheme 1 Gram-scale reactions of N-arylation of heterocycles with 4-iodotoluene.



Scheme 2 The recyclability of MOF-199 for N-arylation of pyrrole with 4-iodotoluene. Reaction conditions: 4-iodotoluene (0.5 mmol), pyrrole (0.75 mmol), MOF-199 (10 mol%), NaOH (1.0 mmol), DMSO (1 mL), 120 °C, 12 h; isolated yield.



Scheme 2 X-ray powder diffractogram of the fresh (a: black trace) and reused (b: red trace) MOF-199.



Scheme 3 Plausible reaction mechanism.

Based on previous literature reports[12,25,26], the reaction mechanism for this transformation is proposed and shown in Scheme 3. This reaction involves a heterogeneous process and the catalysis may occur on the exposed copper site. In the presence of KOH, oxidative addition of MOF-199 with aryl halides provided Cu-complex **A**. And then, the nucleophilic

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substitution of intermediate **A** with *N*-containing heterocycles gives **B**, followed by reductive elimination lead to desired *N*-arylated products and regenerate the active copper catalyst.

Conclusions

In conclusion, we have established a simple and efficient copper-based MOF-catalyzed *N*-arylation of *N*-containing heterocycles with aryl iodides, the corresponding target products were obtained in moderate to excellent yields. The convenient approach, the stable and reusable catalyst, as well as the option for efficient large scale preparation, are the features of the catalytic process presented in the current paper. Further investigation into other types copper-based MOFs-catalyzed reactions are currently ongoing in our laboratory and will be reported in due course.

Experimental

General methods

All the reactions were carried out under air using magnetic stirring unless otherwise noted. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance III HD 400 instrument using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model. AAS was obtained on an Agilent 200 Series AA instrument. Column chromatography was performed with silica gel (200-300 mesh) purchased from Qingdao Haiyang Chemical Co., Ltd. All the other reagents were of analytical grade quality, purchased commercially and used as received.

General procedure for MOF-199 catalyzed *N*-arylation of heterocycles with aryliodides

To a 10 mL of sealed tube was added MOF-199 (0.05 mmol), aryl halides (0.50 mmol), *N*-containing heterocycles (0.75 mmol), NaOH (1.0 mmol) and DMSO (1 mL). The reaction mixture was reacted at 120 °C in a preheated oil bath for 12 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (20 mL×3). The combined organic phases was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to afford the target product **3a**-**3z**.

Recycling of the catalyst MOF-199

After completion of the first run, the reaction mixture was cooled to room temperature, and the MOF-199 catalyst was separated from the reaction mixture by simple centrifugation, washed with copious amounts of H_2O, ethyl acetate and ethyl alcohol, and dried 100 $^{\circ}$C under vacuum in 6 h. The recovered MOF-199 catalyst was then reused as catalyst in further transformation under identical conditions. This process was then repeated.

Metal leaching test of catalyst MOF-199

After completion of the reaction, the reaction mixture was hot filtrated under vacuum. The solid was washed with DMSO, and the liquid phase was analyzed by AAS.

Acknowledgements

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Notes and references

1 For some selected reviews, see: (*a*) Z. Jin, *Nat. Prod. Rep.*, 2005, **22**, 196; (*b*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (*c*) M. Carril, R. SanMartin and E. Domínguez, *Chem. Soc. Rev.*, 2008, **37**, 639; (*d*) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.*, 2008, **47**, 3096.

2 For some selected reviews, see: (*a*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13; (*b*) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.*, 2009, **48**, 6954; (*c*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*d*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337.

3 K. R. Reddy, N. S. Kumar, B. Sreedhar and M. L. Kantam, *J. Mol. Catal. A: Chem.*, 2006, **252**, 136.

4 L. Rout, S. Jammi and T. Punniyamurthy, *Org. Lett.*, 2007, **9**, 3397.

5 S. U. Son, I. K. Park, J. Park and T. Hyeon, *Chem. Commun.*, 2004, 778.

6 M. Nasrollahzadeh, S. M. Sajadi, A. Rostami-Vartooni and S. M. Hussin, *J. Colloid Interface Sci.*, 2016, **466**, 113.

7 J. Németh, N. Debreczeni, I. Gresits, M. Bálint and Z. Hell, *Catal. Lett.*, 2015, **145**, 1113.

8 M. Nasrollahzadeh, F. Babaei, P. Fakhri and B. Jaleh, *RSC Adv.*, 2015, **5**, 10782.

9 A. Khalil, A. Fihri, M. Jouiad and R. Hashaikeh, *Tetrahedron Lett.*, 2014, **55**, 5973.

10 M. Nasrollahzadeh, M. Enayati and M. Khalaj, *RSC Adv.*, 2014, **4**, 26264.

11 S. K. Movahed, M. Dabiri and A. Bazgir, *Appl. Catal. A: Gen.*, 2014, **484**, 79.

12 M. Gopiraman, S. G. Babu, Z. Khatri, W. Kai, Y. A. Kim, M. Endo, R. Karvembu and I. S. Kim, *Carbon*, 2013, **62**, 135.

13 Q. Yang, Y. Wang, D. Lin and M. Zhang, *Tetrahedron Lett.*, 2013, **54**, 1994.

14 X. Qi, L. Zhou, X. Jiang, H. Fan, H. Fu and H. Chen, *Chin. J. Catal.*, 2012, **33**, 1877.

15 F. Heidarizadeh and A. Majdi-nasab, *Tetrahedron Lett.*, 2015, **56**, 6360.

16 R. Xiao, H. Zhao and M. Cai, *Tetrahedron*, 2013, **69**, 5444.

17 B. Kodicherla, P. Perumgani C. and M. R. Mandapati, *Appl. Catal. A: Gen.*, 2014, **483**, 110.

18 S. M. Islam, S. Mondal, P. Mondal, A. S. Roy, K. Tuhina and M. Mobarok, *Inorg. Chem. Commun.*, 2011, **14**, 1352.

19 R. Mostafalu, B. Kaboudin, F. Kazemi and T. Yokomatsu, *RSC Adv.*, 2014, **4**, 49273.

20 For some selected reviews: (*a*) S. E. Miller, M. H. Teplensky, P. Z. Moghadam and D. Fairen-Jimenez, *Interface Focus*, 2016, doi: 10.1098/rsfs.2016.0027; (*b*) S. Ma and H.-C. Zhou, *Chem. Commun.*, 2010, **46**, 44; (*c*) P. Horcajada, R. Gref, T. Baati, P. K. Allan, G. Maurin, P. Couvreur, G. Férey, R. E. Morris and C. Serre, *Chem. Soc. Rev.*, 2012, **112**, 1232; (*d*) L. E. Kreno, K. Leong, O. K. Farha, M. Allendorf, R. P. Van Duyne and J. T. Hupp, *Chem. Rev.*, 2012, **112**, 1105; (e) Z. Hu, B. J. Deibert and J. Li, *Chem. Soc. Rev.*, 2014, **43**, 5815.

View Article Online
DOI: 10.1039/C6OB02068B

21 For some selected reviews: (*a*) A. Corma, H. Garcia and F. X. L. i. Xamena, *Chem. Rev.*, 2010, **110**, 4606; (*b*) J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen and J. T. Hupp, *Chem. Soc. Rev.*, 2009, **38**, 1450; (*c*) J. Liu, L. Chen, H. Cui, J. Zhang, L. Zhang and C.-Y. Su, *Chem. Soc. Rev.*, 2014, **43**, 6011; (*d*) M. Yoon, R. Srirambalaji and K. Kim, *Chem. Rev.*, 2012, **112**, 1196.

22 S. S.-Y. Chui, S. M.-F. Lo, J. P. H. Charmant, A. G. Orpen and I. D. Williams, *Science*, 1999, **283**, 1148.

23 (*a*) L. Alaerts, E. Seguin, H. Poelman, F. Thibault-Starzyk, P. A. Jacobs and D. E. De Vos, *Chem. Eur. J.*, 2006, **12**, 7353, (*b*) L. H. Wee, S. R. Bajpe, N. Janssens, I. Hermans, K. Houthoofd, C. E. A. Kirschhock and J. A. Martens, *Chem. Commun.*, 2010, **46**, 8186; (*c*) N. T. S. Phan, T. T. Nguyen, C. V. Nguyen and T. T. Nguyen, *Appl. Catal. A: Gen.*, 2013, **457**, 69; (*d*) M. Soleiman-Beigi, I. Yavari and F. Sadeghizadeh, *RSC Adv.*, 2015, **5**, 87564; (*e*) N. T. S. Phan, T. T. Nguyen, P. Ho and K. D. Nguyen, *ChemCatChem*, 2013, **5**, 1822; (*f*) A. Dhakshinamoorthy, M. Alvaro and H. Garcia, *Chem. Eur. J.*, 2010, **16**, 8530.

24 (*a*) X.-G. Liu, Z.-H. Li, J.-W. Xie, P. Liu, J. Zhang and B. Dai, *Tetrahedron*, 2016, **72**, 653; (*b*) Z. Li, N. Yan, J. Xie, P. Liu, J. Zhang and B. Dai, *Chin. J. Chem.*, 2015, **33**, 589; (*c*) C. Hao, C. Zhou, J. Xie, J. Zhang, P. Liu and B. Dai, *Chin. J. Chem.*, 2015, **33**, 1317; (*d*) N.-N. Yan, F.-T. Wu, J. Zhang, Q.-B. Wei, P. Liu, J.-W. Xie and B. Dai, *Asian J. Org. Chem.*, 2014, **3**, 1159; (*e*) F. Wu, J. Zhang, Q. Wei, P. Liu, J. Xie, H. Jiang and B. Dai, *Org. Biomol. Chem.*, 2014, **12**, 9696; (*f*) F.-W. Wu, N.-N. Yan, P. Liu, J.-W. Xie, Y. Liu and B. Dai, *Tetrahedron Lett.*, 2014, **55**, 3249.

25 T. Truong, C. V. Nguyen, N. T. Truong and N. T. S. Phan, *RSC Adv.*, 2015, **5**, 107547.

26 S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 1971.

27 T. T. Nguyen and N. T. S. Phan, *Catal. Lett.*, 2014, **144**, 1877.

28 P. Zhang, J. Yuan, H. Li, X. Liu, X. Xu, M. Antoniette and Y. Wang, *RSC Adv.*, 2013, **3**, 1890.

29 A. Y. Kim, H. J. Lee, J. C. Park, H. Kang, H. Yang, H. Song and K. H. Park, *Molecules*, 2009, **14**, 5169.

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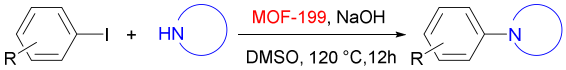
DOI: 10.1039/C6OB02068B



- Operational simplicity
- Gram-scale preparation
- Recoverable catalyst
- 26 examples (50-97% yields)