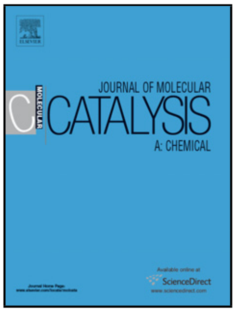


Title: Unprecedented salt-promoted direct arylation of acidic sp^2 C-H bonds under heterogeneous Ni-MOF-74 catalysis: synthesis of bioactive azole derivatives

Author: Huong T.T. Nguyen Duc N.A. Doan Thanh Truong

PII: S1381-1169(16)30483-6
DOI: http://dx.doi.org/doi:10.1016/j.molcata.2016.11.009
Reference: MOLCAA 10106

To appear in: *Journal of Molecular Catalysis A: Chemical*

Received date: 22-7-2016
Revised date: 18-10-2016
Accepted date: 5-11-2016

Please cite this article as: Huong T.T.Nguyen, Duc N.A.Doan, Thanh Truong, Unprecedented salt-promoted direct arylation of acidic sp2 C-H bonds under heterogeneous Ni-MOF-74 catalysis: synthesis of bioactive azole derivatives, Journal of Molecular Catalysis A: Chemical http://dx.doi.org/10.1016/j.molcata.2016.11.009

Unprecedented salt-promoted direct arylation of acidic sp^2 C-H bonds under heterogeneous Ni-MOF-74 catalysis: synthesis of bioactive azole derivatives

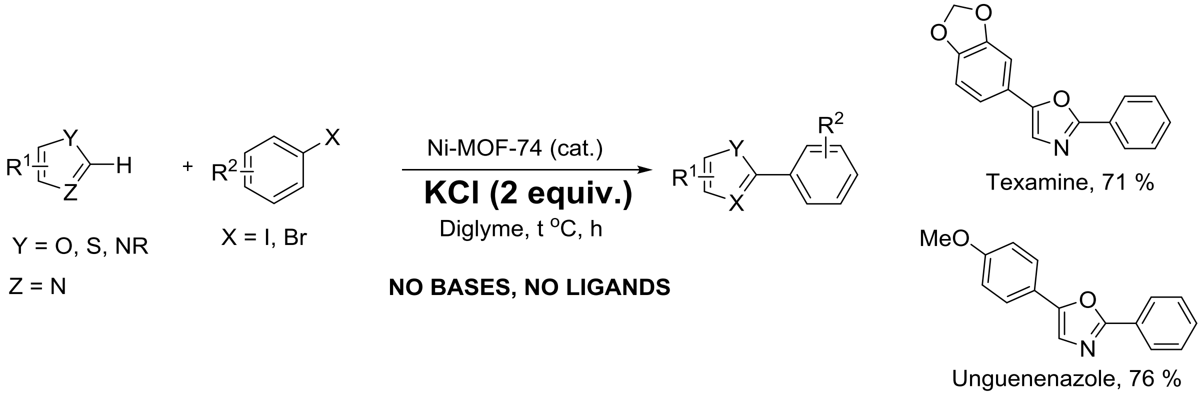
Huong T. T. Nguyen, Duc N. A. Doan, Thanh Truong*

Department of Chemical Engineering, HCMC University of Technology, VNU-HCM,

268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Viet Nam

*Email: tvthanh@hcmut.edu.vn

Graphic abstract



Research Highlights

- Our work provides the unprecedented and general heterogeneous Ni-MOFs-catalyzed direct arylation of heterocycles using KCl as promoter.
- First report using heterogeneous catalysts to approach bioactive azole derivatives.
- The catalyst could be recovered and reused.

Abstract

Herein, nickel-based metal-organic framework, Ni-MOF-74, was synthesized by a solvothermal method and its properties was characterized by a host of techniques. Ni-MOF-74 exhibited exceptional catalytic activity toward the direct arylation of azoles via C-H activation while other Ni-MOFs, nickel-based heterogeneous systems, and homogeneous counter parts displayed lower activity. Optimal conditions involved the use of Li_2CO_3 or KCl salts in diglyme solvent in 18 hours and no additional ligand is required. This is the first and unprecedented report using KCl salt as promoter for arylation of heterocycles. By avoiding the use of strong bases and oxidants, optimized conditions are compatible with wide range of functional groups and heterocycles. Furthermore, by taking advantage of large aperture size of Ni-MOF-74, we are able to utilize optimized conditions to successfully synthesize several bioactive arylated azole derivatives. Previous studies using heterogeneous catalysts to approach these bioactive compounds are not performed in the literature. Leaching tests indicated that homogeneous catalysis via leached active nickel species is unlikely. Thus, the catalyst was facilely separated from the reaction mixture and reused several times without significant degradation of the catalytic reactivity.

Keywords: Metal-organic framework; C-H arylation; heterogeneous catalyst; Ni-MOF-74; bioactive azoles

1. Introduction

Metal-promoted arylation of heterocycle compounds using direct C-H activation has increasingly gained attention [1, 2]. By using C-H bonds as starting materials, the method provides shorter and more efficient synthetic approach than the conventional cross-coupling methods such as the Suzuki–Miyaura, Stille, Negishi and other named reactions. This further improves atom-economical and environmental issues of synthetic procedures [3-5]. Previous works on arylation of heteroarenes with aryl electrophiles through direct C-H functionalization involved the use of palladium-, rhodium-, ruthenium-, or iridium-based catalyst systems [6-13]. More recently, efforts geared toward the use of non-noble metal catalysts have been witnessed in the synthetic community [14]. Specifically, a significant breakthrough on the copper-catalyzed direct heterocycle C-H arylation reaction of various heteroarenes with haloarenes using copper salts as catalysts was investigated by Daugulis group [2, 15], nickel-based catalysts have emerged as promising candidates for organic transformations through direct C-H activation [16]. Miura and co-workers discovered that the combination of $NiBr_2$ and nitrogen-containing compounds such as 2,2'-bipyridine (bipy) or 1,10-phenanthroline as ligands could offer high activity for the direct coupling of azole derivatives and organoboronic acids [17]. $Ni(OAc)_2$/bipy has been established by Itami as an efficient catalytic protocol for the arylation of heteroarenes with aryl halides and triflates [18]. Lei and co-workers demonstrated a novel oxidative arylation of cyclic ethers with arylboronic acid employing $Ni(acac)_2$ as catalyst precursor in the presence of triphenylphosphine (PPh_3) as the ligand and di-*tert*-butyl peroxide as the oxidant [19]. Under the demand of the pharmaceutical and other chemical industries, heterogeneous catalytic systems for direct arylation of heteroarenes were recently disclosed [20]. However, in most cases, palladium-based catalysts were employed or strong bases or oxidants were required for depronation/activation of C-H bonds. Additionally, protocols for bulky bioactive compound synthesis are not disclosed yet. Therefore, the development of milder and more practical processes using heterogeneous catalysts, especially in pharmaceutical industry, should be targeted [21].

Although the application of MOFs in catalysis has just been investigated for the past few years, MOFs have been showed to possess high activity for a variety of organic transformations [22-

26]. Though Cu-based MOFs have been frequently utilized as efficient heterogeneous catalysts, nickel-based MOFs have been rarely reported. In particular, Kim and Chou group disclosed the nickel nanoparticles supported on MOF as heterogeneous for hydrogenation reactions [27, 28]. Recently, Jiang and co-workers employed nickel(salphen)-based MOF as a heterogeneous catalyst for the synthesis of cyclic carbonates [29]. We reported the first nickel-catalyzed direct heterocycle C-H arylation reaction under $Ni_2(BDC)_2(DABCO)$ (H_2BDC= benzene-1,4-dicarboxylic acid, DABCO = 1,4-diazabicyclo[2.2.2]octane) catalysis [30]. However, synthetic protocol involved the use of pre-functionalized arylboronic acids, strong base, and was only applicable for benzoxazoles. Furthermore, the optimal conditions failed to synthesize bulky bioactive compounds. Recently, the discovery of MOF-74 with paddle wheel structure, open metal sites, high coordinate metal ion, and pore apertures are of a size suitable for the inclusion of large organic molecules offered a promising type of MOFs, especially for pharmaceutical industry [31-33]. Herein, we report an efficient route for arylation of azoles via C-H activation over Ni-MOF-74 catalyst using inexpensive and air stable Li_2CO_3 or KCl salts as promoters. This is the first report using KCl salt as promoter for arylation of heterocycles. Interestingly, the use of large pore size Ni-MOF-74 allowed the efficient synthesis of bioactive arylated oxazoles.

2. Experimental

2.1. Materials and instrumentation

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers such as Acros Organics, Sigma–Aldrich and Merck and used as received. All coupling reactions were performed under an atmosphere of Argon gas in dried 8 mL vials, used 7 x 2 mm spinbar and heated in a 34–well reaction block Optochem heater. Monitoring experiments by gas chromatography (GC) was performed with 10 mm vials equipped with caps, septa. Activation and purification procedures were carried out by using Schlenkline system. Nitrogen physisorption measurements were conducted using a Micromeritics 2020 volumetric adsorption analyzer system. Samples were pretreated by heating under vacuum at 150 ^{o}C for 3 h. A Netzsch Thermoanalyzer STA 409 was used for thermogravimetric analysis (TGA) with a heating rate of 10 ^{o}C/min under a nitrogen atmosphere. X-ray powder diffraction (XRD) patterns were recorded using a Cu Kα radiation source on a D8 Advance Bruker powder diffractometer. Scanning electron microscopy studies were conducted on a S4800 Scanning Electron Microscope (SEM). Transmission electron microscopy studies were performed using a JEOL JEM 1400 Transmission Electron Microscope (TEM) at 100 kV. The $Ni_2(BDC)_2(DABCO)$ sample was dispersed on holey carbon grids for TEM observation. Elemental analysis with atomic absorption spectrophotometry (AAS) was performed on an AA-6800 Shimadzu. Fourier transform infrared (FT-IR) spectra were obtained on a Nicolet 6700 instrument, with samples being dispersed on potassium bromide pallets.

Gas chromatographic (GC) analyses were performed using a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for GC analysis heated samples from 120 to 130 ^{o}C at 40 ^{o}C/min; heated from 130 to 180 ^{o}C at 40 ^{o}C/min and held them at 180 ^{o}C for 0.5 min; heated them from 180 to 280 ^{o}C at 50 ^{o}C/min and held them at 280 ^{o}C for 5 min. Inlet and detector temperatures were set constant at 280 ^{o}C. *n*-Hexadecane was used as an internal standard to calculate reaction conversions. GC-MS analyses were performed using a Hewlett Packard GC-MS 5972 with a RTX-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.5 μm). The temperature program for GC-MS analysis heated samples from 60 to 280 ^{o}C at 10 ^{o}C/min and held them at 280 ^{o}C for 5 min. Inlet temperature was set constant at 280 ^{o}C. MS spectra were compared with the spectra gathered in the NIST library. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Bruker NMR spectrometer at 500 MHz and 125 MHz, respectively.

2.2. Synthesis of the metal-organic framework Ni-MOF-74

In a typical preparation [34, 35], a solution of 2,5–dihydroxyterephthalic acid (0.102 g, 0.5 mmol) in 7.5 mL of THF and a solution of nickel acetate tetrahydrate (0.252 g, 1 mmol) in 7.5 mL of water were added into 15 mL pressure tube. The tube was capped and mixture was stirred at room temperature for 15 minutes before being placed in oven at 120 ^{o}C for 24 hours. After cooling to room temperature, the mother liquor was decanted and the solid product was washed by THF three times (3 x 10 mL) each day for 3 days. The products were then dried under reduced pressure at 140 ^{o}C in 8 hours. The sample was cooled to room temperature, yielding 0.1633 g of Ni-MOF-74 in the form of yellow fined–crystalline substance (94 %).

2.3. Catalytic studies

In a typical experiment, a predetermined amount of Ni-MOF-74 was added to the 8 mL vial containing a mixture of iodobenzene (0.1030 g, 0.5 mmol), benzothiazole (0.1379 g, 1.0 mmol), Li_2CO_3 or KCl (1.0 mmol), and diphenyl ether (0.085 g, 0.5 mmol) as standard. 1–Methoxy–2–(2–methoxyethoxy)ethane (diglyme) (1 mL) was added and vial was tightly capped. Reaction mixture was heated at 160 ^{o}C for 24 hours. The catalyst loading was based on the molar ratio of nickel/iodobenzene. The reaction yield was monitored by withdrawing aliquots from the reaction mixture at different time intervals, diluting with ethylacetate (2 mL), quenching with an aqueous KOH solution (1%, 1 mL), and then drying over anhydrous Na_2SO_4 before analyzing by GC with reference to diphenyl ether (internal equation with pure product), and further confirming product identity by GC–MS and NMR. To investigate the recycle ability of Ni-MOF-74, the catalyst was filtered from the reaction mixture after the experiment, washed with ethylacetate, water, THF, and dried at 140°C under vacuum in 8 hours. For the leaching test, a catalytic reaction was stopped after 12 hours, analyzed by GC, and filtered to remove the solid catalyst. The reaction solution was then stirred for a further 12 h. Reaction progress, if any, was monitored by GC as previously described.

3. Results and discussion

3.1. Catalyst synthesis and characterization

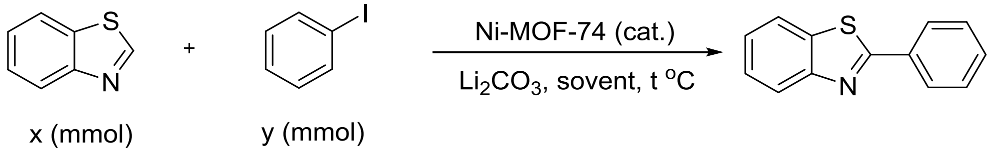
In this work, the Ni-MOF-74 was synthesized in a yield of 94 % by a solvothermal method, according to a slightly modified literature procedure [34, 35]. Its structural properties were characterized by a variety of different techniques, including XRD, SEM, TEM, TGA, FT-IR, AAS, and nitrogen physisorption measurements (Fig. S12 – Fig. S18). The analysis results were in agreement with previous studies [35]. These confirmed that the synthesized Ni-MOF-74 possesses paddle wheel structure, open metal sites, and exceptionally large pore apertures. Specifically, powder X-ray diffraction pattern showed the typical reflections of MOF-74 phase. The basically type-1 adsorption/desorption isotherm indicated the permanent micro-porosity with Brunauer–Emmett–Teller specific surface area of 889 m^2/g, a pore volume of 0.41 cm^3/g and an average pore diameter of about 16 Å. Scanning electron microscopy analysis showed the homogeneity. Thermal gravimetric analysis (TGA) of activated Ni-MOF-74 shows high thermal stability (>300 °C) and the measured mass percent of residue NiO is consistent with the EA data. AAS provided 33.3 % copper content which is close to the calculated value of 34.2 %. Finally, FT-IR spectra of Ni-MOF-74 indicated the presence of bonded carboxylate organic linkers.

3.2 Catalytic studies

It is worth mentioning that in previous report using homogeneous $Ni(OAc)_2$ catalysts, bidentate ligand was required to obtain good yields [18]. In addition, air-sensitive ^{t}BuOLi base was employed under inert atmosphere [18, 19]. Under the industrial view of point, synthetic protocols without homogeneous ligands, strong bases, and under atmospheric conditions are highly needed. Within this study, we aim to develop more simple and practical procedure without added ligands and using bench-top reagents. We hypothesized that Li_2CO_3/diglyme would promote the arylation of azoles on the basis of following considerations: (1) strong binding constant of of Li cation in diglyme solvent due to high coordination of Li with oxygen atom [36], (2) σ-adduct formation at the metal center is favored by the carboxylate anion [37, 38, 39].

In reaction screening, the catalytic activity of Ni-MOF-74 was investigated in the direct arylation of benzothiazole using iodobenzene as coupling partner (Table 1). Gratifyingly, with respect to amount of catalyst, 90 % GC yield was obtained when 10 % catalyst was employed (entry 3). Decreasing amount of catalyst led to significant drop in reaction yields (entries 1, 2) while no further improvement was obtained when amount of catalyst was increased (entry 4). Solvents such as mesitylene, dimethylformamide (DMF), dimethyl propylene urea (DMPU), dimethyl sulfoxide (DMSO), and *N*-methyl-2-pyrolidone (NMP) are not suitable under tested conditions when < 6 % yield was achieved (entries 5-9). Reactions in dimethylacetamide (DMA) afforded only 24 % (entry 10). This confirmed the synergetic effect of Li_2CO_3/diglyme system. Optimization of reagent ratios and reaction concentration indicated that using 2 equivalents of iodobenzene at 0.5 M was optimal (entries 11-14).

Table 1. Condition optimization[a]

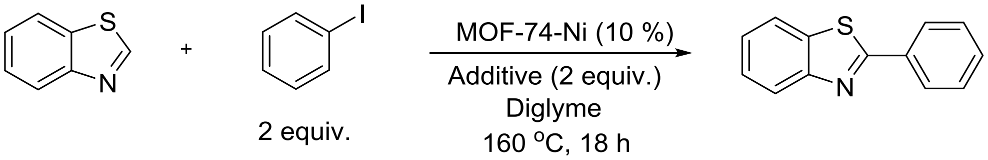


Entry	Amount of catalyst (%)	Solvent	Temperature (°C)	Ratio y/x	GC yield (%)
1	5	Diglyme	160	2	58
2	7.5	Diglyme	160	2	75
3	**10**	Diglyme	160	**2**	**90 (89)**
4	12.5	Diglyme	160	2	87
5	10	Mesitylene	160	2	<2
6	10	DMF	160	2	<2
7	10	DMPU	160	2	<2
8	10	DMSO	160	2	6
9	10	NMP	160	2	4
10	10	DMA	160	2	24
11	10	Diglyme	140	2	10
12	10	Diglyme	150	2	36
13	10	Diglyme	160	1.5	32
14	10	Diglyme	160	2.5	89
15[b]	10	Diglyme	160	2	6
16[c]	10	Diglyme	160	2	81
17[d]	10	Diglyme	160	2	84
18[e]	10	Diglyme	160	2	81

[a] Li_2CO_3 (2 equiv.), 1.0 mmol scale, 0.5 M, 18 h. [b] Reaction at 0.25 M. [c] Reaction at 0.75 M. [d] Reaction using 2.5 equiv. of base. [e] Reaction using 1.5 equiv. of Li_2CO_3 Numbers in parentheses indicate the isolated yields. Kinetic studies of reaction temperature were placed in Supporting Information.

It was reported that pKa of benzothiazole in DMSO was about 30 [40] while pKa of Li_2CO_3 was estimated to be about 10 [41]. To further invesitgate the special role of Li_2CO_3, several control experiments using a variety of bases were conducted (Table 2). Remarkably, replacing Li_2CO_3 by stronger carbonate bases such as Na_2CO_3, K_2CO_3, and Cs_2CO_3, which were commonly used in previous studies of cross coupling reactions, completely retarded the reactions (entries 2-4). Undetectable amount of desired product was observed when benzothiazole was arylated using K_3PO_4 (entry 5). *Tert*-butoxide bases which were employed in homogeneous protocols were showed to be inactive (entries 6, 7). These results confirm the combinatory roles of lithium cation and carbonate anion in diglyme media. The hypothesis was supported by the inefficiency of $LiNO_3$, Li_2SO_4, LiOH, and $LiHCO_3$ bases (entries 8-11). Unprecedentedly, substantial amount of desired product was observed when LiCl, NaCl, or KCl was employed instead of Li_2CO_3. In particular, up to 91 % yield was obtained with KCl promoter while undetected amount of product was obtained in the absence of KCl. Though it is well recognized that diglyme possesses great ability to chelate small cations and make anion more active [42], studies on KCl/diglyme system for depronation has not been reported. Furthermore, addition of frequently used ligands in previous homogeneous studies shut down the reaction when either Li_2CO_3 or KCl was utilized. This could be rationalized by the fact that the added ligands might occupy the open site of nickel by coordination. Unlike homogeneous counterpart, association of ligand in MOFs can permanently saturate the metal center [43].

Table 2. Effect of various bases to reaction yields.



Entry	Additive	Added ligand	GC Yield[a]
1	Li_2CO_3	-	90
2	Na_2CO_3	-	<2

3	K_2CO_3	-	<2
4	Cs_2CO_3	-	<2
5	K_3PO_4	-	<2
6	^{t}BuOLi	-	4
7	^{t}BuONa	-	<2
8	$LiHCO_3$	-	<2
9	$LiNO_3$	-	<2
10	LiOH	-	<2
11	Li_2SO_4	-	<2
12	LiCl	-	66
	NaCl	-	81
13	**KCl**	**-**	**91**
	-	-	<2
14	KCl or Li_2CO_3	1,10-phenanthroline	<2
15	KCl or Li_2CO_3	TMEDA	<2
16	KCl or Li_2CO_3	2,2-bipyridine	<2

[a] 1.0 mmol scale, 0.5 M.

To gain more insights about interaction of diglyme, experiments using various etheral solvents with different chelating affinity were conducted using KCl as additive (Table 3). Interestingly, decreasing the chelating affinity of sovent by using solvents containing less oxygen atoms resulted in an significant drop in reaction rate (entries 2, 3). Specifically, reactions using monoglyme afforded 47 % yields while solvent containing one oxygen atom (dibutyl ether) was inactive. Moreover, only 57 % yield was observed when triglyme was employed (entry 4). 18-Crown-6, which is known to possess exceptionally high affinity for potassium cation, completely inhibited the reactions. Similar results was obtained when 12-crown-4 solvent and Li_2CO_3 were used. These data could be rationalized by the occupacy of open nickel site by strong chelating solvents.

Table 3. Reactions with various ether solvents

Entry	Sovent	GC Yield[a]
1	Diglyme	91 (90)
2[a]	Monoglyme (dimethoxyethane)	47 (38)
3	Dibutyl ether	<2
4	Triglyme (triethylene glycol dimethyl ether)	57 (62)
5	18-Crown-6	<2
6[b]	12-Crown-4	<2

Reaction conditions: Ni-MOF-74 (10 %), KCl (2 equiv.), 160 °C, 18h, 1 mmol scale, 0.5 M, iodobenzene/benzothiazole = 2/1. Numbers in parentheses indicate GC yields when Li_2CO_3 was employed. [a] Reactions in pressure vessel. [b] Reactions using Li_2CO_3.

To highlight the activity of Ni-MOF-74, reactions using frequently used catalysts for organic transformations were carried out under optimized conditions (Table 4). Notably, removing the –OH group in the linker, Ni-BDC, resulted in significant drop in catalytic activity even with added ligands (entries 2, 3). Remarkably lower conversions were obtained with $Ni_3(BTC)_2$ (H_3BTC = benzene-1,3,5-tricarboxylic acid) and Ni(HBTC)(BPY) (BPY = 4,4′-bipyridine) with 4 % and 12 %, respectively (entries 4, 5). All tested Ni-MOFs contain open metal sites and possess similar surface areas. High reactivity of Ni-MOF-74 could be rationalized by the aperture size and the additional coordination of –OH group in Ni center. In addition, the use of Ni-MOF-74 is technically preferred for the synthesis of other product derivatives which often have bulk size.

It is worth mentioning that heterogeneous Ni-based mesoporous or magnetic nano particle catalysts were showed to be unsuitable (entries 6-8). Other transition-metal-based organic frameworks such as Cu-MOF-74, Zn-MOF-74 or Co-MOF-74 are not effective and unappreciable amount of product was observed (entries 9-11). This observation confirms the necessity of nickel metal site in MOFs structure. It is worth mentioning that as compared to homogeneous counter-parts, traditional heterogeneous catalysts often provide lower activity. However, in this report, heterogeneous Ni-MOF-74 possesses similar or better activity than other tested Ni salts which were frequently used as homogeneous catalysts in typical cross-coupling reactions (entries 12-16).

Table 4. Reactivity of other catalysts

Entry	Type	Catalyst (10 %)	Linker (acid)	GC yield (%)
1	Heterogeneous Ni-based catalysts	Ni-MOF-74	2,5–dihydroxyterephthalic	91
2		Ni-BDC	terephthalic	52
3		$Ni_2(BDC)_2(DABCO)$	terephthalic	61
4		Ni(HBTC)(BPY)	1,3,5-benzenetricarboxylic	12
5		$Ni_3(BTC)_2$	1,3,5-benzenetricarboxylic	4
6		$NiFe_2O_4$		32
7		Ni/Zeolite X		15
8		Ni/ZSM-5		31
9	Other MOFs	MOF-74-Cu	2,5–dihydroxyterephthalic	3
10		MOF-74-Co	2,5–dihydroxyterephthalic	<2
11		MOF-74-Zn	2,5–dihydroxyterephthalic	4
12	Homogeneous Ni(II) salts	$Ni(OAc)_2$		82
13		$NiSO_4$		81
14		$Ni(NO_3)_2$		84
15		$NiBr_2$		80
16		$NiCl_2$		<2

[a] 1.0 mmol scale, 160 ^{o}C. 0.5 M, iodobenzene/benzothiophen = 2/1.

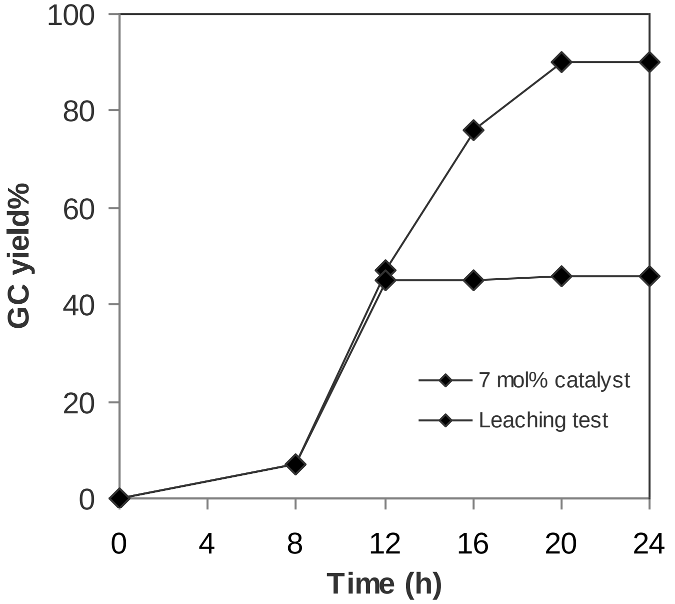


Fig. 1. Leaching test

In leaching test, a control experiment was carried out using a simple hot filtration during the course of the reaction (Fig. 1). The direct coupling reaction was conducted under optimal conditions involving the use of KCl salt (2 equiv.) in diglyme solvent at 160 ^{o}C in 24 hours. After 12 hours with 42 % yield being detected, the Ni-MOF-74 catalyst was removed from the reaction mixture by hot filtration. The liquid phase was then transferred to a new reactor vessel, and magnetically stirred for an additional 12 hours with aliquots being sampled at different time intervals, and analyzed by GC. It was observed that no further conversion was detected in the reaction mixture after the Ni-MOF-74 catalyst was separated from the reaction mixture (Fig. 2). In addition, ICP-MS revealed less than 1 ppm of nickel in the filtrate from reaction mixture. Therefore, it is likely that reactions could only proceed in the presence of the solid Ni-MOF-74 catalyst, and there should be no contribution from leached active nickel species in the liquid phase.

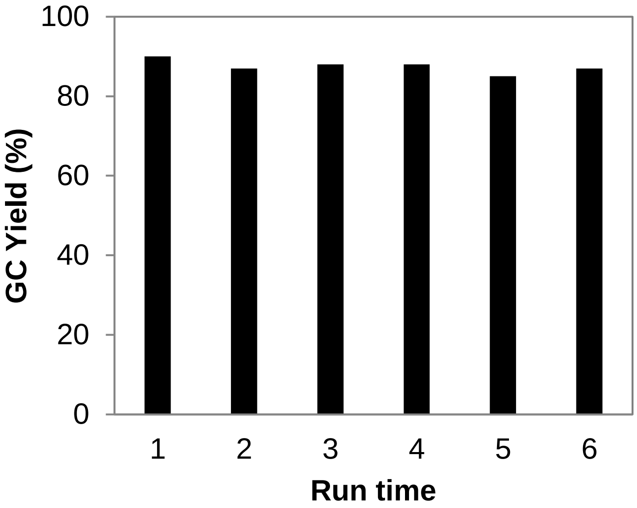


Fig. 2. Catalyst recycling studies.

The recoverability and reusability of the Ni-MOF-74 catalyst were investigated by repeatedly separating the solid catalyst from the reaction mixture after the reaction (Fig. 2). The cross coupling reactions was carried out using 2 equiv. of KCl in diglyme at 160 ^{o}C for 24 hours, in the presence of 10 mol% Ni-MOF-74 catalyst. After the experiment, the Ni-MOF-74 catalyst was separated from the reaction mixture by simple centrifugation, washed with copious amounts of ethylacetate, water and THF, dried at 140^{o}C under vacuum in 8 hours and reused in further reactions under identical conditions to the first run. It was found that the Ni-MOF-74 catalyst could be recovered and reused several times without a significant degradation in catalytic activity. Indeed, a yield of 87 % was still achieved in the 6th run. As compared to the FT-IR result of the fresh catalyst, the spectra of reused Ni-MOF-74 exhibited a similar absorption (Fig. 4). Moreover, the XRD result of the recovered Ni-MOF-74 indicated that the crystallinity could be maintained (Fig. 3).

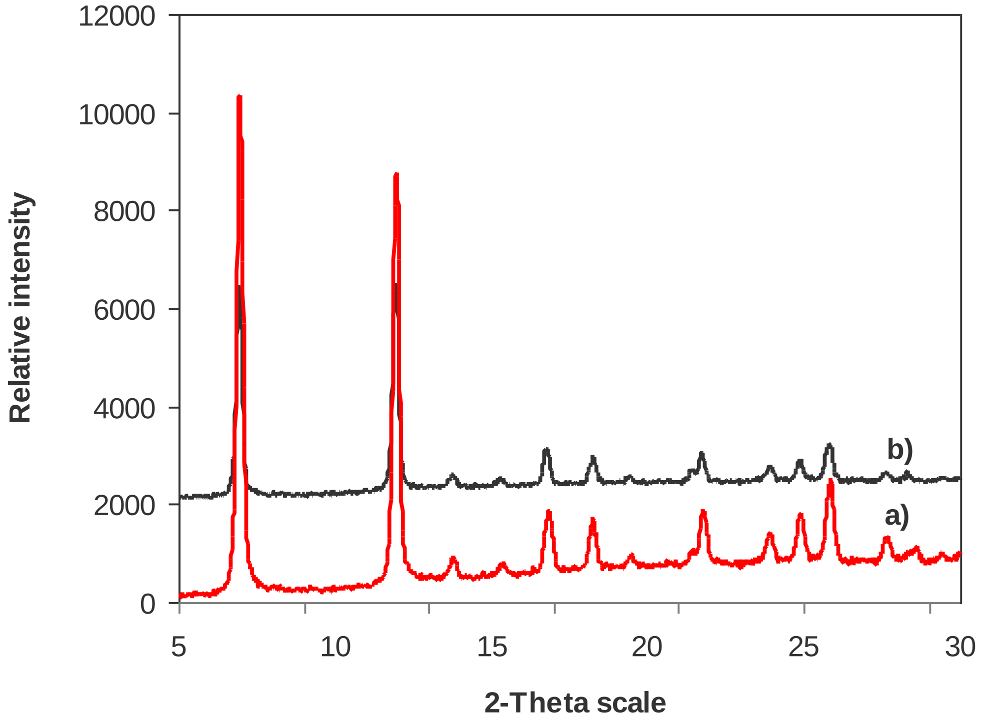


Fig. 3. X-ray powder diffractograms of fresh Ni-MOF-74 catalyst (a) and the 6th re-used (b).

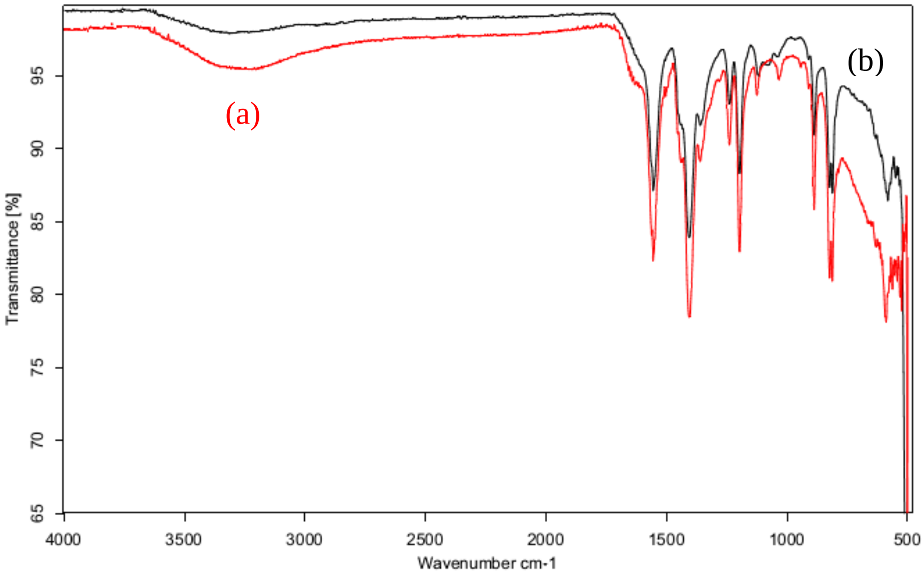


Fig. 4. FT-IR spectra of fresh Ni-MOF-74 catalyst (a) and the reused (b).

To preliminary address the issue of where the catalysis occurs, experiments using grinded Ni-MOF-74 were conducted under identical conditions (Fig. 5). It was observed that similar reaction conversions were obtained during the reaction course in both cases. In addition, the cavity size according to the Ni-MOF-74 structure is about 15-17 Å while the kinetic diameters of aromatic reactant and product are calculated to be 7.1 ^{o}A and 10.5 ^{o}A, respectively [44]. Furthermore, pore flexibility in MOFs upon temperature and guest molecules has been previously reported [45]. Though it is likely that reactions take place inside the catalyst pores, further spectroscopic studies are still needed.

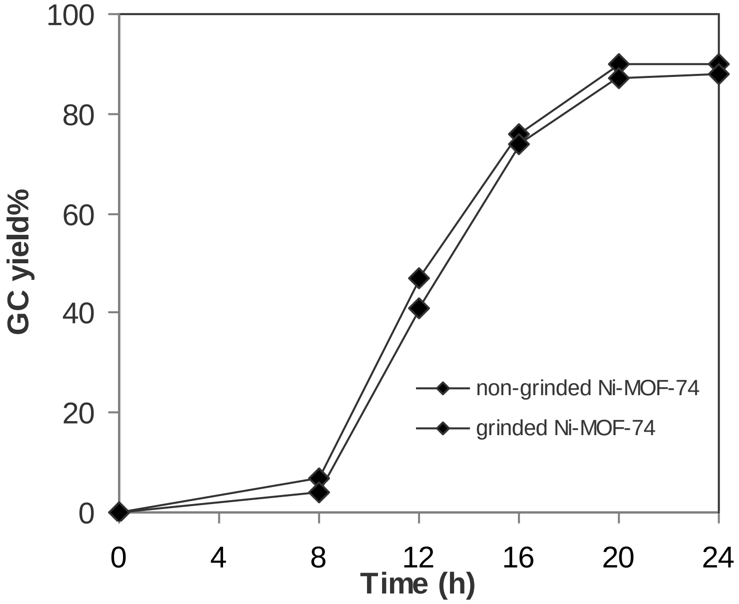
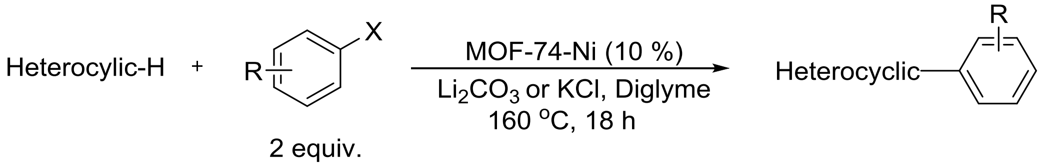
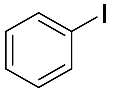
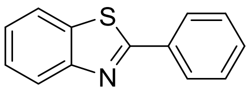
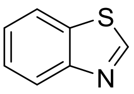
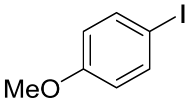
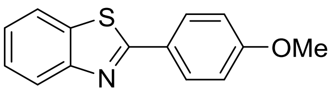
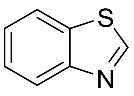
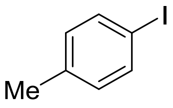
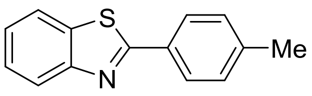
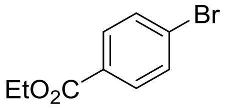
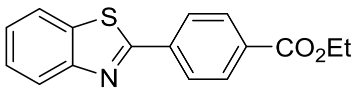
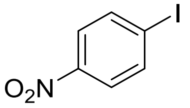
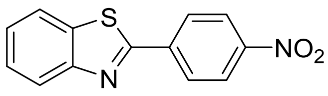


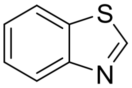
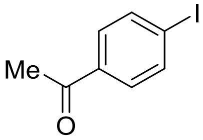
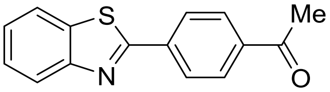
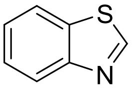
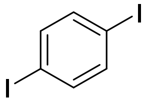
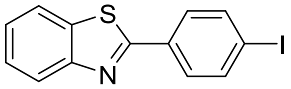
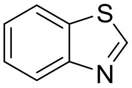
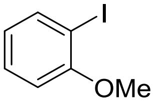
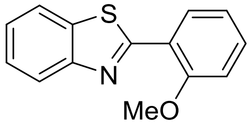
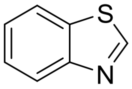
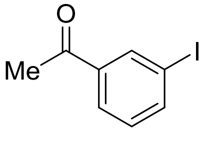
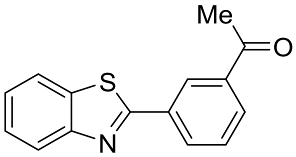
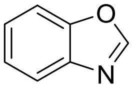
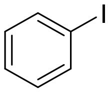
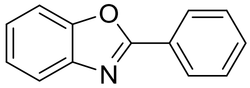
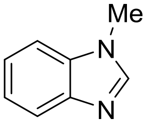
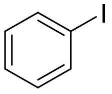
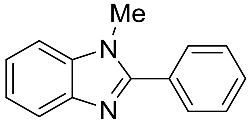
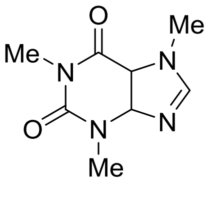
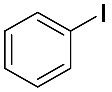
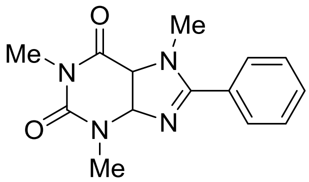
Fig. 5. Reactions with grinded Ni-MOF-74

The generality of optimal conditions using Ni-MOF-74 on other derivatives of coupling components were described in Table 5. Functionality occurs at most acidic C-H bonds in all cases. Reaction at larger scale and reaction with added (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) gave similar results (entries 1b, 1c). Aryl halides with electron donating groups such as methyl and methoxy are active and cross coupling products were achieved in reasonable yields (entries 2, 3). Arylation using iodobenzene containing electron withdrawing groups (ketone, nitro, ester) is also possible and C2-arylated benzothiazole was obtained in excellent yields (entries 4-6). Reported procedures using strong bases were not compatible with these functional groups [18, 19]. Selective mono-arylation of 1,4-diiodobenzene could be done (entry 7). Optimized conditions are also applicable for aryl halides with substituents at *ortho* or *meta*-position (entries 8, 9). With respect to heterocycles, reactions is not only limited to benzothiazole. In particular, good yields were achieved for arylation of 4,5-dimethylthiazole, benzoxazole, 1-methylimidazole, and caffeine (entries 10-12). It is worth mentioning that previous reported conditions using Cu-MOFs catalysts for arylation of heterocycles were only active for benzoxazole [46].

Table 5. Reactions scope of coupling components

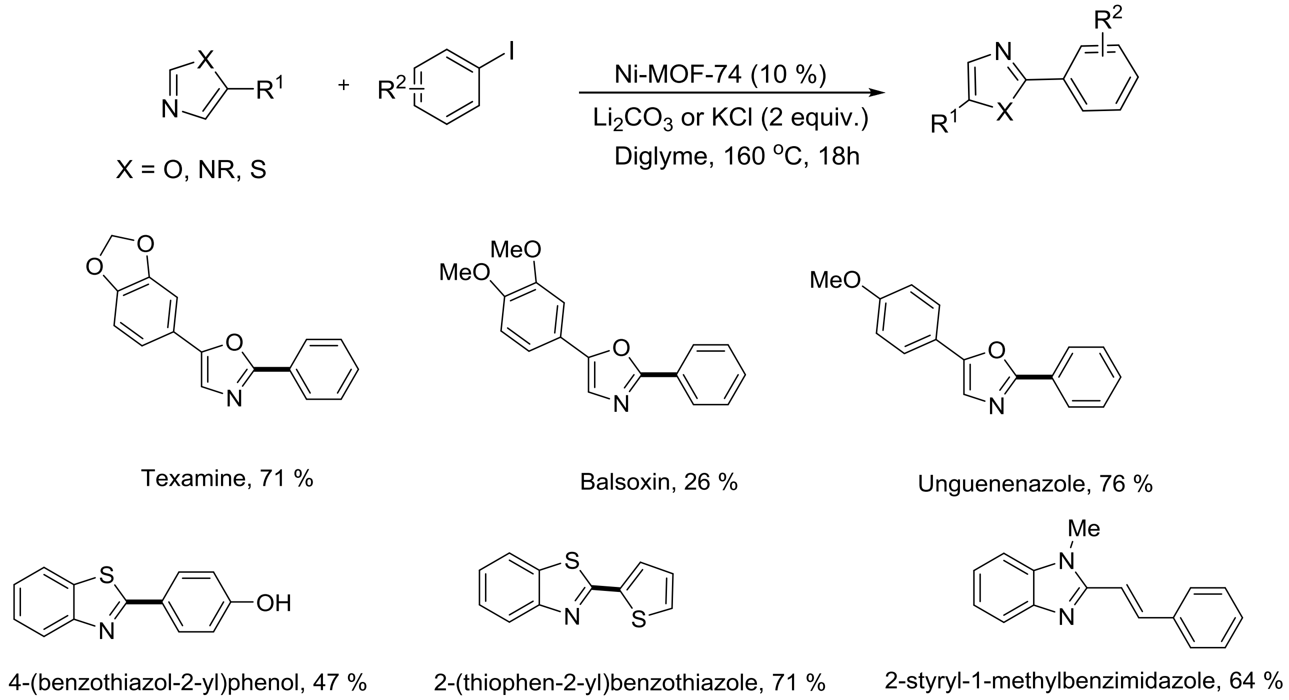


Entry	Heterocycle	Aryl halides	Product	Yields (%)
1				89, 87^{b}, 88^{c} 80^{d}
2				50
3				53 41^{d}
4				87
5				55

6				80
7				32
8				47
9				97 82^d
10				52
11				97
12	 Caffeine			38

Conditions: Diglyme (4 mL), heterocycles (0.5 mmol), 18 h.[b] 5 mmol scale. [c] Reaction with added TEMPO (10 %). [d] Reaction using bromoarenes

Under pharmaceutical viewpoint, the use of homogeneous catalysts often represents a major problem regarding purification of contaminated metals in final products, further increase the cost of entire process [47]. To further expand on the potential of Ni-MOF-74 to be used in practical applications, we utilized this heterogeneous catalyst in the synthesis of pharmaceutically relevant oxazoles possessing bioactivity (Scheme 2). In particular, Texamine, an alkaloid isolated from roots of *amyris texana* and possessing mitoinhibitory properties [48], was obtained in 71 % yield under Ni-MOF-74 catalysis via direct arylation of 5-(1,3-benzodioxol-5-yl)oxazole. Balsoxin, an antimycobacterial agent which was reported to be constructed by 7 steps, was achieved in 26 % yield [49]. Similarly, optimized conditions were successfully utilized to synthesize bioactive unguenenazole in good yield [50]. The reaction conditions are not limited to oxazole derivatives. Bioactive arylated benzothiazoles such as 4-(benzothiazol-2-yl)phenol and 2-(thiophen-2-yl)benzothiazole were obtained in acceptable yields under optimized conditions. These compounds were showed to serve as multifunctional vasodilators on rat artery and possess antidiabetic potential [51, 52]. In addition, 2-styryl-1-methylbenzimidazole, an inhibitor of monoamine oxidase B (MAO-B) [53], was also obtained by arylation of 1-methylbenzimidazole using 1-iodo-2-phenylethene. It is noted that these compounds were not previously synthesized using heterogeneous catalysts. One can argue that increasing efficiency in such reactions makes the chemical processes more "green" by recycling the catalysts and reducing the amount of steps in the purification.



Scheme 2. Synthesis of bioactive compounds using the heterogeneous Ni-MOF-74 catalyst.

4. Conclusions

In brief, we have described a practical method for salt-promoted arylation of wide range of heterocycles under heterogeneous Ni-MOF-74 catalysis. The optimal reaction conditions involve the use of KCl or Li_2CO_3 salts in diglyme solvent at 160 °C in 18 hours. For the first time, KCl salts was used as efficient promoter for arylation of acidic heterocycles. The method is advantageous compared to the existing routes by avoiding the utilization of strong bases and soluble ligands, which has not been previously described under heterogeneous catalytic systems. Subsequently, the substrate scope of Ni-MOF-74 was demonstrated to be widely applicable to various substituted aryl halides and heterocycles. The first synthesis of bioactive azole compounds under heteterogeneous catalyst was also described. Interestingly, Ni-MOF-74 exhibited higher catalytic activity than other Ni-based heterogeneous catalysts and homogeneous nickel salts. In addition, Ni-MOF-74 were showed to be recovered and reused several times without a significant degradation in catalytic activity and contribution from homogeneous leached active copper species, if any, is negligible.

Acknowledgements

Vietnam National University – Ho Chi Minh City (VNU-HCM) is acknowledged for financial support via grant No. B2015-20-04. Huong T. T. Nguyen is grateful to HCMC University of Technology, VNU-HCM via grant No. TSĐH-2015-KTHH-05

References

1. C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* 2009, **131**, 10844-10845.
2. H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc*. 2008, **130**, 1128-1129.
3. C.-J. Li, *Acc. Chem. Res*. 2009, **42**, 335-344.
4. Z. Li, C.-J. Li, *J. Am. Chem. Soc*. 2005, **127**, 3672-3673.
5. G.S. Kumar, C.U. Maheswari, R.A. Kumar, M.L. Kantam, K.R. Reddy, *Angew. Chem. Int. Ed. 2011*, **50**, 11748-11751.
6. S. Chuprakov, N. Chernyak, A.S. Dudnik, V. Gevorgyan, *Org. Lett.* 2007, **9**, 2333-2336.
7. L.-C. Campeau, D.J. Schipper, K. Fagnou, *J. Am. Chem. Soc*. 2008, **130**, 3266-3267.
8. S.I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc*. 2008, **130**, 10848-10849.
9. R.B. Bedford, S.J. Coles, M.B. Hursthouse, M.E. Limmert, *Angew. Chem. Int. Ed*. 2003, **42**, 112-114.
10. S. Proch, R. Kempe, *Angew. Chem. Int. Ed.* 2007, **46**, 3135-3138.
11. I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P.H. Dixneuf, *J. Am. Chem. Soc*. 2008, **130**, 1156-1157.
12. L. Ackermann, M. Mulzer, *Org. Lett.* 2008, **10**, 5043-5045.
13. K.-i. Fujita, M. Nonogawa, R. Yamaguchi, *Chem. Commun*. 2004, **7**, 1926-1927.
14. O. Daugulis, V. G. Zaitsev, D. Shabashov; Q.-N. Pham, A. Lazareva Synlett, 2006, 15, 3382
15. (a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc*. 2007, **129**, 12404-12405. (b) H.-Q. Do, R.M.K. Khan, O. Daugulis, *J. Am. Chem. Soc*. 2008, **130**, 15185-15192.
16. (a) J. Yamaguchi, K. Muto,K. Itami, *Eur. J. Org. Chem*. 2013, 19–30. (b) S. A. Johnson, *Dalton Trans.*, 2015, **44**, 10905
17. H. Hachiya, K. Hirano, T. Satoh, M. Miura, *ChemCatChem*. 2010, **2**, 1403-1406.
18. J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett*., 2009, **11**, 8.
19. D. Liu, C. Liu, H. Li, A. Lei, *Angew. Chem. Int. Ed*. 2013, **52**, 4453-4456.
20. R. Cano, A. F. Schmidt, G. P. McGlacken, *Chem. Sci.* 2015, **6**, 5338 - 5346.
21. M.L. Kantam, S. Laha, J. Yadav, S. Jha, *Tetrahedron Lett*. 2009, **50**, 4467-4469.
22. (a) H.K. Chae, D.Y. Siberio-Perez, J. Kim, Y. Go, M. Eddaoudi, A.J. Matzger, M. O'Keeffe, O.M. Yaghi, *Nature* 2004, **427**, 523-527. (b) D.J. Tranchemontagne, M.O.k. Z.

Ni, O.M. Yaghi, *Angew. Chem. Int. Ed*. 2008, **47**, 5136-5147. (c) S.S. Kaye, A. Dailly, O.M. Yaghi, J.R. Long, *J. Am. Chem. Soc*. 2007, **129**, 14176-14177.

23. (a) P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J.F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.S. Chang, Y.K. Hwang, V. Marsaud, P.N. Bories, L. Cynober, S. Gil, G. Fe´rey, P. Couvreur, R. Gref, *Nature Mater*. 2010, **9**, 172-178. (b) H. Furukawa, N. Ko, Y.B. Go, N. Aratani, S.B. Choi, E. Choi, A.O. Yazaydin, R.Q. Snurr, M. O'Keeffe, J. Kim, O.M. Yaghi, *Science*, 2010, **239**, 424-428.
24. R.J. Kuppler, D.J. Timmons, Q.-R. Fang, J.-R. Li, T.A. Makal, M.D. Young, D. Yuan, D. Zhao, W. Zhuang, H.-C. Zhou, *Coord. Chem. Rev*. 2009, **253**, 3042-3066.
25. (a) A. Corma, H. García, F.X. Llabrés i Xamena, *Chem. Rev*. 2010, **110**, 4606-4655. (b) I. Luz, F.X. Llabrés i Xamena, A. Corma, *J. Catal*. 2012, **258**, 285-291.
26. (a) A. Dhakshinamoorthy, H. Garcia, *Chem. Soc. Rev*. 2012, **41**, 5262-5284. (b) T. Truong, V. T. Nguyen, H.T.X. Le, N.T.S. Phan, *RSC Adv*. 2014, **4**, 52307-52315. (c) H. T. N. Le, T. V. Tran, N. T. S. Phan, T. Truong, *Catal. Sci. Technol*. 2015, **5**, 851-859. (d) N. T. T. Tran, Q. H. Tran, T. Truong, *J. Catal*. 2014, **320**, 9-15.
27. Y.K. Park, S.B. Choi, H.J. Nam, D.-Y. Jung, H.C. Ahn, K. Choi, H. Furukawad, J. Kim, *Chem. Commun*. 2010, **46**, 3086-3088.
28. H. Zhao, H. Song, L. Chou, Inorg. *Chem. Commun.* 2012, **15**, 261-265.
29. Y. Ren, Y. Shi, J. Chen, S. Yang, C. Qi, H. Jiang, *RSC Adv*. 2013, **3**, 2167-2170.
30. T. Truong, C. K. Nguyen, T. V. Tran, T. T. Nguyen, N.T.S. Phan, *Cat. Sci. Technol*., 2014, **4**, 1276.
31. H. Deng, S. Grunder, K. E. Cordova, C. Valente, H. Furukawa, M. Hmadeh, F. Gándara, A. C. Whalley, Z. Liu, S. Asahina, H. Kazumori, M. O'Keeffe, O. Terasaki, J. F. Stoddart, O. M. Yaghi, *Science* 2012, **336**, 1018-1023.
32. (a) G. R. Calleja, R. Sanz, G. Orcajo, D. Briones, P. Leo, F. Martínez, *Catalysis Today* 2014, **227**, 130–137. (b) *J. Catal*. 2016, 337, 167.
33. (a) D. Ruano, M. D. Garcia, A. Alfayate, M. S. -Sanchez, *ChemCatChem*, 2015, **7**, 674-681. (b) T. Truong, G. H. Dang, N. V. Tran, N. T. Truong, D. T. Le, N. T. S. Phan*J. Mol. Cat. A: Chem*. 2015, 409, 110-116.
34. N. L. Rosi , J. Kim ,M. Eddaoudi , B. Chen , M. O'Keeffe, O. M. Yaghi *J. Am. Chem. Soc*, 2005. **127**, 1504-1518.
35. P. D. C. Dietzel, B. Panella, M. Hirscher, R. Bloma, H. Fjellvåg, *Chem. Commun*., 2006, **9**, 959-961.
36. H. Iddir, L. A. Curtiss, *J. Phys. Chem. C*, 2010, **114** (48), 20903–20906
37. W. Zhang, Q. Zeng, X. Zhang, Y.Tian, Y. Yue, Y. Guo, Z. Wang *J. Org. Chem.* 2011, **76**, 4741–4745.
38. Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed*. 2007, **46**, 5583
39. (a) J. M. Crawford, K. E. Shelton, E. K. Reeves, B. K. Sadarananda, D. Kalyani, Org. Chem. Front., 2015, 2, 726-729; (b) L.W. Sardzinski, W. C. Wertjes, A. M. Schnaith, D. Kalyani, Org. Lett., 2015, **17** (5), 1256.
40. K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, Tetrahedron 63 (2007) 1568–1576
41. I. R. Katritzky, R. J. K. Taylor (2005), Comprehensive Organic Functional Group Transformations II, Elsevier, ISBN: 978-0-08-044655-4,
42. J. W. Steed; J. L. Atwood (2009). Supramolecular Chemistry, 2nd edition. Wiley. ISBN 978-0-470-51233-3.
43. H.-C. Zhou and S. Kitagawa, *Chem. Soc. Rev*., 2014,**43**, 5867-5895

44. (a) H. Wang, M. Frenklach, *Combust. Flame*, 1994, **96**, 163-170. (b) J. Jae, G.A. Tompsett, A.J. Foster, K.D. Hammond, S.M. Auerbach, R.F. Lobo, G.W. Huber, *J. Catal.*, 2011, **279**, 257-268.
45. Y. Kubota, M. Takata, R. Matsuda, R. Kitaura, S. Kitagawa, T.C. Kobayashi, *Angew. Chem. Int. Ed.*, 2006, **45**, 4932-4936.
46. H. T.N. Le, T. T. Nguyen, P. H. L. Vu, T. Truong, N. T.S. Phan*J. Mol. Catal. A: Chem.*, 2014, **391**, 74-82.
47. C. E. Garrett, K. Prasad, *Adv. Synth. Catal*., 2004, **346,** 889-900
48. X. A. Domínguez, G. D. Fuente, A. G. González, M. Reina, I. Timón, Heterocycles, 1988, **27**, 35-38.
49. K. J. Hodgetts, M. T. Kershaw, *Org. Lett*., 2002, **4**, 2905
50. F. Besselièvre, S. Lebrequier, F. Mahuteau-Betzer, S. Piguel, *Synthesis* 2009, 3511.
51. F. Fusi, M. Durante, G. Sgaragli, N. M. Cuong, P. T. P. Dung, N. H. Nguyen, Eur. J. Pharmacology. 2013, 714, 178–187.
52. N. V. Puranik, H. M. Puntambekar, P. Srivastava, Med. Chem. Res 2016, 25, 805–816.
53. (a) D. Berg, K. R. Zoellner, M. O. Ogunrombi, S. F. Malan, G. Terre’Blanche, N. Castagnoli Jr., J. J. Bergh, Jacobus P. Petzer, Bioorg. Med. Chem. 2007, 15, 3692-3702. (b) B. Song, T. Xiao, X. Qi, L.-N Li, K. Qin, S. Nian, G.-X Hu, Y. Yu, G. Liang , F. Ye Bioorg. Med. Chem. Lett. 2012, 22, 1739-1742.