

Green asymmetric synthesis of binol *via* oxidative cross-coupling in the presence of L-cysteine@Fe₃O₄ nanoparticles

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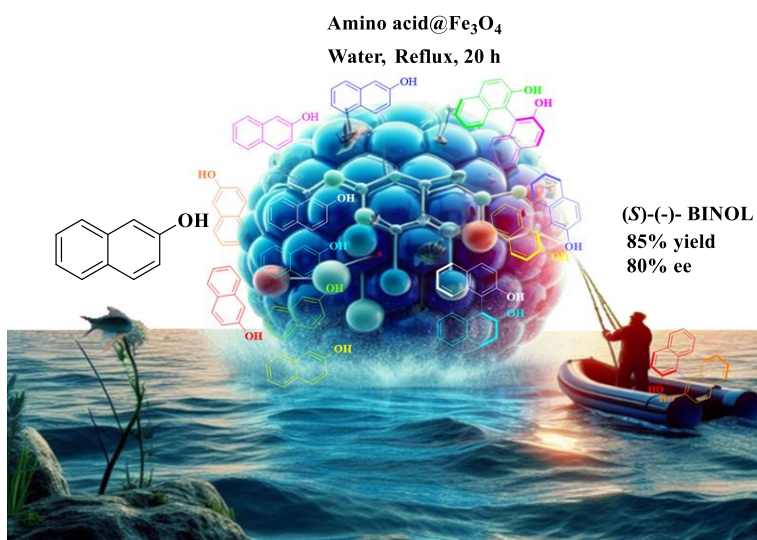
Received 09-09-2024

Accepted 11-20-2024

Published on line 12-04-2024

Abstract

A green synthesis method was used to prepare racemic binol for the first time, yielding up to 92% in the presence of Fe₃O₄ magnetic nanoparticles in water. Additionally, an enantioselective cross-coupling of 2-naphthols was conducted using a chiral magnetic nano catalyst L-cysteine@Fe₃O₄, leading to the preparation of the S-binol enantiomer with up to 85% yield and 80% enantioselectivity. The structure and morphology of the magnetic nanoparticles were characterized using various techniques, including energy-dispersive X-ray spectroscopy (EDAX), scanning electron microscopy (SEM), thermogravimetric analysis (TGA), X-ray diffraction (XRD), vibrating-sample magnetometer (VSM) analysis, and Fourier-transform infrared (FT-IR) spectroscopy.



Keywords: Chiral magnetic nano catalyst, cross-coupling reaction, amino acid, Binol, green synthesis

Introduction

Atropisomers are compounds with a conformational chirality resulting from hindered rotation around a single bond¹. This property is critical in enantioselective reactions catalyzed by these compounds². The unique property of atropisomers have made them important tools in medicinal chemistry for developing new drugs with enhanced stereoselectivity and biological activity³. Due to their ability to control stereochemistry, these compounds are valuable in various fields, including natural product and pesticide synthesis^{4,5}. Studying such compounds has opened new possibilities for designing molecules with specific chirality for the synthesis of complex molecules and materials with tailored properties, making them essential tools in modern organic chemistry.

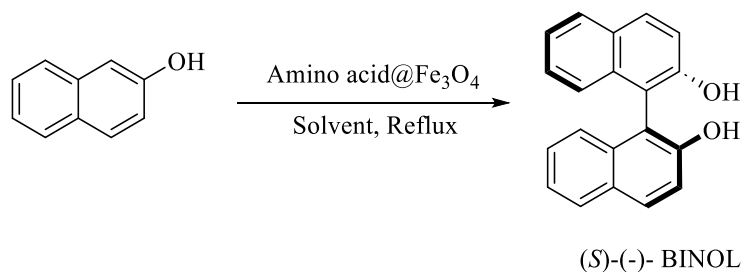
Binol (1,1'-bi-2-naphthol) is a well-known example of a compound exhibiting atropisomeric stereoisomers. Binol derivatives, derived from binaphthyl compounds, are widely used as efficient catalysts in various chemical reactions and industries⁶, finds applications in the production of chiral drugs^{7,8}, enantioselective recognition⁹, enantioselective fluorescent sensors¹⁰, and antibacterial property¹¹. Binol also serves as a powerful chiral ligand or catalyst, facilitating the production of chiral compounds with high yield and selectivity, making it highly valuable in the chemical and pharmaceutical industries. Moreover, binol derivatives can be converted into other useful ligands, such as phosphoramidites¹², hydrogen phosphonates¹³, binol phosphoric acid¹⁴, and binol phosphate¹⁵.

The synthesis of chiral binol typically involves the reaction of the 2-naphthol in the presence of a chiral ligand and transition metal¹⁶. The chiral ligands play a pivotal role in controlling the stereochemistry of the reaction, enabling the selective formation of the desired enantiomer of binol. Various catalytic methods exist for synthesizing biaryl compounds in organic chemistry. One prevalent approach is the Suzuki-Miyaura cross-coupling reaction, which involves coupling of an aryl halide with an arylboronic acid or boronate ester in the presence of various catalytic systems^{17,18}. Another popular method is the Ullmann reaction¹⁹ which entails the direct coupling of two aryl halides with a copper catalyst. Additionally, using an oxidizing agent, the Scholl reaction can be employed for synthesizing biaryls through the oxidative coupling of phenols or arylamines²⁰. Other transition metals such as nickel²¹, iron²², and palladium¹⁸ have been explored as catalysts for biaryl synthesis, offering chemists a wide range of options for designing efficient and selective reactions to access diverse biaryl structures.

Using nanomagnetic catalysts for biaryl synthesis offers a convenient and efficient method for carrying out these reactions²³⁻²⁵, with potential advantages in such catalyst recovery and reusability. One commonly used nanomagnetic catalyst is Fe₃O₄, which can be functionalized with different ligands to enhance its catalytic activity and selectivity in various reactions.

While ferric salts have been used for preparing binol derivatives. Therefore, we report the preparation of chiral binol in the presence of Fe₃O₄ coated with amino acids as a chiral magnetic nano-ligand for the first time (Scheme 1).

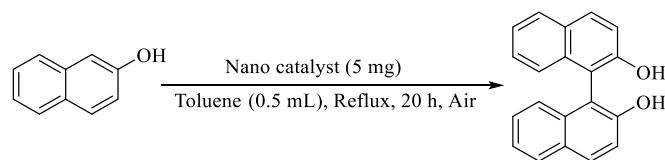
Previously, chiral binol has been prepared through oxidative coupling in various studies using different metals and chiral mediums¹⁶. , the use of nanomagnetic Fe₃O₄ for synthesizing racemic binols and chiral magnetic nano catalyst involving Fe₃O₄ and amino acids has not been extensively explored. Therefore, we report the preparation of chiral binol in the presence of Fe₃O₄ coated with amino acids as a chiral magnetic nano catalyst as a novel approach (Scheme 1).



Scheme 1. Green synthesis of (S)-binol in the presence of chiral amino acid@Fe₃O₄.

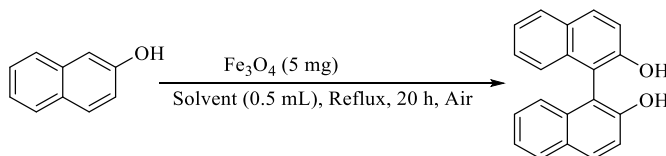
Results and Discussion

Initially, the cross-coupling of 2-naphthols was performed in toluene for 20 hours in the presence of various nanoparticles as catalysts. As indicated in Table 1, no product was obtained when HZSMS-5, CuO, and TiO₂ nanoparticles (entries 1-3). The yield of racemic binol was low when Montmorillonite (K10), MCM-41, and MCM-41@Fe₃O₄ were used (entries 4-6). The yield of isolated racemic binol was obtained 85% when the reaction was carried out in the presence of Fe₃O₄ nanoparticles. However, when the reaction was run in the presence of CuO@Fe₃O₄, the yield of racemic binol was lower than Fe₃O₄ (entries 7 and 8). In the next step, the effect of various solvents on the reaction yield was examined (Table 2). Several solvents, such as tetrahydrofuran, dichloromethane, acetone, and nitromethane, did not produce the desired product (entries 1-4). 1,2-dichlorobenzene and chloroform resulted in partial yields (entries 5 and 6). The yield of binol was moderate using xylene derivatives, acetonitrile, and ethanol (entries 7-11). The results obtained with toluene and water were nearly the same, so water was selected as the green solvent for this reaction (entries 12 and 13). We also investigated the effect of temperature on the reaction yield, showing higher yields at reflux temperature (entry 14). In addition, as oxygen in the air is essential for the oxidation step, no product was observed when using the nitrogen atmosphere (entry 15). The reaction was performed with varying amounts of Fe₃O₄ nanoparticles (1, 5, 10, 20, and 25 mg). Using 1 mg of Fe₃O₄ nanoparticles decreased the yield. The yield of the product with 20 and 25 mg of Fe₃O₄ nanoparticles was nearly the same, yielding 90%, so 20 mg of Fe₃O₄ nanoparticles was selected as the optimum amount (not mentioned in the table).

Table 1. Influence of various nano catalysts on the model reaction

Entry ^a	Nano catalyst	Yield (%) ^b
1	HZSMS-5	No product
2	CuO	No product
3	TiO ₂	No product
4	K10	20
5	MCM-41	10
6	MCM@Fe ₃ O ₄	30
7	Fe ₃ O ₄	85
8	Cu@Fe ₃ O ₄	65
9	-	No product

^a Reaction condition: 2-naphthol (0.1 mmol), nano catalyst (5 mg), toluene (0.5 mL), ^b isolated yields.

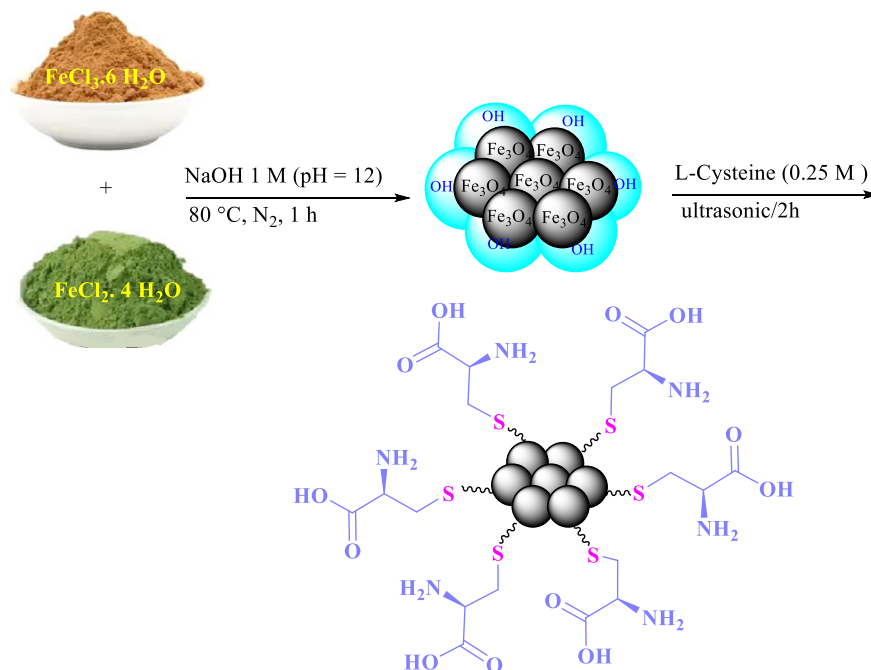
Table 2. Influence of various solvents on the model reaction

Entry ^a	Solvent	Yield (%) ^b
1	Tetrahydrofuran	No product
2	Dichloromethane	No product
3	Acetone	No product
4	Nitromethane	No product
5	1, 2-Dichlorobenzene	trace
6	Chloroform	trace
7	<i>o</i> -Xylene	40
8	<i>m</i> -Xylene	42
9	<i>p</i> -Xylene	55
10	Acetonitrile	44
11	Ethanol	75
12	Toluene	85
13	H ₂ O	80
14 ^c	H ₂ O	43
15 ^d	H ₂ O	No product

^a Reaction condition: 2-naphthol (0.1 mmol), Fe₃O₄ nanoparticles (5 mg), solvent (0.5 mL), ^b isolated yields. ^c at room temperature,

^d under nitrogen atmosphere.

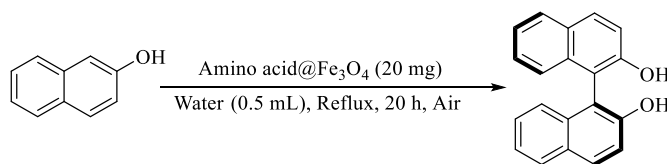
The chiral amino acid-coated magnetic nanoparticles (amino acid@Fe₃O₄) were synthesized as follows: First, Fe₃O₄ was prepared by coprecipitating ferric and ferrous salts in a basic solution²⁶. Next, amino acids (L-proline, L-alanine, and L-cysteine) were immobilized onto the Fe₃O₄ nanoparticles, as illustrated in Scheme 2²⁷.



Scheme 2. The preparation of Fe₃O₄ nanoparticles and L-cysteine@Fe₃O₄.

Asymmetric Synthesis of Binol

The asymmetric synthesis of binol was conducted under optimized conditions with chiral magnetic nano catalysts. The reaction utilized immobilized chiral magnetic nano catalysts, including L-Alanine@Fe₃O₄, L-Proline@Fe₃O₄, and L-cysteine. In the presence of L-Alanine@Fe₃O₄ and L-Proline@Fe₃O₄, the reaction yielded 72% and 65% with enantioselectivities of 68% and 72% for *S*-binol, respectively. The highest yield and enantioselectivity were achieved with L-cysteine@Fe₃O₄, resulting in an 85% yield and 80% enantiomeric excess (ee) of *S*-binol.

Table 3. Effect of chiral magnetic nano catalysts on the reaction

Entry ^a	Chiral magnetic nano catalyst	Yield (%) ^b	ee (%) ^c
1	L-Alanine@Fe ₃ O ₄	72	68
2	L-Proline@Fe ₃ O ₄	65	72
3	L-Cysteine@Fe ₃ O ₄	85	80

^a Reaction condition: 2-naphthol (0.1 mmol), chiral magnetic nano catalyst (20 mg), water (0.5 mL), ^b isolated yields. ^cdetermined by HPLC using a chiral stationary phase, *S*-binol was obtained as a major enantiomer.

Conclusions

In summary, we have developed a novel and environmentally friendly approach for synthesizing racemic binol using a recyclable Fe₃O₄ catalyst, achieving high yield alongside an asymmetric oxidative cross-coupling of 2-naphthols. Using L-cysteine@Fe₃O₄ as a chiral magnetic nano catalyst, this method achieved an 85% yield and 80% enantioselectivity in water, which served as the green solvent. The nano catalyst maintained its catalytic efficiency over five cycles without significant loss in yield and up to three cycles for enantioselectivity.

Experimental Section

General: Chemicals and equipment.

All chemicals were purchased from Sigma-Aldrich or Merck Chemicals. Solvents were distilled and dried before being used according to the literature procedure. Deionized water was obtained from an ultra-pure water system Elga (UK). The composition of nanoparticles was determined using a DX-2700 X-ray diffractometer with a Cu K α X-ray source ($\lambda = 1.542 \text{ \AA}$) in a step scan mode with a scanning rate of $0.03^\circ \text{ s}^{-1}$ in the range from 10° to 80° . FT-IR (KBr) spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer. Magnetic properties of the nanoparticles were investigated using a vibrating sample magnetometer (VSM, MPMS (SQUID) XL-7, Quantum Design, USA) with an applied field between $-20,000$ and $20,000$ Oe at 300 K. The morphology and size of the particles were recorded by scanning electron microscope (SEM) recorded by MIRA3 FEG-SEM-TESCAN that this device has a resolution of up to 1 nm and a magnification of up to 1 million times the applied voltage of 30 kv equipped with energy diffraction X-ray spectroscopy (EDX)-detectors. TGA measurement of temperature and mass changes, was determined by Bahr STA 503 with a maximum temperature of 1500°C and speeds of 0.01-100 K/min. The ^1H NMR spectrum was recorded on Bruker AvIII HD- 400 MHz using TMS as the internal standard. High-performance liquid chromatography (HPLC) was performed on a Shimadzu Prominence.

Preparation of Fe₃O₄ coated with amino acid (amino acid@Fe₃O₄)

Fe₃O₄ nanoparticles were synthesized *via* a standard co-precipitation method²⁸. Subsequently, amino acids were immobilized on the Fe₃O₄ nanoparticles to prepare amino acid@Fe₃O₄. In this process, 1 g of Fe₃O₄ nanoparticles was dispersed in 10 mL H₂O using an ultrasonic bath for 15 minutes. Then, a 0.25 M solution of the amino acid (10 mL) was added, and the mixture was stirred for 2 hours. The amino acid@Fe₃O₄ was collected using an external magnet, washed with a water-ethanol mixture, and dried overnight²⁹. Characterization of the synthesized nano catalysts was confirmed by methods described in the literature (refer to Supplementary Material).

Heterogeneous Catalytic procedure

In a 25 mL round-bottom flask, 2 mmol (0.29 g) of dark brown 2-naphthol powder was dissolved in 10 mL water and refluxed for 15 minutes. Then, 400 mg amino acid@Fe₃O₄ was added, and the mixture was stirred for 20 hours. After the reaction (monitored by TLC) was complete, the reaction mixture was cooled, and the amino acid@Fe₃O₄ was recovered using an external magnet, washed with a 1:1 water-ethanol solution, and stored for subsequent reactions. The reaction mixture was extracted with ethyl acetate three times, followed by purification by column chromatography on silica gel (eluent: 3:1 ethyl acetate/hexane), yielding 0.48 g of pure *S*-Binol (85% yield). For the racemic procedure, the method was the same. Melting point (M.P) was recorded as 209-211 °C, and optical rotation was measured as $[\alpha]_D^{22}$ ($c = 0.6$ THF) -23.8° for 80 % ee³⁰. ¹H NMR (400 MHz, CDCl₃) δ 5.08 (2H, s), 7.20 (2H, d, $J=8.3$ Hz), 7.32-7.40 (2H, m), 7.42-7.45 (4H, m), 7.94 (2H, d, $J=7.8$ Hz), 8.02 (2H, d, $J=8.9$ Hz)³¹. HPLC: (Chiralcel OD-H column with 90:10 *n*-hexane:isopropanol as eluent 0.5 mL/min, 20 °C, $\lambda=254$ nm), retention times: $t_{\text{major}}=27.1$ min, $t_{\text{minor}}=33.4$ min³².

Catalyst Stability and Reusability

The stability and catalytic activity of the nanomagnetic catalysts were evaluated through recovery and reusability studies. The synthesis of binol was successfully repeated five times using recycled L-Cysteine@Fe₃O₄ without a significant decrease in yield. However, enantioselectivity declined after three cycles, with the fourth cycle yielding 50% ee, as shown in Figure 1.

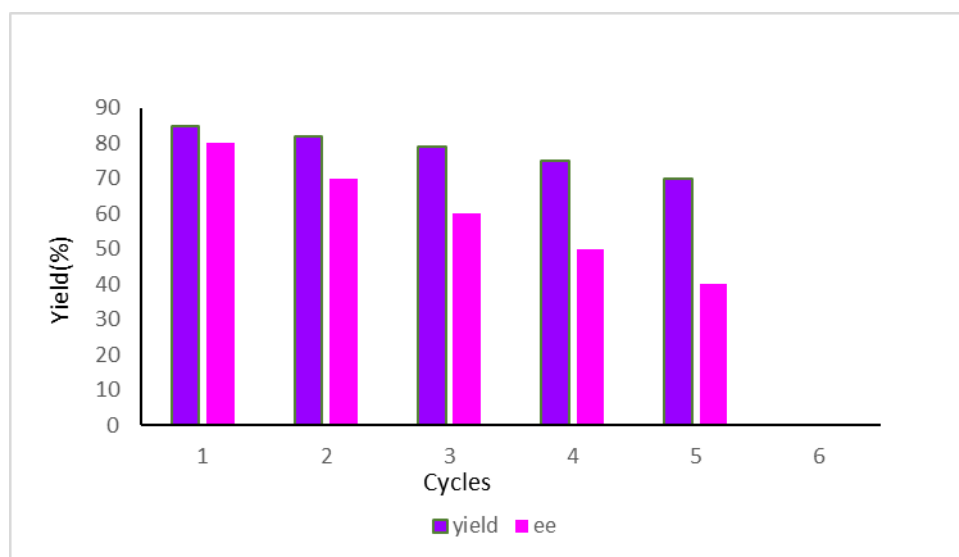


Figure 1. correlation between the recyclability of the catalyst and both the yield and enantiomeric excess (ee).

Acknowledgements

We are grateful to the University of Kurdistan Research Council for the support of this work.

Funding - There is no funding for this work. **Data Availability** - The authors declaration this is an original article. Everything covered herein was cited in the reference section. **Declarations: Competing interest** - The authors declare no competing interest. **Conflict of interest** - The authors declare that they have no conflicts to share.

Supplementary Material

Supplementary material is available online - copies of the NMR, HPLC spectra and nano ligand analyses data are given in the supplementary material a file associated with this manuscript

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