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Authors: Yangxin Jin, Yali Cao, Guoyong Fang, Fei Ruan, and Qingping Ke

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Micropores Induced Stereoselective Synthesis of E-imines: Synergistic Effect between Cerium Species and Micropores in CeAlPO-5 Molecular Sieve

Yangxin Jin,[a] Yali Cao,[a] Guoyong Fang,[b] Fei Ruan[a] and Qingping Ke*[a]

Dedication ((optional))

Abstract: Metal-doped zeolitic microporous materials are often viewed as something extremely negative as catalysis for the reactions involving aromatic molecules because of severe diffusion limitation. For these reasons, many chemists aim to development of the large microporous or hierarchical micro-mesoporous zeolites as supports that allow for the access of the “bulky” reactants. But the “small” micropore with respect to an aromatic molecules-involving reaction is not always a negative point. Here we employed a hierarchical micro-mesoporous CeAlPO-5 molecular sieve (HP-CeAlPO-5) as the catalyst that can catalyze stereoselective synthesis of E-imines through the reaction of alcohols with amines. Control reactions, DFT calculations and GC-MS analyses demonstrated that the feature of the uniform “small” micropore in the HP-CeAlPO-5 catalyst play a key role in the stereoselective synthesis of E-imines. In addition, the reaction tolerates a broad range of alcohols and amines, and can be performed with as little as 0.89 mole percent catalyst in more than 90.6 percent yield and about 99.7:0.3 stereoselective ratio. This zeolitic catalyst provides a conceptually new and practical protocol to stereoselective synthesis of E-imine compounds.

In the past 50 years, transition metals-catalyzed cross-coupling reactions have emerged as highly efficient methods for selective synthesizing structurally diverse organic compounds. Among them, imines possess fundamentally important functional groups of carbon-nitrogen double bonds in organic chemistry[1]. Imines synthesis by oxidation coupling of amines and alcohols[2] has attracted considerable attention. To date, many metal species, including palladium[3], iron[4], copper[5] and others[6], have been employed as homogeneous catalysts to catalyze the oxidation coupling. In contrast, imines syntheses catalyzed by heterogeneous catalysts that can meet the requirements of industrial technology are rarely reported[2d, 7]. Furthermore, a synthetically useful cross-coupling process must address the additional complexity that results from the need to simultaneously control stereoselectivity in the carbon-nitrogen bond forming event. Therefore, the development of a heterogeneous catalyst to accomplish the cross-coupling of alcohols and amines in a stereoselective manner would represent a significant advance and provide a fundamentally new strategy for the synthesis of the stereo-defined imines.

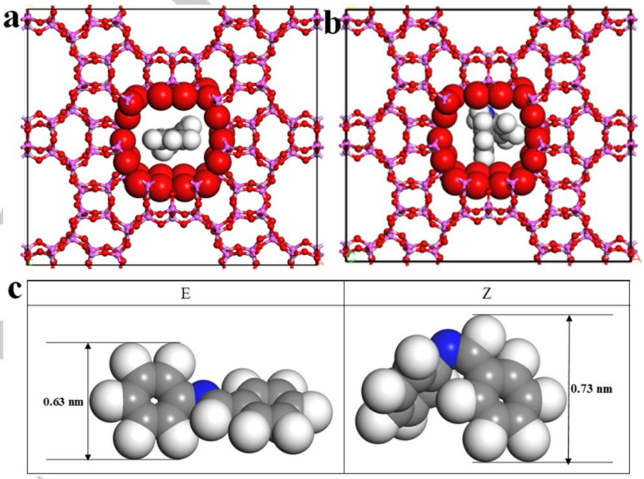

Figure 1. DFT calculation of N-benzylideneaniline confined in AlPO-5 micropores. (a) (E)-N-benzylideneaniline confined in micropores; (b) (Z)-N-benzylideneaniline confined in micropores; (c) the diameter of benzylideneaniline molecule. Red refers to Al/P atom, gray refers to C atom, white refers to H atom and blue refers to N atom, respectively.

Zeolitic based materials have recently attracted great attentions for their shape-selectivity to product in the confined micropores[8]. However, there are only a few examples reported the product stereoselectivity over zeolitic catalysts[9]. Notably, AlPO-5 molecular sieve, containing one dimensional hexagonally-arrayed and straight channel with associated 0.73 nm pore opening, could employ as a catalyst support for stereoselectivity synthesis of the imine by cross-coupling reactions of alcohols and amines. As shown in **Figure 1**, the diameter of (Z)-N-benzylideneaniline (Z-NBA) is ~0.73 nm (**Figure 1b**), which could not stably exist in the micropores; however, (E)-N-benzylideneaniline (E-NBA) with a diameter of ~0.63 nm could produce in the micropores (**Figure 1a**).

Herein, we report a method for stereo-selective synthesis of E-imines that is based on structurally controlling the product on cerium species doped hierarchical porous AlPO-5 molecular sieve (HP-CeAlPO-5), whereby the advantages of cerium active sites (large formal oxidation potential, $E°(Ce^{IV/III})=1.3$ V versus Fc[10]), abundant micropores (0.73 nm micropores for stereoselective synthesis of E-imines) and mesopores (fast mass diffusion) are synergistically combined. The mechanism of

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[a] Y. Jin, Y. Cao, F. Ruan, Dr. Q. Ke
College of Chemistry and Chemical Engineering
Anhui University of Technology
Maanshan, Anhui 243002, P. R. China
E-mail: Qingke@ahut.edu.cn; kqp1982@163.com
[b] G. Fang
College of Chemistry and Materials Engineering
Wenzhou University
Wenzhou, Zhejiang 325035, P. R. China

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Formation of the E-imine occurred in the micropores of HP-CeAlPO-5 catalyst were fully studied.

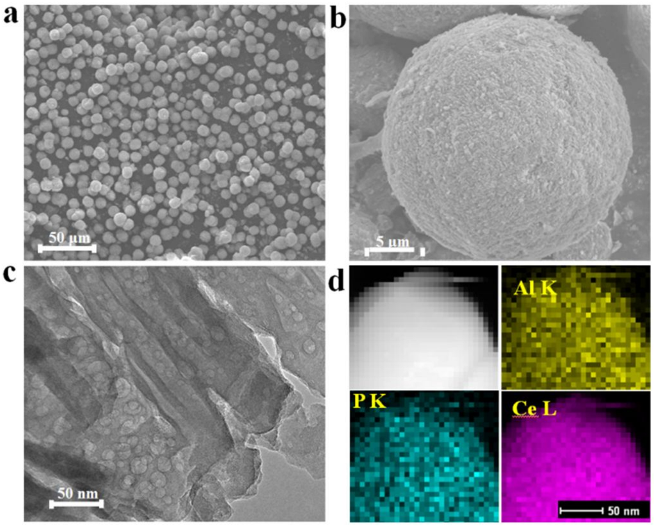
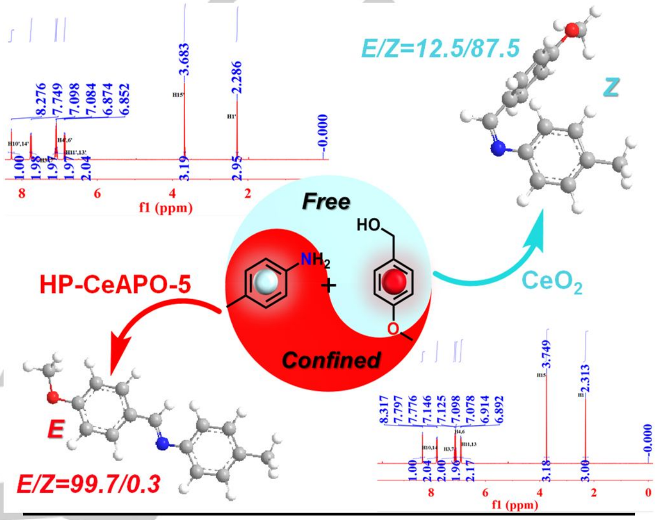


Figure 2. HP-CeAlPO-5 catalyst characterization. (a-b) SEM images, (c) TEM image, (d) EDS mapping images: yellow-Al-K, sky blue-P-K and pink-Ce-K.

The final composition of the synthesized HP-CeAlPO-5 is $Ce_{0.03}Al_{0.96}PO_{3.95}$, determined by ICP and XPS (data not shown). X-ray diffraction (XRD) pattern of the HP-CeAlPO-5 catalyst in **Figure S1** contains strong diffraction peaks related to the AFI structure, indicating that a sample with a high degree of both crystallinity and purity was prepared. Scanning electron microscopy (SEM) image at low resolution shows that the HP-CeAlPO-5 is composed of uniform sphere particles (**Figure 2a**). The diameters of these sphere particles are in the range of 12-20 μm. SEM image at high resolution indicated that the sphere particles are assembled by nanoscale grain structures (**Figure 2b**). Both of these abundant intracrystalline and intercrystalline mesopores were observed at transmission electron microscopy (TEM) thin-section image (**Figure 2c**). Nitrogen sorption isotherm of the HP-CeAlPO-5 catalyst is a typical type IV curve (**Figure S2**), in which a step can be identified over the range of 0.45<P/P0<0.95. This step testified the presence of mesopores in the sample. The Brunauer—Emmett—Teller surface area, microporous volume, mesoporous volume of the sample were determined to be 324 $m^2 \cdot g^{-1}$, 0.11 $cm^3 \cdot g^{-1}$ and 0.20 $cm^3 \cdot g^{-1}$, respectively. It can be seen from the energy dispersive X-ray spectroscopy mapping image (**Figure 2d**) that cerium species are highly dispersed in the HP-CeAlPO-5 catalyst.

Scheme 1 presents catalytic data in the cross-coupling reaction of 4-methoxylbenzyl alcohol and 4-methylaniline over various catalysts. To our surprising, using air as single oxidant, only 1.0 mol% cerium species in HP-CeAlPO-5 catalyst already afforded the E-N-(4-methoxybenzylidene)-4-methylaniline (E-NMBMA) isomer in 90.6% yield and 99.7% product stereoselectivity (TOF=53.5 h^{-1}, **Scheme 1**, **entry 1**), exhibits superior stereoselectivity and excellent catalytic activity. The superior stereoselectivity for E-NMBMA was also observed over T-CeAlPO-5 catalyst (**Table S1**, **entry 9**). Noteworthy is that, for CeO_2 and $Ce(NO_3)_3 \cdot 6H_2O$, major product of Z-NMBMA was obtained (**Scheme 1**, **entries 2** and **3**). The Z/E-NMBMA structure was confirmed by ^{1}H-NMR spectra (**Scheme 1**), ^{13}C-NMR spectroscopy (**Figure S3**) and H-H noesy (**Figure S4** and **S5**). The significant differences in stereoselectivity of E/Z-NMBMA over AlPO-5 molecular sieve based catalysts and CeO_2 catalyst should be due to their different materials structure and will be discussed in further paragraphs.



Entry	Catalyst	Time (h)	Yield (%)[a]	E/Z (%)	TOF (h^{-1})
1	HP-CeAlPO-5	2	95.4(90.0)	99.7:0.3	53.5
2	$Ce(NO_3)_3 \cdot 6H_2O$	2	86.5(84.0)	2.6:97.4	32.3
3	CeO_2 (2.3 mg)	4	88.6(87.0)	12.5:87.5	16.5

Scheme 1. Synthesis of (E)/(Z)-N-(4-methoxybenzylidene)-4-methylaniline from 4-methoxy benzyl alcohol and 4-methylaniline over various catalysts.

In addition to the superior stereoselectivity, the competitiveness catalytic activity of HP-CeAlPO-5 relative with the reported catalysts is also surprised. As shown in **Table S1**, HP-CeAlPO-5 is the most efficient catalyst for this coupling reaction (TOF=53.5 h^{-1}, **Table S1**, **entry 1**) among HP-CeAlPO-5, $Ce(NO_3)_3 \cdot 6H_2O$, CeO_2[6a], $Fe(NO_3)_3$[4], $Cu(ClO_4)_2$[5], $Pd(OAc)_2$[3b] and K-OMS-2[2d] catalysts (**Table S1**, **entries 1-8**).

To probe the reaction mechanism, further study about the effect of reaction time on the E-NBA synthesis over HP-CeAlPO-5 in the range 15-120 min was conducted (**Figure S6**). The reaction proceeds smoothly afford the desired product in 90.6% conversion and 99.7% selectivity in 2 h, and the initial TOF (15 min, Conversion: 15.4%) was 67 h^{-1}. E-N-benzylaniline was observed at the initial stage and the amount slowly decreased with time according to the GC-MS analysis, indicating that N-benzylaniline is an intermediate for this oxidative coupling when using HP-CeAlPO-5 as catalyst. Benzaldehyde, an intermediate

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was observed over mostly catalysts in the reported literatures[7], was not found in this study.

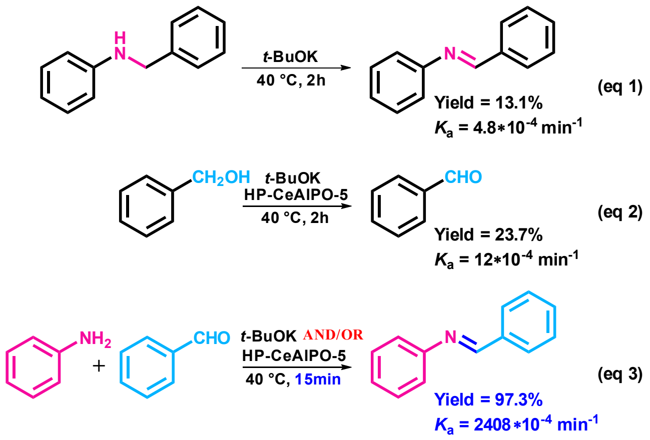
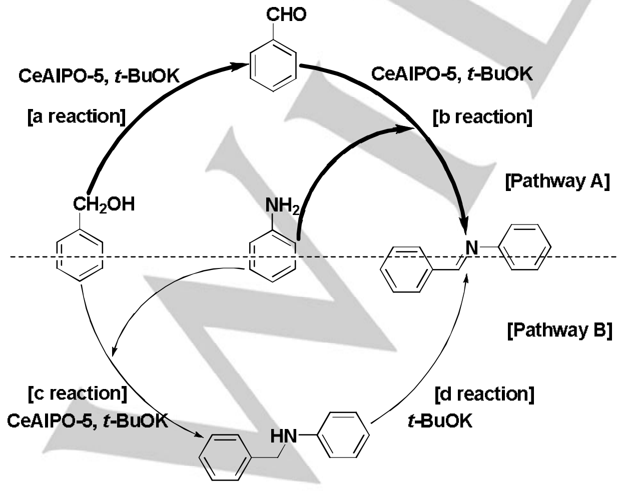


Figure 3. Control experiments.

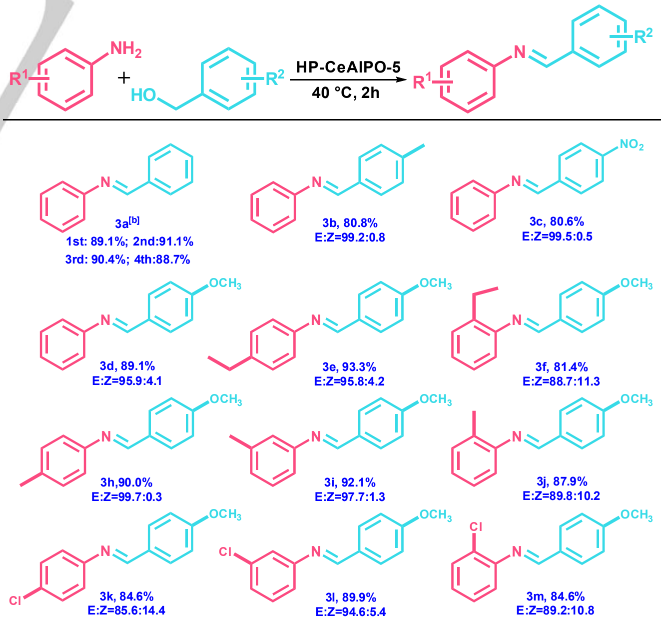
For clarifying the reaction mechanism, several control experiments were conducted (**Table S2**). Firstly, oxidation of N-benzylaniline to N-benzylideneaniline (**Figure 3**, **eq 1**) indicates that the oxidation reaction is a slow reaction, which should not the main pathway since E-NBA formation is a fast process. Secondly, the oxidation of benzyl alcohol to benzaldehyde (**Figure 3**, **eq 2**) was carried out (**Table S2**). The apparent rate constant of 12×10^{-4} min^{-1} for the oxidation reaction over HP-CeAlPO-5 was observed (**Figure 3**, **eq 2**), which is 2.5-fold higher than that of oxidation of N-benzylaniline (**Figure 3**, **eq 1**). According to the results of control experiments, it is reasonable to deduction that oxidation of benzyl alcohol to the corresponding benzaldehyde and sequent condensation of benzaldehyde with aniline to form imine is the main route. Further study shown in **Table S3** indicates that the condensation of benzaldehyde with aniline into imine product was rapidly completed (**Figure 3**, **eq 3**), which explains why the intermediate of benzaldehyde intermediate was not detected by GC-MS.



Scheme 2. Reaction pathways for (E)-N-benzylideneaniline formation.

Basis of the above analysis, a plausible reaction mechanism for E-NBA formation from benzyl alcohol and aniline though two pathways over HP-CeAlPO-5 is proposed **in Scheme 2**. For **pathway A**, **a reaction** was firstly occurred in the presence of HP-CeAlPO-5 and *t*-BuOK. Since the apparent rate of **b reaction** (2408×10^{-4} min^{-1}) is more than 200-fold higher than that of **a reaction** (12×10^{-4} min^{-1}), it is confirmed that **a reaction** is the rate-determining step for **pathway A**. Hanson and co-workers[6d] found that **a reaction** is reversible dehydrogenation reaction. Therefore, the fast apparent rate of **b reaction** is help for **a reaction** proceeds in positive direction. For **pathway B**, N-benzylaniline was firstly formed by HP-CeAlPO-5-catalyzed **c reaction**, and then converted to benzylideneaniline via dehydrogenation **d reaction** in the presence of *t*-BuOK. Although **pathway A** is proposed as the main reaction route, further investigation for accelerating the apparent rate of **d reaction** or restraining the occurrence of **c reaction** in **pathway B** is of great importance to improve the catalytic performance for HP-CeAlPO-5 and other similarly catalysts. This point is beyond the scope of the current stage of study and will be pursued in our future work. Above all, we demonstrated the first time that the HP-CeAlPO-5 molecules sieve can serve as heterogeneous zeolite catalyst for fast and stereoselectivity synthesis of trans-imines from alcohols and amines. Tamura et al[7] claimed that the oxygen species at the redox sites of CeO_2 are active species for the oxidative dehydrogenation of benzyl alcohol at low temperature (30-60 °C).

Table 1. HP-CeAlPO-5-catalyzed oxidative coupling of alcohols and amines to E-imines under air.[a]



[a] Reaction condition is provided in supporting information, isolated yields. [b] 1st, 2nd, 3rd and 4th refer to first, second, third and fourth reuse, respectively.

Finally, the tolerances for alcohols and amines and recyclability of the HP-CeAlPO-5 under optimized conditions were investigated. **Table 1** shows the scope of alcohols and amines in HP-CeAlPO-5-catalyzed E-imines synthesis. Under the optimized conditions, aniline was alkylated with various benzyl alcohol derivatives (**Table 1**, **3a-3d**). Substituted benzyl alcohols with different functional groups (halides, alkyl, nitro, trifluoromethyl) were isolated in excellent yields (80.6-89.1%, **Table 1**, **3a-3d**). In subsequent trials, various amines reacted with 4-methoxyl-benzyl alcohol were also conducted. As can be seen from **Table 1** (**3e-3m**), 81.4-95.4% isolated yields of the desired products were obtained over HP-CeAlPO-5. These data indicate that substitutes with various electronic properties did not have significant influence for the catalytic activity of HP-CeAlPO-5 catalyst. Notably, the excellent isolated yields (81.4-87.9%) of the corresponding imines by the *ortho*-substituted ones (**Table 1**, **3f, 3j, 3m**) were obtained over HP-CeAlPO-5 catalyst. This is of interest because these yields are difficult to obtain by reported homogeneous Pd[2b] and Cu[4] catalysts as well as CeO$_2$ catalyst[7].

Recycling ability of HP-CeAlPO-5 catalyst was examined by conducting the cross-coupling reaction of benzyl alcohol with aniline. Once the reaction was finished, the catalyst was filtered with a mediate-rate filter paper, washed with toluene and reused for other cycles, and the catalyst can be reused at least four times without remarkable loss of the isolated yield (88.7-91.1%, **Table 1**, **3a**). Meanwhile, the inductively coupled plasma atomic emission spectroscopy (ICP-AES) analyses showed that no cerium species was detected in the solution after hot filtering (<10 ppm). These results indicate that HP-CeAlPO-5 is an intrinsically reusable heterogeneous zeolite catalyst.

In summary, we have demonstrated that the hierarchical porous CeAlPO-5 molecule sieve exhibits excellent catalytic performance, in terms of high conversion, high stereoselectivity, high turnover of frequency numbers, excellent tolerances to alcohol and amine substrates, and therefore presents a promising alternative for industrial applications. The micropores in hierarchical porous CeAlPO-5 molecule sieve were found to play a key role in the stereoselective synthesis of (E)-N-(4-methoxybenzylidene)-4-methylaniline, which provides a valuable guidance for the future development of hierarchical zeolite catalysts for the stereoselectivity synthesizes of many useful organic molecules.

Experimental Section

Catalytic activity test

A mixture of alcohol (1 mmol), toluene (2 mL), catalyst (50 mg, ~2.5wt% of Ln), *t*-BuOK (113 mg, 1.2 mmol), and amine (1.5 mmol) was added to a 10 mL round-bottomed flask. The mixture was stirred at 40 °C for 2-4 h under air atmosphere. After cooling to RT, the catalyst was separated by filtration. The filtrate was diluted with diethyl ether (~5 mL) and washed twice with water (~5 mL). Before purification of the products by silica-gel chromatography with an eluent consisting of diethyl ether and petroleum ether, the reactant conversion and product selectivity were determined by using GC (Agilent 7890) equipped with a flame ionization detector and a DB-1301 column (30 m×0.25 mm), and the product yields are based on isolated yields. The products were then characterized by ^{1}H and ^{13}C NMR spectroscopy.

Acknowledgements

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Keywords: Micropore • Stereoselective • E-imines • CeAlPO-5 • N-benzylaniline

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

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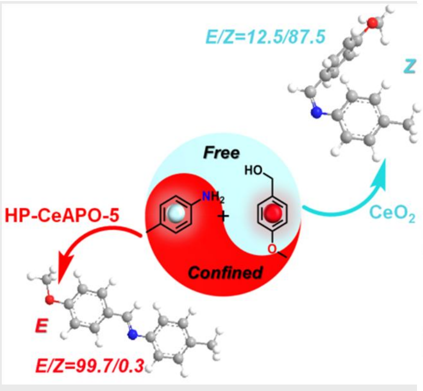

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