

Nanocrystalline MgO for Asymmetric Henry and Michael Reactions

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Abstract: Nanomaterials with their three-dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates for unidirectional introduction of reacting species to induce an asymmetric center. We herein report the design and development of a truly recyclable heterogeneous catalyst, nanocrystalline magnesium oxide, for the asymmetric Henry reaction (AH) to afford chiral nitro alcohols with excellent yields and good to excellent enantioselectivities (ee's) for the first time. Bronsted hydroxyls are the sole contributors for the ee, while they add on to the activity in AH. It is demonstrated that the hydrogen bond interactions between the -OH groups of (S)-(-)-binol and the -OH groups of MgO are essential for the induction of enantioselectivity. Further, to prove the above hypothesis, we have successfully carried out another reaction, asymmetric Michael reaction (AM) with nanocrystalline MgO. The reusable and suitably aligned nanocrystalline MgO-catalyzed AH and AM reactions afforded chiral products with comparable ee's to that of the homogeneous system.

Introduction

The carbon-carbon bond forming reactions are ubiquitous in synthetic organic chemistry, which generated increasing interest from both industrial and academic researchers over the last few decades to find ways for economical processes.^{1,2} Nitroaldol and Michael reactions are the fundamental synthetic tools for the construction of C-C bonds.³ The nitro group of these products can undergo the Nef reaction,⁴ reduction to amino group, or nucleophilic displacement.⁵ The asymmetric Henry (AH) reactions with impressive enantioselectivities (ee's) are realized using a dinuclear zinc-chiral semi-azacrown⁶ complex or copper bisoxazoline complexes.⁷ Asymmetric Michael (AM)

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reactions with good to excellent ee's are accomplished using alkaloids,^{8,9} chiral crown ethers in the presence of bases,¹⁰ proline and proline-derived catalysts,11 diamines,12 natural proteins,¹³ amino alcohols,¹⁴ and binol-derived complexes¹⁵ in homogeneous media. In the area of heterogenized catalysts, chiral polymers provide moderate ee's in the AM reactions.¹⁶

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A breakthrough both in AM and AH catalytic reactions is achieved with the introduction of in situ prepared heterobimetallic catalysts, composed of both Lewis acidic sites and Lewis/ Bronsted basic sites.¹⁷ Transition metal chiral complexes, singlesite catalysts with a defined shape and stereochemistry, induces, in general, higher enantioselectivity in asymmetric synthesis since they permit unidirectional introduction of the reacting species onto a prochiral substrate in the three-dimensional space to generate the asymmetric center. Conversely, heterogeneous catalysts are not as effective as transition metal chiral complexes due to their multisite active sites resulting from assorted crystal structures with different shapes and sizes and also their steric restrictions. Hence, creation of desired stereochemistry with defined shape and size in heterogeneous catalysts to build the asymmetric center is a challenging problem. Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals and catalysts for various organic transformations.^{18,19} Nanomaterials with their three-dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates for unidirectional introduction of reacting species to induce an asymmetric center.^{19d} Recently, we evolved the single-site nanocrystalline MgO for the synthesis of chiral epoxy ketones.19d

We herein report the design and development of a truly recyclable heterogeneous catalyst, nanocrystalline magnesium oxide, for the AH and AM reactions to afford chiral nitro alcohols and Michael adducts in good to excellent yields and enantioselectivities for the first time (Scheme 1).

Results and Discussion

Various magnesium oxide crystals²⁰ [commercial MgO, CM-MgO (SSA: 30 m²/g), conventionally prepared MgO, NA-MgO (SSA: 250 m²/g), and aerogel-prepared MgO, NAP-MgO (SSA: 590 m²/g)] were initially screened in the achiral Henry reaction between benzaldehyde and nitromethane at room temperature. NAP-MgO and NA-MgO gave nitro alcohols with

Table 1. Achiral Henry Reaction Catalyzed by Different Crystallites of MgO between Benzaldehyde and Nitromethane at $25 \, ^\circ C^a$

entry	catalyst	time (h)	yield (%) ^b
1	NAP-MgO	6	95
2	NA-MgO	10	95
3	CM-MgO	18	20^{c}
4	Sil-NAP-MgO	20	90
5	Sil-NA-MgO	30	90

 a Conditions: benzaldehyde (1.0 mmol, 0.1 mL), nitromethane (5.0 mmol, 0.305 g), NAP-MgO (0.125 g), dry THF (5 mL). b Isolated yields. c The byproduct was dehydrated Henry product (olefin).

Table 2. Asymmetric Henry Reaction between Nitromethane and Benzaldehyde Catalyzed by NAP-MgO with Different Ligands at $-78\ ^{\circ}\text{C}$

entry	ligand	yield (%) ^a	ee (%) ^b
1	(<i>S</i>)-(-)-binol	95, 70, ^c 50, ^d	90, 58, ^c 10, ^d
		$40,^{e}95,^{f}0,^{f}0^{g}$	$0,^{e} 90^{f}$
2	protected $-OHs$ of (S)-($-$)-binol	95	0
3	(S)- $(-)$ -1,1'-binaphthyl-2,2'-diamine	90	30
4	(1R,2R)- $(-)$ -1,2-diaminocyclohexane	90	40
5	(DHQD) ₂ PHAL	80	30
6	L-proline	NR	0
7	(+)-diethyl L-tartrate	90	20

^{*a*} Isolated yields. ^{*b*} Absolute configurations were determined to be *S*. ^{*c*} With NA-MgO. ^{*d*} With CM-MgO. ^{*e*} With silylated NAP-MgO. ^{*f*} Fifth cycle. ^{*g*} Without catalyst; ee's were measured by Diacel Chiralcel HPLC using OD column with 3% 2-propanol in hexane. Conditions: benzaldehyde (1.0 mmol), nitromethane (5.0 mmol), NAP-MgO (0.125 g), dry THF (5 mL), (*S*)-(-)-binol (0.040 g).

Table 3. Asymmetric Henry Reaction between Benzaldehyde and Nitromethane Catalyzed by NAP-MgO with Different Solvents at 25 $^\circ C^a$

entry	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	methanol	24	40	40
2	acetonitrile	24	30	30
3	1,2-dichloroethane	24	0	0
4	toluene	15	95^d	55
5	THF	06	95^d	60

 a Conditions: benzaldehyde (1.0 mmol, 0.1 mL), nitromethane (5.0 mmol, 0.305 g), NAP-MgO (0.125 g), solvent (5 mL). b Isolated yields. The byproduct was dehydrated Henry product (olefin) in case of entries 1 and 2. c Absolute configurations were determined to be S. d No byproduct

good yields, while CM-MgO afforded olefin product (major) along with nitroaldol product (Table 1).

Encouraged with the initial success in the achiral Henry reaction, we carried out AH reaction of benzaldehyde with nitromethane. In the process of optimization of the AH reaction, we explored different samples of MgO (Table 2, entry 1) with various chiral auxiliaries (Table 2) and solvents (Table 3) at different temperatures (Table 4). Among the MgO samples screened in the AH reaction, the NAP-MgO was found to be superior than the NA-MgO and CM-MgO in terms of yields and ee's. The ee's of the AH product are 90, 58, and 10% using the NAP-MgO, NA-MgO, and assorted crystals of CM-MgO, respectively (Table 2). (S)-(-)-1,1'-Bi-2-naphthol [(S)-(-)-binol], a versatile chiral auxiliary in various asymmetric organic transformations,²¹ offered optimum ee in the AH reaction of benzaldehyde with nitromethane. As the temperature decreases, ee increases remarkably with decrease of rate of

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Table 4. Asymmetric Henry Reaction between Benzaldehyde and Nitromethane Catalyzed by NAP-MgO at Different Temperatures^a

entry	<i>T</i> (° C)	time (h)	yield (%) ^b	ee (%)
1	40	4	70^{c}	30
2	25	6	90	60
3	0	7	95	70
4	-78	12	95	90

^{*a*} Conditions: benzaldehyde (1.0 mmol, 0.1 mL), nitromethane (5.0 mmol, 0.305 g), NAP-MgO (0.125 g), THF (5 mL), (*S*)-binol (5.0 mmol, 0.040 g). ^{*b*} Isolated yields. Conversions are 100% at all temperatures. ^{*c*} The byproduct was dehydrated Henry product (olefin); ee's were measured by Diacel Chiralcel HPLC using OD column with 3% 2-propanol in hexane.

Table 5. Asymmetric Henry Reaction Catalyzed by NAP-MgO with Substituted Benzaldehydes and Nitromethane at -78 °C^a

$\frac{\text{R-CHO} + CH_3NO_2}{1} \frac{NA}{(S)-(-)}$	AP-MgO binol, -78°C
$\mathbf{R} = \mathbf{P}\mathbf{h} : 1\mathbf{a}$	$\mathbf{R} = 4$ -Me- $\mathbf{C}_6 \mathbf{H}_4$: 1h
$R = 4 - NO_2 - C_6 H_4$:1b	$\mathbf{R} = 2 \cdot \mathbf{Me} \cdot \mathbf{C}_6 \mathbf{H}_4 : \mathbf{1i}$
$R = 2 - NO_2 - C_6 H_4 : 1c$	R = Cyclohexyl: 1j
$R = 4-Cl-C_6H_4 : 1d$	R = t-Bu: 1k
$R=2-Cl-C_6H_4$: 1e	R = n-Bu: 11
$R = 4$ -OMe- C_6H_4 : 1f	
$\mathbf{R} = 2$ -OMe- $\mathbf{C}_6\mathbf{H}_4$: 1g	

entry	substrate	time (h)	product	yield (%) ^b	ee (%) ^c
1	1a	12	3a	95	90
2	1b	18	3b	95	98
3	1c	15	3c	95	80
4	1d	16	3d	90	98
5	1e	15	3e	90	77
6	1f	20	3f	80	85
7	1g	20	3g	95	70
8	1ĥ	15	3h	90	70
9	1i	15	3i	90	60
10	1j	18	3j	80	86
11	1k	18	3k	70	70
12	11	15	31	70	60

^{*a*} Conditions: benzaldehyde (1.0 mmol), nitromethane (5.0 mmol), NAP-MgO (0.125 g), dry THF (5 mL), (*S*)-(-)-binol (0.040 g). ^{*b*} Isolated yields. ^{*c*} Absolute configurations were determined to be *S*.

reaction. The solvent THF and temperature of -78 °C showed optimum ee's.

To widen the scope, NAP-MgO was tested in the AH reaction of aromatic, aliphatic, and cyclic aldehydes with nitromethane. When benzaldehydes are substituted at the 4-position with electron-withdrawing (EW) groups, higher ee's are observed than the one bearing electron-donating (ED) groups at the 4-position (Table 5, entries 2, 4, 6, and 8). On the other hand, in the AH reaction using NAP-MgO, 2-substituted benzaldehydes with either EW or ED groups exhibit a decrease of ee when compared with the corresponding 4-substituted benzaldehydes, which may be ascribed to the steric hindrance for the unidirectional entry of reacting species (Table 5, entries 2-9).

NAP-MgO catalyzed the AH reaction of α -keto esters with nitromethane to β -nitro α -hydroxy esters, which are vital chiral intermediates with quaternary carbon centers in higher ee's than reported²² using (*S*)-binol as a chiral auxiliary (Scheme 2).

Even though the three forms of magnesium oxide crystals catalyze this reaction, only NAP-MgO induces the enantioselectivity (Table 6).

Spurred with the success of AH reactions, another important C-C bond formation, asymmetric Michael (AM) reaction

Scheme 2. Asymmetric Henry Reaction of $\alpha\text{-Keto}$ Esters with Nitromethane Catalyzed by NAP-MgO at $-78\ ^{\circ}\text{C}$



Table 6. Asymmetric Henry Reaction between $\alpha\text{-Keto}$ Esters and Nitromethane Catalyzed by NAP-MgO at $-78~^\circ\text{C}$

entry	substrate	time (h)	product	yield (%) ^a	ee (%) ^d
1	4a	20	5a	75, 40, ^b 30 ^c	98, 0, ^c 0 ^d
2	4b	24	5b	70	98

 a Isolated yields. b With NA-MgO. c With CM-MgO. d Absolute configurations were determined to be S.

Table 7. Effect of Ligand on AM Reaction between Chalcone and Nitromethane Catalyzed by NAP-MgO at 25 $^\circ C^a$

entry	ligand	time (h)	yield (%) ^b	ee (%)
1	(1R,2R)- $(-)$ -1,2-diaminocyclohexane	8	95	90
2	(1R,2R)- $(+)$ -1,2-diphenylethylenediamine	8	95	82
3	(1S,2R)- $(+)$ -2-amino-1,2-diphenylethanol	12	90	60
4	(1R,2S)- $(-)$ - N -methylephedrine	12	90	0
5	(+)-diethyl L-tartrate	18	50	0
6	(S)- $(-)$ -1,1'-binaphthyl-2,2'-diamine	12	90	60
7	(<i>S</i>)-(-)-binol	15	NR	0
8	L-proline	15	NR	0
9	L-proline methyl ester	12	90	80

 a In all cases 25 mol % of ligand was used. Conditions: chalcone (1.0 mmol, 0.208 g), nitromethane (50.0 mmol, 3.05 g), NAP-MgO (0.125 g), dry THF (5 mL). b Isolated yields.

between chalcone and nitromethane, was studied using nanomaterials. When we tried the asymmetric Michael (AM) reaction with the (S)-(-)-binol, no reaction took place due to inadequate basicity.^{10,17d} To enhance the basicity, we have evaluated several chiral amine ligands in the asymmetric Michael reaction (Table 7). Among the MgO samples screened in the AM reaction of chalcone with nitromethane using (1R,2R)-(-)-diaminocyclohexane (DAC) as chiral auxiliary, the NAP-MgO was found to be superior to NA-MgO and CM-MgO in terms of yields and ee's. The ee's of the product are 90, 46, and 5% using the NAP-MgO, NA-MgO, and assorted crystals of CM-MgO, respectively. In an attempt to optimize the AM reaction, the effect of solvent and temperatures was studied. NAP-MgO, using DAC as chiral auxiliary in THF at -20 °C, was found to be the best system.

In general, chiral bidentate systems composed of primary and secondary amines afforded better ee's (Table 7, entries 1-3, 6, and 9), while chelation with tertiary amine, -COOH, or -OH displayed no ee's (Table 7, entries 4, 5, 7, and 8). In the AM reaction with NAP-MgO, the rate of the reaction is faster in the presence of chiral auxiliary. As the ligand concentration increases, the rate of the reaction increases with the increase of ee (Figure 1). These results are in consonance with the earlier reported ligand acceleration effects²³ that include metal-diamine accelerated asymmetric Michael reactions.²⁴

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Figure 1. Effect of ligand concentration on the rate of the reaction as a function of time at -20 °C.

Table 8. Asymmetric Michael Reaction between Nitroalkanes and Various Michael Acceptors Catalyzed by NAP-MgO at -20 °C Using (1R,2R)-(-)-1,2-Diaminocyclohexane

Ar ¹		+ H-C	$\frac{R^{1}}{NO_{2}}$	NAP-MgC	D, THF auxiliary Ar^1	$\mathbf{Ar}^{\mathbf{R}}$
	6	2 R= 29 R	=R ¹ =H =R ¹ =CH		$Ar^{1} = 4 - Cl - C \cdot H \cdot A$	$r^2 = C_1 H_1 \cdot 6d$
$Ar^{l} = A$.r²= C ₆ H₅: 6	a	к сн ₃		$Ar^{1} = 4-Me-C_{6}H_{4};$	$Ar^2 = C_6 H_5 : 6e$
$Ar^{1} = C_{0}$ $Ar^{1} = C$	$_{6}^{5}H_{5}$.; $Ar^{2}=4$ $_{6}^{6}H_{5}$.; $Ar^{2}=4$	4-Cl-C ₆ H ₄ : 2-naphthyl	6b :6c		$Ar^{1} = C_{6}H_{5}; Ar^{2} = 4$ $Ar^{1} = C_{6}H_{5}; Ar^{2} = 4$ $Ar^{1} = CH_{3}; Ar^{2} = C$ $Ar^{1} = C_{6}H_{5}; Ar^{2} = 0$	1-NO ₂ -C ₆ H ₄ :6f 1-Me-C ₆ H ₄ : 6g ₆ H ₅ :6h CH ₃ :6i
	Michael	Michael				
entry	acceptor	donor	time (h)	product	yield (%) ^a	ee (%) ^b
1	6a	2	12	7a	95, 70, ^c 30, ^d	96, 48, ^c 5, ^d
					95, ^f 0 ^g	0, ^e 96 ^f
2	6b	2	15	7b	90	95
3	6c	2	18	7c	70	70
4	6a	2a	16	7d	95	82
5	6d	2a	24	7e	90	68
6	6e	2a	24	7f	84	66
7	6f	2a	20	7g	90	80
8	6g	2a	30	7h	74	63
9	6h	2a	72	7i	NR	0
10	6i	2a	72	7j	NR	0

^a Isolated yields. ^b Absolute configurations were found to be R. ^c With NA-MgO. d With CM-MgO. e With silvlated NAP-MgO. f Fifth cycle. ^g Without catalyst. Absolute configurations were determined to be R.

To widen the scope, a system composed of NAP-MgO-DAC in THF was evaluated in the AM reaction of different acyclic enones with nitromethane and 2-nitropropane. Chalcones provided good to excellent yields and ee's (Table 8, entries 1-7). Conversely, no AM reaction was observed using aliphatic enones.

It can be seen that the unsubstituted phenyls of chalcone gave the best ee. Substitution on either of the phenyls of the chalcones and the nature of substituents have a considerable impact on the stereochemistry of the products. With respect to the effect of substituents on the Ar² group, EW substituents gave higher enantioselectivity than did the ED substituents. Evaluating the effect of substituents in the Ar¹ group, the lowest asymmetric induction was found with the EW and ED substituents compared to Ar^2 (Table 8).

To understand the relation between structure and reactivity in both AH and AM reactions, it is better to know the structure and nature of the reactive sites of NAP-MgO. NAP-MgO has three-dimensional polyhedral structure, which having the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001, and 111) leads to inherently high surface reactivity per unit area. Thus, NAP-MgO indeed displayed the highest activity compared to that of NA-MgO and CM-MgO. Besides this, the NAP-MgO has a Lewis acid site Mg²⁺, Lewis basic sites O²⁻ and O⁻, lattice bound and isolated Bronsted hydroxyls, and anionic and cationic vacancies.²⁵ Both Henry and Michael reactions are known to be driven by base catalysts,²⁶ and accordingly, the surface -OH and O²⁻ of these oxide crystals are expected to trigger these reactions. To examine the role of -OH, the Sil-NA-MgO and Sil-NAP-MgO,²⁷ devoid of free -OH, were tested in AH and AM reactions. It is found that the silvlated MgO samples had reaction times longer than that of the corresponding MgO samples in both reactions, and no ee is observed (Tables 2 and 8, entry 1). These results indicate that Bronsted hydroxyls are the sole contributors for the ee, while they add on to the activity in AH and AM reactions, which is largely driven by Lewis basic O^{2-} and O^{-} sites. When protected hydroxyls of (S)-(-)-binol (Table 2) were used in place of (S)-(-)-binol in the AH reaction catalyzed by NAP-MgO, no ee was observed. Similarly, in the AM reaction, a bidentate system composed of at least one primary or secondary amine gave better ee's and tertiary amine gave no ee. These results establish that the hydrogen bond interactions between the -OH or -NH groups of chiral auxiliary and -OH groups of MgO are essential for the induction of enantioselectivity. Although both the NAP-MgO and NA-MgO possess defined shapes and the same average concentrations of surface -OH groups, a possible rationale for the display of higher ee by the NAP-MgO is that the -OH groups present on edge and corner sites on the NAP-MgO, which are stretched in three-dimensional space, are more isolated and accessible for the chiral ligand for greater alignment, whereas the hindered -OHs situated on flat planes in closer proximity with each other present in relatively large numbers on NA-MgO²⁸ disable proper alignment for the chiral ligand.

The XPS spectrum of the CH₃-NO₂ treated NAP-MgO for the Mg 2p exhibits two lines at 48.70 and 49.65 eV, which can be attributed to magnesium in NAP-MgO and Mg-C of O2N-H₂C-MgO (8),²⁹ respectively (Figure 1, Supporting Information). An endotherm at 450 °C that gives off a fragment (m/z =60 amu), corresponding to NO₂CH₂^{+•} in DTA-TGA-MS of the nitromethane-treated NAP-MgO (Figure 2, Supporting Information), further reiterates the formation of surface 8 moiety. When the nitromethane-treated NA-MgO was subjected to DTA-TGA-MS, no such endotherm is visible corresponding to 8. This is

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Scheme 3. Proposed Mechanism for Asymmetric Henry and Michael Reactions Catalyzed by NAP-MgO



due to the presence of low concentrations of Mg^+ ion (0.5%) in NA-MgO. In AH and AM reactions, O^{2-}/O^- of NAP-MgO abstracts an acidic proton of the nitromethane, giving a carbanion, which forms a complex with the unsaturated Mg^+ site (Lewis acid-type) of NAP-MgO. The AH and AM reactions proceed via dual activation of both substrates (nucleophiles and electrophiles) by NAP-MgO. Thus, the Lewis base (O^{2-}/O^-) of the catalyst activates nitroalkanes, and the Lewis acid moiety (Mg^{2+}/Mg^+) activates the carbonyls of aldehydes and enones (Scheme 3).³⁰

The activation of carbonyl through the Lewis acid site is indeed observed earlier in achiral Henry reaction.^{31a,b} The activation of carbonyls through hydrogen bonding by Lewis acids is also known.^{31c} Similarly, acid–base dichotomy is wellknown in biological systems.³² The chiral auxiliaries, binol, or DAC bound to NAP-MgO with proper alignment via hydrogen bonds direct the delivery of ⁻CH₂NO₂ stereoselectively to the Mg⁺ (Lewis acid)-activated carbonyl of aldehydes or chalcones via oxygen coordination to afford the chiral nitro alcohols or Michael adducts. The NAP-MgO was reused after heating the catalyst at 250 °C for 1 h under nitrogen atmosphere. Thus, the catalyst was reused five times, which showed consistent yields and ee's both in AH and AM reactions (Table 2, entry 1 and Table 8, entry 1). The reusable and suitably aligned nanocrystalline MgO with reactants catalyzed AH and AM reactions affords chiral nitro alcohols and Michael adducts with comparable ee's to that of the homogeneous systems.

Acknowledgment. K.V.S.R. and U.P. thank the CSIR India for the award of fellowship. Nanocrystalline MgO catalysts were obtained from NanoScale Materials Inc., Manhattan, Kansas, USA.

Note Added after ASAP Publication. In the version published on the Internet September 1, 2005, there was an error in Scheme 3. It is correct in the version published September 9, 2005, and in the print version.

Supporting Information Available: Experimental section and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0440248

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