



## Nickel Oxide NPs as a Catalyst in Diastereoselective Aldolization of Heteroaromatic aldehydes

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### Abstract

A fast and diastereoselective protocol was developed for the synthesis of aldol derivatives in the presence of a catalytic amount of nickel oxide nanoparticles at room temperature. Aldol adducts were obtained in moderate to good yields and complete diastereoselectivities in short reaction times. In this method, heteroaromatic aldehydes readily participate as electrophilic cross aldol partners with a range of cycloalkanones as ketone donors.

**Keywords:** Aldolization, Nickel Oxide NPs, Heteroaromatic aldehydes

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### Introduction

The inadequacy of naturally occurring precious compounds prompted several minds of scientists to synthesize them in a laboratory for a thorough evaluation of their medicinal and clinical properties. Finding an optimized methodology to synthesize chiral products has always been challenging in synthetic organic chemistry, particularly the formation of carbon-carbon bonds adhering to the existing stereochemistry [1-3].

Cross aldol reaction is a fundamental C-C bond-forming protocol for increasing molecular complexity in organic synthesis [4-6]. The reaction has proven to be a powerful and general method for the stereocontrolled construction of  $\beta$ -hydroxy ketone derivatives [7-10] and has relevant application in the synthesis of carbohydrates, amino sugars, steroids, natural heteroatomic molecules, fine chemicals and pharmaceuticals [11-14]. There are several methods to synthesized aldol products. Also, many efforts have been addressed towards the synthesis of organocatalysts that have produced systems able to afford good stereoselectivities [15-19]. Since the control of stereochemistry during aldol additions is a crucial problem, the metal catalyzed direct aldol reaction of aldehydes with unmodified ketones still remains a challenge for synthetic chemist [20, 21]. Zi-Bin Qiu et al. used  $MgBr_2 \cdot OEt_2$  as an efficient catalyst for the synthesis of aldol derivatives with up to 99%

diastereoselectivity at 5 °C [22]. An enantioselective reductive aldol reaction of unprotected  $\alpha,\beta$ -unsaturated carboxylic acids was developed by employing a copper/bisphosphine catalyst [23]. In situ pre-conversion of carboxylic acids to siloxy esters facilitated the boron-catalyzed asymmetric aldol reaction [24]. A catalytic enantioselective aldol reaction of alkenyl esters with isatins was achieved using a DM-BINAP-AgOTf complex as the chiral precatalyst and *N,N*-diisopropylethylamine as the base precatalyst in the presence of methanol or 2,2,2-trifluoroethanol [25]. Bhangare et al. developed catalytic  $Sc(OTf)_3$  mediated direct asymmetric aldol reaction of (-)-menthyl isothiocyanatoacetate with aldehydes by using (-)-menthol as chiral auxiliary [26]. Synergistic gold-iron catalytic system was developed for synthesis of crossed aldol reactions under mild conditions [27]. A degenerate zinc-templated catalytic system containing two bipyridine ligands was applied to the asymmetric aldol reaction [28]. On the other hand, metal oxide nanoparticles find excellent applications as catalysts for various organic transformations [29, 30]. Choudary et al. reported direct asymmetric aldol reaction catalyzed by MgO NPs [31]. Yang et al. used self-assembled bio-organometallic nanocatalysts for enantioselective direct aldol reactions [32]. Kantam et al. reported direct asymmetric aldol reaction of aldehydes with acetone using CuO NPs to afford optically active



$\beta$ -hydroxy carbonyl compounds [33]. Despite these reports, it is still important to develop new efficient method for the cross aldol reactions in mild reaction conditions with high diastereoselectivity [34, 35]. This study describes a mild and diastereoselective cross aldol reaction between various heteroaromatic aldehydes and cycloalkanones. In the present work, NiO NPs catalyzed the aldol reaction at room temperature with complete diastereoselectivity.

## Materials and Methods

### General

Solvents, organic and inorganic compounds were purchased from Merck and used without further purification. The synthesis of NiO NPs has been carried out according to literature procedure. The isolation of pure products was carried out via preparative thin layer chromatography (Silica Gel 60 GF<sub>254</sub>; Merck). IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. <sup>1</sup>H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and <sup>13</sup>C NMR were achieved on a Bruker DRX-125 Avance spectrometer. Samples were analyzed in CDCl<sub>3</sub>, and the chemical shift values are expressed relative to Me<sub>4</sub>Si as an internal standard. Elemental analyses were made by a Carlo-Erba EA1110 CHNO-S analyser and agreed with the calculated values.

### Typical procedure for NiO NPs-catalyzed aldol reaction

In the presence of NiO NPs (3.6 mg), KOH (0.35 mmol) and dioxane (2.5 mL), a mixture of cycloalkanone (3.5 mmol) and heteroaromatic aldehyde (1 mmol) was stirred for the appropriate time at room temperature. Completion of the reaction was indicated by TLC monitoring. After the indicated reaction time, the reaction mixture directly purified by thin layer chromatography (silica gel, petroleum

ether/ethyl acetate 12:3), affording corresponding aldol.

## Results and Discussion

As a part of our ongoing interest to develop efficient synthetic strategies for the preparation of  $\beta$ -hydroxy ketone moiety units [36-39], a facile and efficient nano catalytic approach for the one-pot synthesis of aldol products have been developed. In this study, NiO NPs were successfully synthesized by sol-gel method [40], and then annealed at two temperature (400 and 700 °C). The annealing temperature played an important role in controlling the particle size. NiO NPs with two size distributions were used as the efficient catalyst for synthesis of aldol adducts using cycloalkanones and heteroaromatic aldehydes. At first, to find the most effective NiO NPs catalyst for the synthesis of aldol adduct, the NiO NPs with two size distributions were studied. When the aldol reaction was carried out in the presence of 400 °C annealed NiO nanoparticle, yield obtained was higher (71 %) as compared to that carried out in the presence of 700 °C (65 %). This may be due to decrease in surface area of NiO NPs. The surface-to-volume ratio of the catalyst increases tremendously when size decreases, which are responsible for the higher activity and enhanced yield of NiO NP at 400 °C. To get the optimum conditions for the reaction, reaction of cyclohexanone and 4-(methylthio)benzaldehyde for synthesis of aldol product was selected as model reaction and different parameters such as the solvent type, amount of catalyst and temperature were tested. The effect of different solvents such as dichloromethane, acetonitrile and dioxane was studied for synthesis of 2-(hydroxy(3-(methylthio)phenyl)methyl)cyclohexanone in the presence of 400 °C annealed NiO nanoparticle as a catalyst. The obtained results in table 1 shows that the best product yield was achieved in dioxane as a solvent.

Table 1: Optimization of solvent type for the model reaction.

Entry	Solvent	Yield (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	60
2	CH <sub>3</sub> CN	65
3	Dioxane	71

The amount of catalyst was optimized for the model reaction using different quantities of NiO NP. It can be seen that the best yield was achieved by 3.6 mg of catalyst. Moreover, in the

absence of NiO NPs, no product was obtained after 4 h. Therefore, it is shown that the NiO Np is necessary for this reaction (Table 2).

Table 2: Optimization of Catalyst amount for the model reaction.



Entry	Catalyst amount (mg)	Yield (%)
1	-	-
2	2.5	60
3	3	61
4	3.2	65
5	3.6	71
6	4.2	70

For the optimization of the reaction temperature, reaction was performed in different temperature. The best yield was obtained at RT. Finally, after some preliminary experiments, we found that a mixture of cyclohexanone (3 mmol) and 4-(methylthio)benzaldehyde (1 mmol) in the

presence of NiO NPs (3.6 mg) afforded aldol product at room temperature in good yield. The generality of the reaction was assessed using cycloalkanones and various heteroaromatic aldehydes (Table 3).

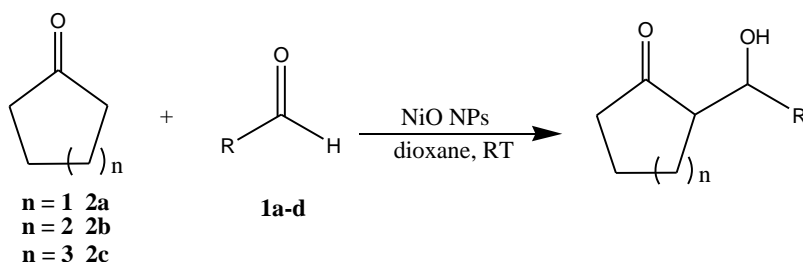


Table 3: Aldol reaction of cycloalkanones with heteroaromatic aldehydes by NiO NPs<sup>a</sup> (annealed at 400 °C).

Entr y <sup>e</sup>	R	Product <sup>b</sup>	Yield (%) <sup>c</sup>	Time (h)	Dr (syn:anti) <sup>d</sup>
1	4-MeSC <sub>6</sub> H <sub>4</sub> -	<b>3aa</b>	73	4.5	100:0
2	3-Methylthiophen-2-yl	<b>3ba</b>	76	2	100:0
3	5-Methylthiophen-2-yl	<b>3ca</b>	74	1.5	100:0
4	4-MeSC <sub>6</sub> H <sub>4</sub> -	<b>3ab</b>	71	4	100:0
5	3-Methylthiophen-2-yl	<b>3bb</b>	70	2.5	100:0
6	5-Methylthiophen-2-yl	<b>3cb</b>	68	3	100:0
7	4-MeSC <sub>6</sub> H <sub>4</sub> -	<b>3ac</b>	64	4.5	100:0
8	3-Methylthiophen-2-yl	<b>3bc</b>	72	2.5	100:0
9	5-Methylthiophen-2-yl	<b>3cc</b>	71	2.5	100:0
10	Thiophen-2-yl	<b>3dc</b>	65	1.5	100:0

<sup>a</sup>Reaction conditions: aldehyde ( 1 mmol), cycloalkanone ( 3.5 mmol), KOH ( 0.35 mmol), NiO NPs catalyst, solvent, RT.

<sup>b</sup>All products were characterized by <sup>1</sup>HNMR, <sup>13</sup>CNMR and IR data. <sup>c</sup>Yields after purification by chromatography.

<sup>d</sup>Determined by <sup>1</sup>HNMR analysis. <sup>e</sup>Identified by comparison with authentic samples [37].

## Conclusions

In brief, the cross aldol reaction of cycloalkanones with heteroaromatic aldehydes using catalytic amount of NiO NPs proceeded smoothly under

mild conditions to give the corresponding aldol adducts in moderate to good yields with complete diastereoselectivity. A low annealing temperature would be useful to gain a high



specific surface area of NiO NPs, as an efficient catalytic process. On the other hand, loadings as low as 3.6 mg of catalyst have been successfully used for the diastereoselective aldol reaction with heteroaromatic aldehydes. The aldolization can efficiently proceed at room temperature with a small excess of ketone. Also, the reactions can be performed over a short period of time without preactivation of the donor substrates. Moreover, the readily available initial materials and an easy work up make this protocol a useful methodology in synthetic chemistry. Further studies, including catalyst design modifications to improve the stereoselectivity and mechanistic investigations are currently underway.

#### Conflicts of Interest

"The author declares that there is no conflict of interest regarding the publication of this paper."

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