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Magnetic Nano-Fe_3O_4-Supported 1-Benzyl-1,4-dihydronicotinamide (BNAH): Synthesis and Application in the Catalytic Reduction of α,β-Epoxy Ketones

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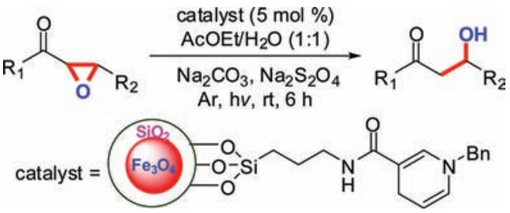
ABSTRACT



A novel magnetically recoverable organic hydride compound was successfully constructed by using silica-coated magnetic nanoparticles as a support. An as-prepared magnetic organic hydride compound, BNAH (1-benzyl-1,4-dihydronicotinamide), showed efficient activity in the catalytic reduction of α,β-epoxy ketones. After reaction, the magnetic nanoparticle-supported BNAH can be separated by simple magnetic separation which made the separation of the product easier.

In recent years, organic hydride compounds has attracted more attention due to the catalytic reduction of various substrates by hydride transfer. There are many natural organic hydride compounds, such as nicotinamide adenine dinucleotide (NADH) and its phosphate derivative (NADPH), flavin adenine dinucleotide (FADH), vitamins C and E, coenzyme F420, and so on. NADH (or NADPH) is a very famous biological catalyst which has been used widely in biological redox reactions.[1] Due to much effort from various research groups, it is already clear that NADH acts as a coenzyme in hydrogenation reactions and the active core is 1,4-dihydropyridine. Therefore, a number of NADH models with this core, such as BNAH, Hantzsch ester (HEH), and 10-methyl-9,10-dihydroacridine ($AcrH_2$) have been successfully synthesized and applied in organic synthesis.[2] They and their analogues are already known to reduce α,β-unsaturated aldehydes or ketones, activated olefins, imines, α,β-epoxy ketones, β-nitroacrylates, and tertiary amides, alone or accompanied by other catalysts.[3]

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Despite their wide employment,[3–5] their separation is very difficult due to the homogeneous reaction system. Recently, to address this problem effort has been focused mainly on loading the homogeneous catalyst on some solid supports.[6] Polymer (Merrifield resin)[7] and SiO_2[8] are popular solid supports in the immobilization of organic hydride compounds in the past few decades. However, Merrifield resin is affected largely by solvent and SiO_2 often leads to the low reactivity of organic hydride compounds. To solve these problems, Zhu et al. reported the synthesis of polysiloxane-BNAH and its application in the reduction of some activated olefins.[9] Meanwhile, magnetic separation provides a very convenient approach for removing and recycling magnetic nanoparticles (MNPs) with an external magnet. Recently, the MNPs have been served as highly promising supports of organocatalysts in some prestigious work. DMAP, a phase-transfer catalyst, and aa chiral catalyst which show high catalytic properties and recyclabilities have been developed successfully and used in organic reactions.[10] However, to the best of our knowledge, no example of an MNP-supported organic hydride compound was discovered. Herein, we reported the catalytic reduction of α,β-epoxy ketones with a magnetically recoverable MNPs-BNAH for the first time.

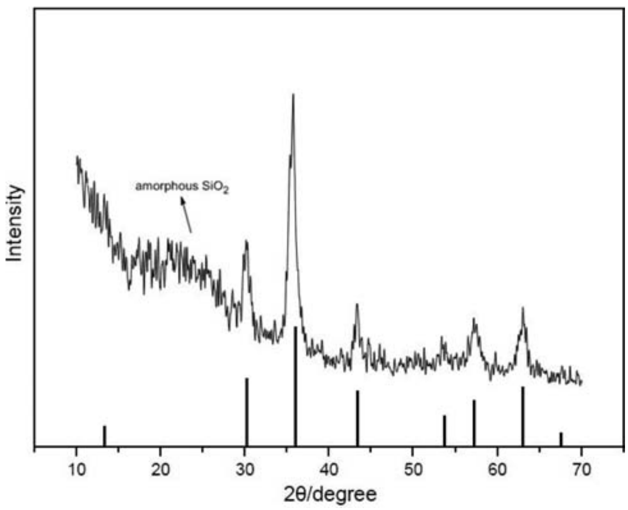

Figure 1. XRD pattern of **2**. The bottom row of tick marks indicates the reflection positions for a standard magnetite pattern (JCPDS no. 00-002-1035).

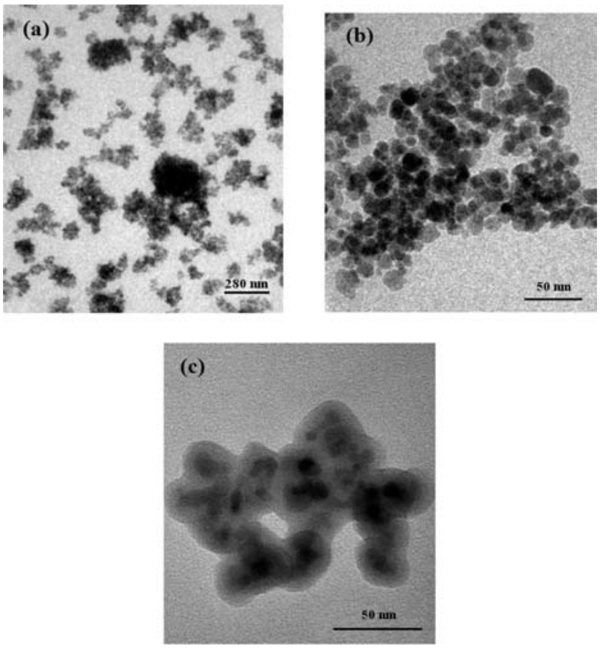

Figure 2. TEM images of MNPs-BNAH **1** aggregation (a) as well as Fe_3O_4 (b) and $Fe_3O_4@SiO_2$ (c) nanoparticles.

Magnetite nanoparticles (Fe_3O_4) and silica-coated magnetite nanoparticles ($Fe_3O_4@SiO_2$) were selected as supports, with the former prepared by coprecipitation[11] and the latter prepared according to the literature.[12] BNAH was covalently immobilized onto the surface of the MNPs by forming Fe−Si−O or Si−O−Si bond between MNPs and 3-aminopropyltriethoxysilane (APTS) (Scheme 1). The loading steps proceeded cleanly and could be monitored quantitatively by elemental analysis; the loadings of MNPs-BNAH **1** and **2** were determined to be 0.52 and 0.57 mmol/g, respectively.

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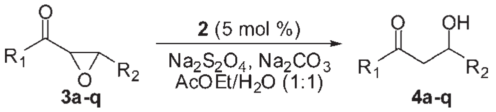
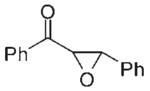
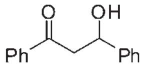
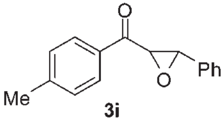
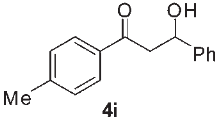
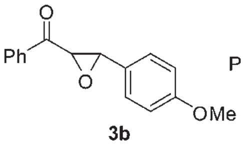
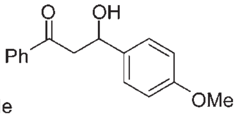
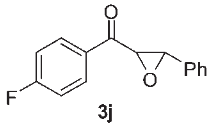
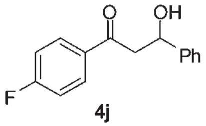
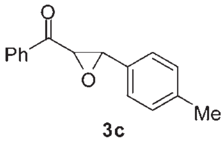
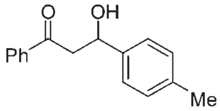
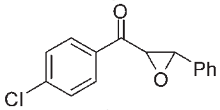
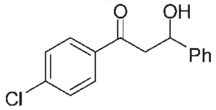
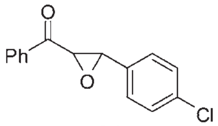
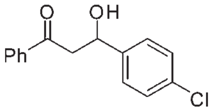
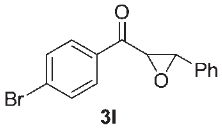
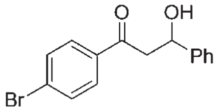
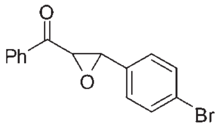
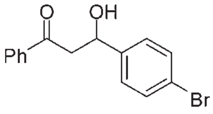
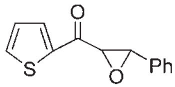
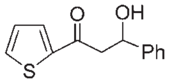
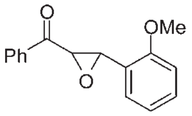
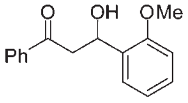
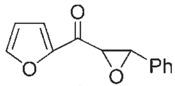
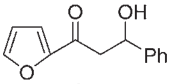
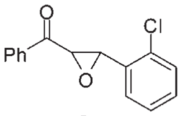
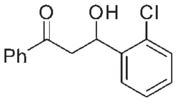
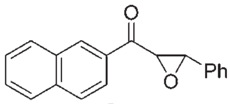
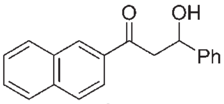
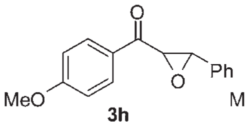
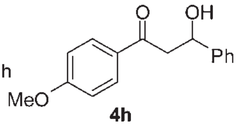
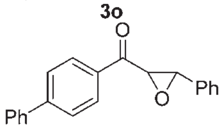
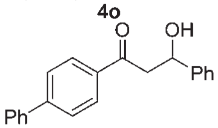
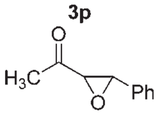
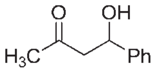
Table 1. Hydrogenation of α,β-Epoxy Ketones to β-Hydroxy Ketones Catalyzed by **2**



substrates	products	yield (%)[a]	substrates	products	yield (%)[a]
 **3a**	 **4a**	94	 **3i**	 **4i**	91
 **3b**	 **4b**	93	 **3j**	 **4j**	90
 **3c**	 **4c**	90	 **3k**	 **4k**	95
 **3d**	 **4d**	96	 **3l**	 **4l**	98
 **3e**	 **4e**	97	 **3m**	 **4m**	86
 **3f**	 **4f**	86	 **3n**	 **4n**	88
 **3g**	 **4g**	89	 **3o**	 **4o**	89
 **3h**	 **4h**	93	 **3p**	 **4p**	85
			 **3q**	 **4q**	75

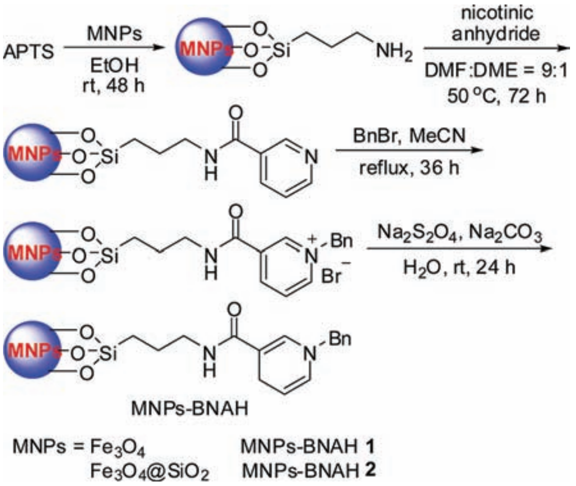
[a] Reaction conditions: α,β-epoxy ketones (0.5 mmol), Na_2CO_3 (2.5 mmol), $Na_2S_2O_4$ (1.5 mmol), and **2** (0.025 mmol, 44 mg) in 10 mL of AcOEt/H_2O (v/v = 1:1), 6 h, rt, under argon atmosphere. Isolated yield.

According to our previous work,[3q] MNPs-BNAH was examined in the reduction of phenyl(3-phenyloxiran-2-yl)methanone (Scheme 2) and **2** showed higher catalytic activity than **1**. The reason may be the slight aggregation of bare Fe_3O_4 nanoparticles of **1**, which influenced the activity (Figure 2a). Therefore, **2** was selected for further investigation.

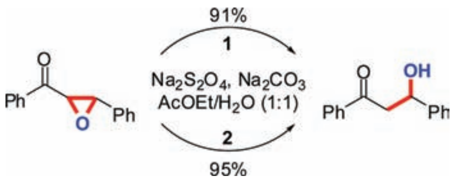
The crystalline structure of **2** was characterized by X-ray diffraction (XRD). The diffraction pattern showed characteristic peaks, and the relative intensity matched well with those of standard Fe_3O_4 nanoparticles (JCPDS card no. 00-002-1035, Figure 1). Moreover, we also could see the peaks of amorphous silica from $2\theta = 20°$ to $30°$. It was demomstrated roughly that the Fe_3O_4 nanoparticles were successfully coated with SiO_2. Transmission electron microscope (TEM) analysis (Figure 2b and c) of the Fe_3O_4 and $Fe_3O_4@SiO_2$ nanoparticles showed a uniform-sized dark Fe_3O_4 nanoparticles core with an average size range of 10–16 nm surrounded by a gray silica shell about 8–10 nm thick. And TG curves confirmed the anchoring of BNAH on MNPs (see Supporting Information).

As shown in Table 1, a series of α,β-epoxy ketones were investigated; the corresponding hydrogenation products β-hydroxyketones were obtained with good to excellent

Scheme 1. Preparation of MNPs-BNAH



Scheme 2. Comparation of Catalytic Activity of **1** and **2**



yields, catalyzed by **2**. When R_1 and R_2 were aryl or heteroaryl, the substituent and steric effect were not very visible in this system (**3a**–**p**). The yield would decrease slightly when R_1 was an aliphatic substituting group (**3q**). Moreover, a series of imines were also tried; unfortunately, no reaction was observed in the current system. It is known that imines could not be reduced directly by BNAH, which is in accord with the results reported by Zhu et al.[13]

Easy and rapid separation by magnetism is the most advantageous feature of MNPs-BNAH. It was concentrated on the sidewall of a reaction vessel with an external magnet after the reaction, and the aqueous and organic phases were separated by magnetic decantation. Compared with our previous report that free BNA^+Br^- or BNAH cannot be separated from the homogeneous system,[3q] a more simple separation of MNPs-BNAH could be achieved in our current protocol.

Table 2. Recyclable Experiments of **2**

$$\mathbf{3l} \xrightarrow[\substack{\text{Na}_2\text{S}_2\text{O}_4,\ \text{Na}_2\text{CO}_3 \\ \text{Ar},\ h\nu,\ \text{rt},\ 6\ \text{h}}]{\substack{\mathbf{2}\ (5\ \text{mol}\ \%) \\ \text{AcOEt/H}_2\text{O}\ (1:1)}} \mathbf{4l}$$

cycle	1	2	3	4	5	6
yield (%)	98	97	97	94	93	90

For practical application to heterogeneous systems, the lifetime of MNPs-BNAH and their level of reusability are very important factors. To clarify this issue, we established a set of experiments for the catalytic hydrogenation of 4-bromophenyl-3-phenyloxiran-2-yl-methanone (**3l**) with **2**. It was shown that **2** could be used at least six times with little change in the activity (Table 2).

In conclusion, we have developed the first example of an MNP-supported organic hydride compound, BNAH, which was used in the catalytic hydrogenation of α,*β*-epoxy ketones. Between as-prepared MNPs-BNAH **1** and **2**, **2** demonstrated higher activity in the reaction and could be recycled six times with little loss in activity. Due to their low toxicity, easy separation from the reaction system with an external magnet, and the sustained activity in recyclable processes, such a magnetic particle is a potential alternative in both laboratory research and scale production.

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Supporting Information Available. Synthesis and characterizations of MNPs-supported BNAH and copies of ^{1}H and ^{13}C NMR spectra for the products in Table 1. These materials are available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.