

Bifunctional Nanocrystalline MgO for Chiral Epoxy Ketones via Claisen–Schmidt Condensation–Asymmetric Epoxidation Reactions

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Industry favors the catalytic process induced by a heterogeneous catalyst over the homogeneous one in view of its ease of handling, simple workup and regenerability. Heterogenization of the homogeneous catalysts presents a complex problem of conceptual transfer of molecular chemistry to surface metal–organic chemistry to realize a single-site catalyst with the retention of activity and enantioselectivity. We selected asymmetric epoxidation (AE) of the α,β -unsaturated ketones, an important organic transformation, since the resulting chiral epoxy ketones are versatile precursors to many natural products and drug molecules.¹ These epoxidation reactions were effected using various basic chiral auxiliaries such as polypeptides² under the phase-transfer conditions or in situ prepared chiral metal complexes, La/Yb/Zn-BINOL,³ magnesium tartrate,^{4a,b} and zinc ephedrine^{4c} systems in homogeneous media. In the direction of heterogenization, polymer-supported polypeptides,⁵ designed and synthesized by a simple process of anchoring, were employed successfully in AE of the α,β -unsaturated ketones. We chose a complex system based on nanocrystalline MgO to evolve a single-site catalyst, since the nanomaterial is expected to have a well-defined shape and size. We herein report the design and development of a truly recyclable, bifunctional nano heterogeneous catalyst for the Claisen–Schmidt condensation (CSC) of the benzaldehydes with acetophenones to yield chalcones followed by AE to afford chiral epoxy ketones with moderate to good yields and impressive enantioselectivities (ee's) in a two-pot reaction (Scheme 1, Table 1, method A).

Various magnesium oxide crystals⁶ [commercial MgO, CM-MgO (SSA: 30 m²/g), conventionally prepared MgO, NA-MgO (SSA: 250 m²/g), aerogel prepared MgO, NAP-MgO (SSA: 590 m²/g)] were initially evaluated in CSC and AE reactions separately in order to understand the relationship between structure and reactivity. All these MgO samples catalyzed both CSC of benzaldehyde with acetophenone to form chalcone quantitatively and selectively, and subsequent AE using (+)-diethyl tartrate (DET) as chiral auxiliary to obtain chiral epoxy ketone with good yield and impressive ee in a two-pot system. However, the nanocrystalline MgO (NAP-MgO) was found to be more active than the NA-MgO and CM-MgO in the condensation and epoxidation reactions (Figure 1, Table 1, Supporting Information [SI]). On the other hand, the ee of the product was shown to be 90, 60, and 0% using NAP-MgO, NA-MgO, and CM-MgO, respectively (Table 1, entry 1). When either of the benzaldehydes or acetophenones are substituted with electron-withdrawing groups, higher ee's were obtained than ee's for the ones bearing electron-donating groups using NAP-MgO (Table 1, entries 2–7). The CSC and AE with heteroaromatic compounds⁷ were also carried out by NAP-MgO, which gave very good ee's (Table 1, entries 8–10). Identical activity was observed for five cycles for the CSC (Figure 1, SI) and epoxidation (Table 1, entry 1) reactions.

Scheme 1. Claisen–Schmidt Condensation–Asymmetric Epoxidation Catalyzed by Nanocrystalline Magnesium Oxide

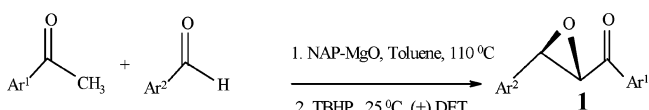


Table 1. Synthesis of Chiral Epoxides Using Nanocrystalline Magnesium Oxide

entry	Ar ¹	Ar ²	method	yield ^a (%)	ee (%) ^b
1	Ph	Ph	A	70, 58, ^c 30, ^d 0, ^e 70, ^f 0 ^g	90, 60, ^c 0, ^d 90 ^f
			B	60(68), ^h 15, ^b 0, ^c 0, ^d 60 ^f	82 (86), 0, ^c 82 ^f
2	4-MeC ₆ H ₄	Ph	A	70	80
			B	58(60)	50(54)
3	4-ClC ₆ H ₄	Ph	A	70	96
			B	40(58)	48(60)
4	4-OMeC ₆ H ₄	Ph	A	68	53
			B	56(59)	40(43)
5	Ph	4-ClC ₆ H ₄	A	52	97
			B	40(46)	58(70)
6	Ph	4-MeC ₆ H ₄	A	62	69
			B	51(53)	39(42)
7	Ph	4-NO ₂ C ₆ H ₄	A	52	98
			B	48(60)	48(63)
8	2-C ₄ H ₃ S	Ph	A	68	71
			B	(50)	(48)
9	2-C ₄ H ₃ O	Ph	A	70	84
			B	(48)	(46)
10	C ₆ H ₅	2-C ₃ H ₄ N	A	64	80
			B	(47)	(45)

^a Isolated yields. ^b Absolute configurations were determined to be ($\alpha R, \beta S$). See ref 2c. ^c With NA-MgO. ^d With CM-MgO. ^e With silylated NAP-MgO. ^f Fifth cycle. ^g Without catalyst. ^h Values in the parenthesis are after addition of 4Å molecular sieves. Method A: direct AE; method B: tandem CSC–AE.

These catalytic CSC reactions are very impressive when compared with the other systems, AlCl₃, BF₃, POCl₃, alumina, and Ba(OH)₂, which require more than the stoichiometric quantities, are nonregenerable, and offer low selectivity or conversions to desired products and the recently reported hydrotalcites and zeolites.^{8,9}

In the studies regarding the influence of various oxidants, chiral auxiliaries, solvents, and temperatures on enantioselectivity in the AE reaction, *tert*-butyl hydroperoxide (TBHP), DET, toluene, and –20 °C provided optimum results (SI, Tables 2–6). However, in the bifunctional single-pot CSC followed by AE reaction (Table 1, B), the ee's and conversions are lower than in the independent AE reactions. This is due to the poisoning effect of water adsorbed on the catalyst formed in situ in the CSC. Drying the catalyst under nitrogen flow for 1 h at 250 °C immediately after the CSC gave similar ee's in the AE which supports the above theory.

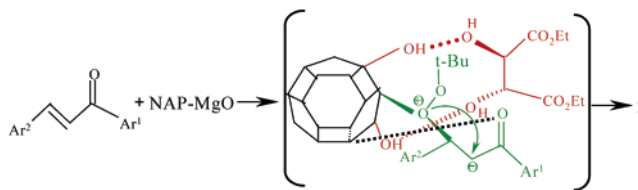
To understand the relationship between structure and reactivity, it is better to know the nature of the reactive sites of MgO, i.e.

(i) Mg^{2+} site, which is of Lewis-acid type, (ii) O^{2-} site, which is of Lewis-base type, (iii) lattice-bound hydroxyls, (iv) isolated hydroxyls, and (v) anionic and cationic vacancies.¹⁰ NAP-MgO has single-crystallite polyhedral structure, which has high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001, 111), which leads to inherently high surface reactivity per unit area. Thus, NAP-MgO indeed display the highest activity compared to that of NA-MgO and CM-MgO. CSC and epoxidation of deactivated olefins are naturally driven by base catalysts, and accordingly, the surface $-\text{OH}$ and O^{2-} of these oxide crystals are expected to trigger these reactions. To examine the role of $-\text{OH}$, the Sil-NA-MgO and Sil-NAP-MgO,^{10c} devoid of free $-\text{OH}$, are tested in CSC and epoxidation reactions. It was found that the silylated MgO samples had longer reaction times than the corresponding MgO samples in CSC and there was essentially no epoxidation reaction. These results indicate that Brønsted hydroxyls are sole contributors for the epoxidation reaction, while they add on to the CSC, which is largely driven by Lewis-basic O^{2-} sites. When protected hydroxyls of DET, (+)-diethyl-2,3-*O*-isopropylethene-*R,R*-tartrate (Table 3, SI), was used in place of DET in the AE reaction, no ee was observed, which establishes that the hydrogen-bond interactions between the $-\text{OH}$ groups of DET and 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 $-\text{OH}$ groups, a possible rationale for the display of higher ee by the NAP-MgO is that the $-\text{OH}$ groups present on edge and corner sites on the NAP-MgO are more isolated and accessible for the DET, whereas on NA-MgO relatively large portions of the $-\text{OH}$'s are situated on flat planes in closer proximity with each other and thus are hindered.^{6b} Conversely, CM-MgO, which showed no ee, has assorted crystals.

XPS spectrum of the TBHP treated-NAP-MgO for the O 1s exhibit two lines at 530.3 and 532.0, which can be attributed to lattice oxygen in MgO and dioxygen of magnesium peroxide,¹¹ respectively (Figure 2, SI). This provides evidence that peroxide is formed on interaction with the Lewis-acidic site of Mg^{2+} of NAP-MgO. An endotherm at 310 °C that gives off a fragment ($m/z = 89$ amu) corresponding to *tert*-butyl peroxide in DTA-TGA-MS of the TBHP-treated NAP-MgO (Figure 3, SI) further reiterates the formation of surface *tert*-butyl peroxide. When the TBHP-treated NA-MgO and CM-MgO are subjected to DTA-TGA-MS, no such endotherm is visible that corresponds to magnesium peroxide. This is due to presence of higher concentrations of Mg^{2+} ion (20%) in NAP-MgO. This also reinforces the argument in favor of a higher activity of NAP-MgO.

In the AE, the Mg ion of MgO reacts with TBHP to produce magnesium peroxide (ROO^-) and also interacts with the oxygen of the carbonyl function. The DET bound to the hydroxyls of NAP-MgO directs the delivery of nucleophilic oxygen of the peroxide¹² stereoselectively to give the chiral epoxy ketones (Scheme 2). The presence of electron-withdrawing groups on either of the two aromatic rings of the chalcone facilitate the formation of resonance-stabilized oxyanion, which might account for the higher ee's.

Scheme 2. Proposed Mechanism for Asymmetric Epoxidation of Unsaturated Ketones Using TBHP as an Oxidant



The chiral epoxy ketones obtained in the present AE reaction catalyzed by NAP-MgO show comparable ee's with an absolute configuration similar to that of the homogeneous system comprising dibutylmagnesium, DET, and TBHP. Thus, the nanocrystalline NAP-MgO with its defined shape, size, and accessible $-\text{OH}$ groups allows the chemisorption of TBHP, DET, and olefin on its surface to evolve successfully the single-site chiral catalyst by the successful transfer of molecular chemistry to surface metal-organic chemistry to provide the optimum ee's.

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Supporting Information Available: Characterization of the catalyst surface intermediates and chiral epoxy ketones; experimental procedures (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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