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N—H Insertion Reactions Catalyzed by a Dirhodium Metal-Organic Cage: A Facile and Recyclable Approach for C—N Bond Formation

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A heterogeneous metal-organic cage based on Rh-Rh bonds [$Rh_4(pbeddb)_4(H_2O)_2(DMAC)_2$] (MOC-18; $pbeddb^{2-}$=3,3'-(1,3-phenylenebis(ethyne-2,1-diyl))dibenzoate) was applied to the N—H insertion reactions with diazo compounds. This method offered an environmentally friendly and highly efficient approach for C—N bond formation.

Keywords porous frameworks, metal-organic cage, heterogeneous catalysis, C—N bond formation, N—H insertion

Introduction

Porous frameworks based on metal-ligand bonds, including metal-organic frameworks (MOFs), metal-organic gels (MOGs), metal-organic cages (MOCs), *etc*., have emerged as a new kind of heterogeneous catalysts, which have displayed a large spectrum of advantages.[1,2] The porous structure endows the catalysts with accessible active sites, considering that both of the external and internal surfaces can be exposed to the coming substances and then the catalytic reactions can be carried out in the cavities as well as the exteriors.

Dirhodium(II) complexes are important homogeneous catalysts, and can promote various reactions, especially the carbene and nitrene transfer reactions.[3-5] As one of the noble metals, recyclability and reuse of Rh-based catalysts become one of the most important and urgent issues, although the rhodium price has dropped 50% in the last 5 years.[6] Incorporations of dirhodium units into porous frameworks have recently been reported by Mori,[7] Kaskel,[8] and us.[9] After the immobilization of dirhodium catalysts into the frameworks, they can be reused for up to ten runs without the loss of the efficiency.

To develop environmentally friendly and highly efficient catalytic methods of C—N bond formation, a lot of efforts have been paid.[10] Among them, dirhodium-catalyzed nitrene transfer reactions or carbene insertion into N—H bonds (*e.g.* in amines, amides, and carbamates) have appealed as the highly efficient methods.[11]

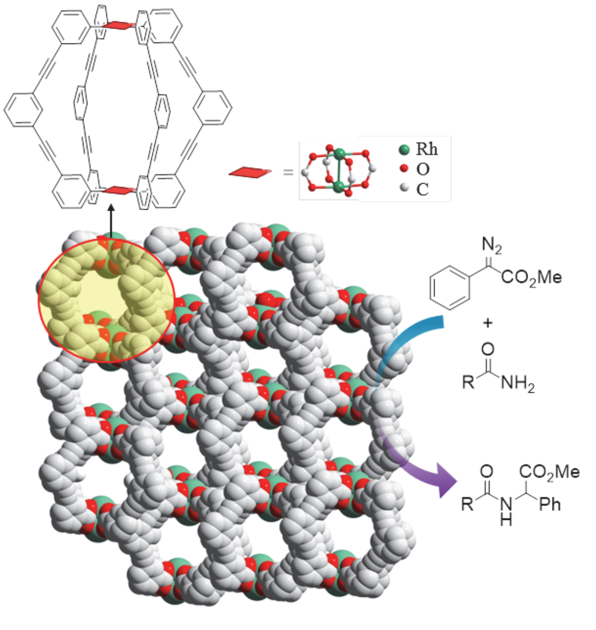

Figure 1 MOC-18-catalyzed N—H insertion reactions.

We have recently reported a metal-organic cage (MOC-18) containing Rh-Rh bonds with the formula of $Rh_4(pbeddb)_4$ ($pbeddb^{2-}$=3,3'-(1,3-phenylenebis(ethyne-2,1-diyl))dibenzoate).[9a] The dimensions of the inner cavity are 9.5 Å×14.8 Å. In the solid phase, the

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In Memory of Professor Enze Min.

cages are aligned by π-π stacking to form one-dimensional channels (9.5 Å×11.1 Å) through cage windows. Such structure feature will help MOC-18 to promote both the in-cage and out-cage reactions with high efficiency. As expected, MOC-18 has been proved to be an excellent heterogeneous catalyst for nitrene transfer reactions of intramolecular C—H amination in our previous work. Herein, we demonstrate that MOC-18 is a highly efficient heterogeneous catalyst for carbene insertion into N—H bonds (Figure 1).

Experimental

General

All the reagents in the present work were obtained from the commercial source and used directly without further purification. HRESI-MS was performed by using a Bruker Daltonics ESI-Q-TOF maXis4G. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 or a Bruker AVANCE III 300. Chemical shifts were quoted in parts per million referenced to the appropriate solvent peak or δ 0 for TMS. Specific rotations were measured on ADP440+B+S. ICP spectroscopy was conducted on a SpectroCiros Vision ICP-OES spectrometer. PXRD patterns were recorded on SmartLab X-ray powder diffractometer (Rigaku Co.) at 40 kV and 30 mA with a Cu target tube.

Cautions

Although we have not experienced any problem in the handling of the diazo compounds, extreme care should be taken when manipulating them due to their explosive nature.

Synthesis of MOC-18

MOC-18 was synthesized by the following procedure:[9a] $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol), H_2pbeddb (9.2 mg, 0.025 mmol), Na_2CO_3 (3 mg, 0.028 mmol) and dimethylacetamide (DMAC, 2 mL) were added into a 10 mL vial with a cap. After the whole mixture was dissolved by ultrasound, the vial was kept at 100 ℃ in an oven for about 48 h to produce the crystals. The bulk purity of as-synthesized crystals was confirmed by the PXRD patterns similar to the simulated ones. Before each catalytic reaction, the as-synthesized sample of MOC-18 has been activated by heating at 110 ℃ under vacuum for 6 h.

Typical procedure for catalytic N—H insertion

4-Fluorobenzamide (83 mg, 0.6 mmol, 1.0 equiv.), MOC-18 (3 mg, 0.0015 mmol, 0.25 mol%) and dichoromethane (DCM, 2 mL) were added into a 10 mL vial, and then methyl 2-diazo-2-phenylacetate (158 mg, 0.9 mmol, 1.5 equiv., dissolved in 1 mL DCM) was added dropwise with stirring at room temperature within 30 min. The resulting solution was stirred for another 30 min. The isolated yield of methyl 2-(4-fluorobenzamido)-2-phenylacetate (**2a**) was 92%.

Recycling experiments and ICP analysis for the leached rhodium

4-Fluorobenzamide (292 mg, 2.1 mmol) and MOC-18 (10.5 mg, 0.00525 mmol, 0.25 mol%) were dissolved in DCM (6 mL), and then a DCM (4 mL) solution containing methyl 2-diazo-2-phenylacetate (MPDA, 554 mg, 3.15 mmol) was dropped slowly to the reaction mixture within 30 min at room temperature. After the reaction was completed, the resulting solution was centrifuged to recycle the catalyst. The obtained catalyst was washed with DCM (2 mL×5) and heated at 110 ℃ in vacuum for 6 h, which was then reused in the next runs. The recycling experiments were conducted for 9 runs.

After the removal of the catalyst in the first run, the reaction solution was collected and concentrated to dryness via vacuum. The residue was digested by nitric acid and concentrated hydrochloric acid in a 10 mL ceramic crucible until a clear and colorless solution was obtained. The obtained solution was concentrated to about 3 mL, which was then diluted to 25 mL with aqueous solution of nitric acid (2%). After then, 15 mL of the solution was taken out and then further diluted to 125 mL with aqueous solution of nitric acid (2%). The final solution was analyzed by an inductively coupled plasma-optical emission spectrometer. The measured Rh content was 0.032 ppm (0.00667 mg) and the leached rhodium was 0.62% (0.00667 mg/1.08045 mg 100%). The Rh contents were measured in ppm based on calibration curves obtained with a series of calibration standard solutions doped with different amounts of Rh.

Results and Discussion

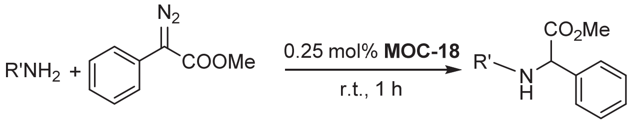
Methyl phenyldiazoacetate (MPDA) is a commonly used carbene precursor and can be readily prepared by methyl phenylacetate.[12] Considering that diazo compounds are easily decomposed and dimerized in the presence of dirhodium complexes, the reactions were conducted at room temperature with slow drop of MPDA. In the typical procedure, 0.25 mol% MOC-18 was loaded and DCM was used as solvent. Different N—H containing compounds have been screened for N—H insertion reaction, and it has been found that 4-fluorobenzamide reacts with MPDA efficiently in the NMR yield of 95% (Table 1, Entry 1). Decreasing the amount of the catalyst to 0.125 mol% or 0.0625 mol%, the NMR yield is still as high as 95% (Entries 2 and 3).

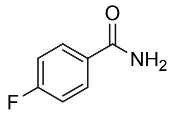
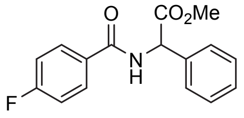
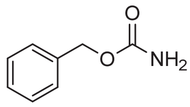
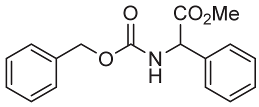
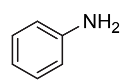
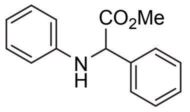
To compare the reactivity with other dirhodium complexes, $Rh_2(OAc)_4$ was used instead of MOC-18 in the reaction of MPDA and 4-fluorobenzamide under the similar reaction condition. When 0.25 mol% $Rh_2(OAc)_4$ was used, the reaction was accomplished in 95% yield (Entry 4), but however, only 25% yield was obtained if the catalyst amount was reduced to 0.125 mol% (Entry 5). Through the comparison, MOC-18 shows much better performances than $Rh_2(OAc)_4$ (Entry 3 vs. 5). MOC-18 displays a lantern-type structure, and a pair of paddlewheel units are bridged, which endows MOC-18 with higher stability than non-bridged catalyst $Rh_2(OAc)_4$ and less ligand exchange possibility.[13]

In the presence of MOC-18, benzyl carbamate can also react with MPDA efficiently in the NMR yield of 95% (Entry 7), but however, aniline did not work at all (Entry 8). When MOC-18 was added to the reaction solution with aniline, the catalyst turned from green to yellow while no nitrogen bubble was released during the addition of MPDA. In comparison, $Rh_2(OAc)_4$ can largely promote the reaction of MPDA and aniline, and the N—H insertion product can be achieved in 95% (Entry 9). Due to the conjugation of amide group (—CONH—), the amide and carbamate groups have weaker coordination effect, and the N—H insertion products are easier to dissociate from the dirhodium catalysts, whereas the amino group is relatively more tightly bound to the dirhodium paddlewheel units of the catalysts.[13,14] The difference of the coordination effect has been further enlarged by the confinement effect of MOC-18, which might explain the inactivity of aniline. It is noted that in the presence of aniline, MOC-18 can not promote the N—H insertion reaction of 4-fluorobenzamide (Entry 6).

To evaluate the catalytic capability of MOC-18, different substituted amides are applied to this reaction in the following research (Table 2). For both electron-deficient and electron-rich *para*-substituted aromatic amides, good yields are obtained (85%—93%, **2a**

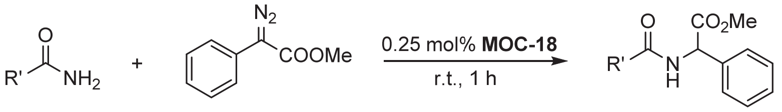
Table 1 Catalytic N—H insertion reaction with different N—H bonds

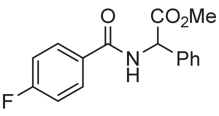
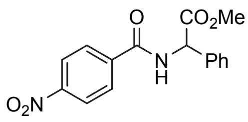
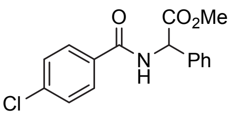
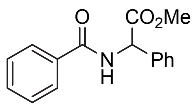
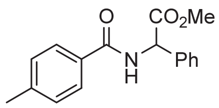
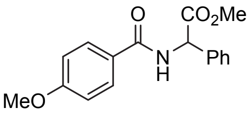
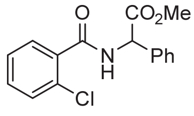
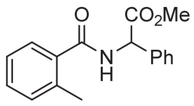
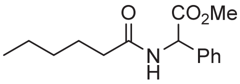
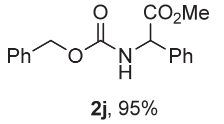
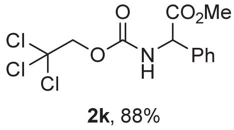
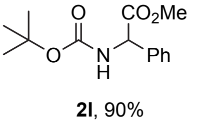


Entry	Substrate	Product	Yield[a]/%
1			95
2			95[b]
3			95[c]
4			95[d]
5			25[e]
6			<5[f]
7			95
8			<5
9			95[d]

[a] The molar ratio of amide and MPDA is 1∶1.5. The NMR yield was determined by the conversion of amine/amide/carbamate to the N—H insertion product. [b] 0.125 mol%. [c] 0.0625 mol%. [d] $Rh_2(OAc)_4$, 0.25 mol%. [e] $Rh_2(OAc)_4$, 0.125 mol%. [f] In the presence of 1 equiv. of aniline.

Table 2 Substrate scope of catalytic N—H insertion reaction[a]



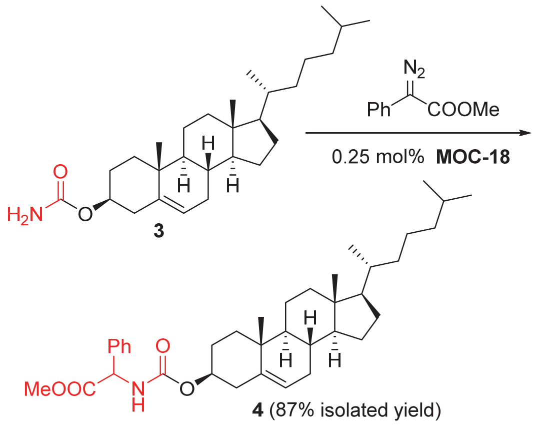
 **2a**, 91%	 **2b**, 86%	 **2c**, 85%
 **2d**, 90%	 **2e**, 92%	 **2f**, 93%
 **2g**, 94%	 **2h**, 89%	 **2i**, 95%
 **2j**, 95%	 **2k**, 88%	 **2l**, 90%

[a] Isolated yield.

—**2f**). *ortho*-Substituents seemed to have no obvious difference in yield (**2g** and **2h**). Non-aromatic amide substrates also resulted in an excellent yield (**2i**, 95%). Carbamates are also good substances for this catalytic reaction, and the N—H insertion products were generated in up to 95% yield (**2j**—**2l**).

MOC-18 has been further employed in the modification of cholesterol derivative (**3**) tailoring with a carbamate group. In the presence of 0.25 mol% of MOC-18, the N—H insertion reaction was accomplished in 95% conversion (Scheme 1). Dirhodium complexes are usually used for the cyclopropanation reaction. It is noted that no cyclopropane product has been detected in the MOC-18-catalyzed reaction, although one C—C double bond is present in **3**,[3] which highlights its high chemoselectivity towards N—H insertion.

Scheme 1 Modification of cholesterol derivative



MOC-18 has been further proved to be an efficient heterogeneous catalyst for N—H insertion reactions of amides and diazoacetates. After the reaction of MPDA and 4-fluorobenzamide was completed, MOC-18 could be easily separated by centrifugation. The isolated MOC-18 can be reused in the next reaction after activation by heating at 110 ℃ under vacuum for 6 h. The results of the recycling experiments showed that the yields were obtained in the range of 83%—98% in the eight runs, whereas it was reduced to 62% in the ninth run, which might be due to the stacked products in the cavities of the MOC-18 (Figure 2). The total turnover number (TON) was calculated to be 3180. The ICP analysis showed that only 0.62% rhodium was leached in the reaction, suggesting that the catalytic reaction was indeed catalyzed by the solid MOC-18 catalyst.

Conclusions

A remarkable heterogeneous metal-organic cage catalyst MOC-18 has been explored in the N—H insertion reactions with diazo compounds, which is highly efficient for a range of amides and carbamates, including bioactive compounds. Besides, MOC-18 is recyclable and can be reused for at least nine runs. In general, MOC-18 is an excellent and environmentally friendly heterogeneous dirhodium catalyst.

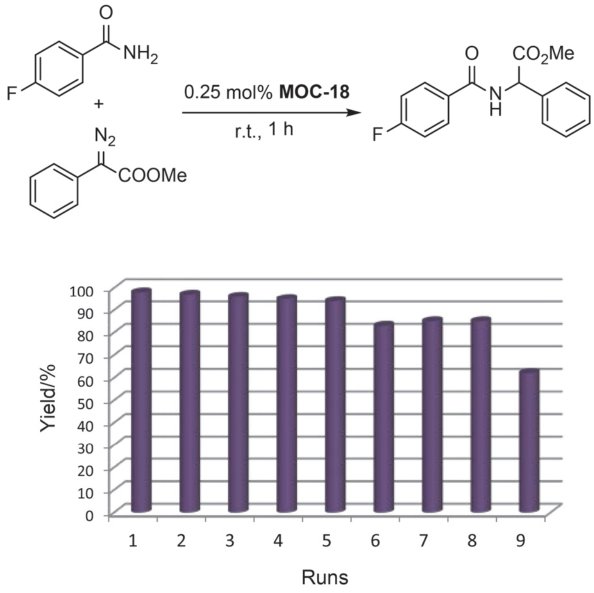


Figure 2 Recycling experiments.

Acknowledgement

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