Bifunctional nanocrystalline MgO for chiral epoxy ketones via Claisen-Schmidt Condensation-asymmetric epoxidation reactions.

Boyapati M.Choudary*, Mannepalli L.Kantam, Kalluri V.S.Ranganath, Koosam Mahendar, Bojja Sreedhar

Indian Institute of Chemical Technology, Hyderabad 500 007, India.

Supporting Information

The commercial magnesium oxide (CM-MgO, S.A: 25 m^2/g) was purchased from Aldrich. The conventionally prepared magnesium oxide (NanoActive^{TM} MgO abbreviated as NA-MgO, S.A: 252 m^2/g) and aerogel prepared magnesium oxide (NanoActive^{TM} MgO Plus abbreviated as NAP-MgO: 590 m^2/gm) samples were purchased from NanoScale Materials Inc, Manhattan, KS 66502, USA. All the samples were activated at 250 ºC before use. Benzaldehyde, substituted benzaldehydes and acetophenones, (+)-diethyl tartrate, (S)-binol, (-)-ephedrine, (-)-pseudoephedrine were purchased from Aldrich and used as such. Toluene was purchased from commercial sources and dried before use. TBHP in toluene was purchased from Fluka and used as such. Silylated NAP-MgO, NA-MgO and (+)-diethyl-2,3-O-isopropyledene-R,R-tartrate were prepared according to the literature.[1,2]

General: ^1H spectra were recorded on a Varian Gemini 200 MHz Spectrometer. Chemical shifts (δ) are reported in ppm, using TMS as an internal standard. High Performance Liquid Chromatography (HPLC) was performed using the following apparatus; SHIMADZU LC-10AT (liquid Chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. TGA-DTA-MS thermograms were recorded on Mettler-Toledo TGA/SDTA 851^e instrument coupled to MS Balzers Thermostar GSD 300T using open alumina crucibles, containing 8-10 mg of the sample with a linear heating in the temperature range of 25 -1000 ºC at a rate of 10 ºC/min in nitrogen atmosphere. ACME silica gel (100-200 mesh) was used for column chromatography and thin layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Optical rotations were obtained on a Jasco P-1020 Polarimeter and reported as follows
$[\alpha]^{temperature}_{wavelength}$, concentration (c = g/100 mL), and solvent.
X-ray photoemission spectra were recorded on a KRATOS AXIS 165 with a dual anode (Mg and Al) apparatus using the Mg Kα anode**.** The pressure in the spectrometer was about 10^{-9} Torr. For energy calibration, we have used the carbon 1s photoelectron line. The carbon 1s binding energy was taken to be 285.0 eV. Spectra were deconvoluted using the Sun Solaris based Vision 2 curve resolver. The location and the full width at half maximum (FWHM) for a species were first determined using the spectrum of a pure sample. The location and FWHM of the products, which were not obtained as pure species, were adjusted until the best fit was obtained. Symmetric Gaussian shapes were

used in all cases. Binding energies for identical samples were, in general, reproducible to within ± 0.1 eV.

General procedure for the preparation of 1,3-diphenyl-2-propenone (chalcone):
A mixture of acetophenone (3mmol, 0.35 mL), benzaldehyde (2.5 m.mol, 0.254 mL) and catalyst (0.175 g) was introduced into a 50 mL round bottomed flask containing 10 mL of dry toluene and stirred under reflux for 12 h under nitrogen atmosphere (to avoid benzaldehyde oxidation to benzoic acid). After completion of the reaction, (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel using 5% ethyl acetate in petroleum ether, the chalcone was obtained.

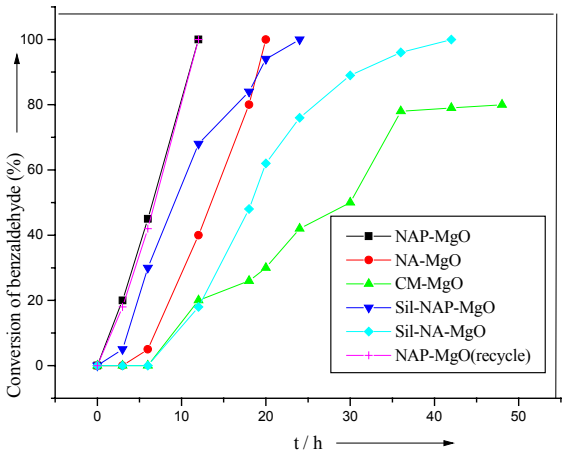

Figure 1: Claisen-Schmidt condensation of benzaldehyde with acetophenone using different crystallites of magnesium oxide at 110 ºC

As can be seen from the Figure 1, that the NAP-MgO can be recycled five times without loss of activity and selectivity by activating the catalyst under nitrogen flow for1 h at 250 ºC.
In CSC, it is observed that any of the reactants with substituent groups in either of the two aromatic rings proceeds at slower rate than the unsubstituted reactants. This can be explained by means of geometric effects related to diffusional problems due to the presence of larger groups.[3]

Table S1: NAP-MgO catalyzed Claisen-Schmidt condensation of benzaldehydes with acetophenones

Entry	Ar^1	Ar^2	Time (h) [a]	Yield (%) [d]
1	C_6H_5	C_6H_5	12	98
2	4-Me-C_6H_4	C_6H_5	13	98
3	4-Cl-C_6H_4	C_6H_5	16	99
4	4-OMe-C_6H_4	C_6H_5	16	98
5	C_6H_5	4-Cl-C_6H_4	17	98
6	C_6H_5	4-Me-C_6H_4	14	97
7	C_6H_5	4-NO_2-C_6H_4	18	97
8	2-OH-C_6H_4	C_6H_5	16[b]	60
9	2-NH_2-C_6H_4	C_6H_5	15[c]	54
10	2,4-OMe-C_6H_3	4-OMe-C_6H_4	20	97
11	2-C_4H_3S	C_6H_5	18	97
12	2-C_4H_3O	C_6H_5	18	97
13	C_6H_5	2-C_5H_4N	13	97

[a] Conditions: ketone (3mmol), aldehyde (2.5 mmol) and catalyst (0.175 g). [b] The byproduct formed is flavanone. [c] The byproduct formed is 2-Aryl-1, 2,3,4-tetrahydro-4-quinolones. [d] Isolated yields. Conversions are 100% in all cases

General procedure for the preparation of chiral epoxide:

Chalcone (0.500 g, 2.5 mmol), TBHP (3.7 M in toluene, 4.0 mL, 15mmol), NAP-MgO (0.200 g), and (+)-diethyl tartrate (0.047l g, 0.275 mmol) were placed under nitrogen atmosphere in a dry 50 mL flask containing 15 mL of dry toluene (additional 1 mL of THF for substituted chalcones) and stirred at 25 ºC for 36 h. After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed with ether. The filtrate was quenched with saturated aqueous NH_4Cl (10 mL), and 10% aqueous Na_2SO_3 (15 mL) and diethyl ether (10 mL) was added. The aqueous layer was washed with diethyl ether (3x10 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel using 20% ethyl acetate in petroleum ether, the corresponding α,β-epoxy ketone was obtained.

(+)-Diethyl tartrate can be recovered quantitatively with no observable change in enantiomeric purity from the same chromatographic column by increasing the proportion of ethyl acetate in the eluent.

General procedure for the Tandem Claisen-Schmidt condensation-asymmetric epoxidation of chalcones.

A mixture of acetophenone (3mmol, 0.35 mL), benzaldehyde (2.5 mmol, 0.254 mL), and 4Aºmolecular sieves (0.500g) and NAP-MgO (0.200 g) was introduced into a 50 mL round bottomed flask containing 15 mL of dry toluene and stirred under reflux for 12 h

under nitrogen atmosphere (to avoid benzaldehyde oxidation to benzoic acid). After completion of the reaction, (monitored by TLC), the heating was stopped and the reaction mixture was allowed to reach 25 ºC. A mixture of anhydrous solution of *tert*-butyl hydroperoxide (3.7M in toluene, 4.0 mL, 15 mmol), (+)-diethyl tartrate (0.047 mL, 0.275 mmol) were added and stirred (additional 1 mL of THF for substituted chalcones). After completion of the epoxide formation (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed with ether. The filtrate was quenched with saturated aqueous NH_4Cl (10 mL), and 10% aqueous Na_2SO_3 (15 mL) and diethyl ether (10 mL) was added. The aqueous layer was washed with diethyl ether (3x10 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel using 20% ethyl acetate in petroleum ether, the α,β-epoxy ketone was formed. (+)-Diethyl tartrate can be recovered quantitatively with no observable change in enantiomeric purity from the same chromatographic column by increasing the proportion of ethyl acetate in the eluent.

Reuse of the catalysts:
The reusability of the catalysts was checked by performing the AE of chalcone on 10-mmol scale. After completion of the reaction, the catalyst was recovered by centrifugation and activated under nitrogen flow for 1 h at 250 ºC.

Characterization of Products: The following compounds are known compounds, and their spectra were in accordance with those reported in the literature. The absolute configuration of epoxide was determined by comparison of the specific rotation with literature value. The enantiomeric excess of the epoxide was determined by HPLC analysis with chiral stationary phases.

***trans*-(2R,3S)-Epoxy-1, 3-diphenylpropan-1-one**. $[\alpha]^{25}{}_{D}$ -220 (c 1.0, CH_2Cl_2) [Lit.[4] -229 (c 1.0, CH_2Cl_2)]; ^{1}H NMR δ 4.07 (d, 1 H, *J*=2.0 Hz,), 4.27 (d, 1 H, *J* =2.0 Hz), 7.25-8.10(m, 10 H); HPLC (Diacel Chiralcel OJ, 10% isopropanol in hexane, flow rate 1.0 mL /min)**:** t_R =11.2 (minor), 11.8 (major).

***trans*-(2R,3S)-Epoxy-1-(4-methylphenyl)-3-phenylpropan-1-one.** $[\alpha]^{25}{}_{D}$ -182 (c 1.0, CH_2Cl_2) [Lit.[4] -198 (c1.0, CH_2Cl_2)]; ^{1}H NMR δ 2.3 (s, 3 H), 4.07 (d, 1 H, J=1.6 Hz), 4.27 (d, 1 H, J=1.6 Hz), 7.30-8.10 (m, 9 H). HPLC (Diacel Chiralcel OJ, 10% isopropanol in hexane, flow rate 1.0 mL /min)**:** t_R =9.5 (minor), 12.0(major).

***trans*-(2R,3S)-Epoxy-1-(4-chlorophenyl)-3-phenylpropan-1-one**. $[\alpha]^{25}{}_{D}$ -198 (c 1.0, CH_2Cl_2) [Lit.[5] -202 (c 2.0, CH_2Cl_2)]; ^{1}H NMR δ 4.21 (d, 1 H, J=1.7 Hz), 4.03 (d, 1 H, J=1.7 Hz), 7.25-8.10(m, 9 H). HPLC (Diacel Chiralcel OJ, 10% isopropanol in hexane, flow rate is 1mL /min) **:** t_R =9.3 (minor), 10.0(major).

***trans*-(2R,3S)-Epoxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one**. $[\alpha]^{25}{}_{D}$ -99 (c 1.0, CH_2Cl_2) [Lit.[5] –164 (c 2.0, CH_2Cl_2)]; ^{1}H NMR (CCl_4) δ 3.65 (s, 3 H), 3.85 (d, 1 H, J=1.8 Hz) 4.05 (d, 1 H, *J*=1.8 Hz), 6.70-7.90(m, 9 H,). HPLC (Diacel Chiralcel OJ, 10% isopropanol in hexane, flow rate is 1.0 mL /min)**:** t_R =13.4 (minor), 15.0(major).

***trans*-(2R,3S)-Epoxy-3-(4-methylphenyl)-1-phenylpropan-1-one.** $[\alpha]^{25}{}_{D}$ -172 (c 1.0, CH_2Cl_2) [Lit.[4] -210 (c 1.0, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 4.27 (d, 1 H, J=1.6 Hz), 4.07 (d, 1 H, , J=1.6 Hz), 7.25-8.10 (m, 9 H,). HPLC (Diacel Chiralcel OD, 10% isopropanol in hexane, flow rate is 0.5mL /min)**:** t_R =18.6 (minor), 20.2 (major).

***trans*-(2R,3S)-Epoxy-3-(4-chlorophenyl)-1-phenylpropan-1-one.** $[\alpha]^{25}_D$ -233 (c 1.0, CH_2Cl_2) [Lit.[4] -195 (c 1.0, CH_2Cl_2)]; ^{1}H NMR δ 4.21 (d, 1 H, *J*=1.8Hz), 4.03 (d, 1 H, *J*=1.8H*z*), 7.20-8.20(m, 9 H). HPLC (Diacel Chiralcel OD,2% isopropanol in hexane , flow rate is 0.5 mL /min)**:** t_R = 38.5 (minor), 40.6(major).

***trans*-(2R,3S)-Epoxy-3-(4-nitrophenyl)-1-phenylpropan-1-one.** $[\alpha]^{25}_D$ -245 (c 1.0, CH_2Cl_2) [Lit.[6] -205 (c 1.184, CH_2Cl_2); ^{1}H NMR δ 4.30 (d, 1 H, *J*=1.5 Hz), 4.21 (d, 1 H, *J*=1.5 Hz), 7.30-8.30 (m, 9 H). HPLC (Diacel Chiralcel OJ, 10% isopropanol in hexane, flow rate is 1.2 mL /min)**:** t_R =17.7 (minor), 19.6 (major).

***trans*-(2R,3S)-Epoxy-1-phenyl-3-(2-pyridyl)propan-1-one.** $[\alpha]^{25}_D$ -153 (c 1.0, $CHCl_3$) [Lit.[7] -161 (c 1.104, $CHCl_3$); ^{1}H NMR δ 4.21 (d, 1 H, J= 2.0 Hz), 4.57 (d, 1H, J=2.0 Hz), 7.30-8.60 (m, 9 H). HPLC (Diacel Chiralpak AD column, 20% isopropanol in hexane, flow rate 1.0 mL/min)**:** t_R= 13.2 (minor), 15.4(major)

***trans*-(2R,3S)-Epoxy-3-phenyl-1-(2-furyl)propan-1-one.** $[\alpha]^{25}_D$ -200 (c 1.0, $CHCl_3$) [Lit. [7] -161 (c 1.1, $CHCl_3$) ; ^{1}H NMR δ 4.13 (d, 1 H, J= 1.8 Hz), 4.15 (d, 1 H, J= 1.8 Hz), 6.6-7.68 (m, 8H). HPLC (Diacel Chiralpak AD column, 10% isopropanol in hexane, flow rate 1.0 mL/min)**:** t_R= 15.35 (minor), 16.8(major)

***trans*-(2R,3S)-Epoxy-3-phenyl-1-(2-thienyl)propan-1-one** $[\alpha]^{25}_D$ -189 (c 1.0, CH_2Cl_2) [Lit.[6] -214 (c 1.04, CH_2Cl_2) ; ^{1}H NMR δ 4.03 (d, 1 H, J= 2.0 Hz), 3.76 (d, 1 H, J= 2.0 Hz), 6.53-7.03 (m, 8 H). HPLC (Diacel Chiralpak AD column, 10% isopropanol in hexane, flow rate 1.0 mL/min)**:** t_R= 11.52 (minor), 12.2(major)

In AE, it is also noticed that any of the chalcone with substituent groups on either of the two aromatic rings gives lower yields than the unsubstituted chalcone. This can be explained by means of geometric effects related to diffusional problems due to the present of larger groups.

Table S2: Effect of oxidant on the epoxidation of 1,3-diphenyl-2-propenone catalyzed by NAP-MgO at 25 ºC

Entry	Oxidant	Time (h)	Yield (%) [a]
1	TBHP	36	70[b], 82[c]
2	30% H_2O_2	48	--
3	$NaIO_4$	48	20
4	m-CPBA	48	28
5	O_2	48	10
6	oxone	72	---

[a] Isolated yields. [b] Conditions: Chalcone (0.500 g, 2.5 mmol), TBHP (3.7 M in toluene, 4.0 mL, 15mmol), NAP-MgO (0.200 g), Toluene (10 mL), (+)-Diethyl tartrate (0.047l g, 0.275 mmol). [c] When 4A° MS was added (powder).

Table S3: Effect of ligand in the asymmetric epoxidation of 1,3-diphenyl-2-propenone catalyzed by NAP-MgO at 25 °C.

Entry	Ligand	Yield	e.e(%)
1	(+)-DET	70	90[a]
2	(-)-DET	70	88[b]
3	(S)-Binol	53	28
4	-(-)Ephedrine	50	--
5	(-) Pseudoephedrine	52	--
6	(+)-Diethyl-2, 3-O-isopropyledene-R,R-tartrate	70	--

[a] Absolute configurations were determined to be (αR, βS)[8]; [b] Absolute configurations were determined to be (αS, βR). In all cases 11 mol% of ligand was used. Enantiomeric excess was measured by Diacel Chiralcel HPLC using OJ column with 10% isopropanol in hexane.

Table S4: Effect of temperature in the asymmetric epoxidation of 1,3-diphenylprop-2-en-1-one catalyzed by NAP-MgO using (+)-DET as a chiral modifier.

Entry	Conversion(%)	Temperature (ºC)	ee (%)
1	70	25	90
2	24	0	94
3	15	-20	96
4	80	40	38

Conditions: Chalcone (0.500 g, 2.5 mmol), TBHP (3.7 M in toluene, 4.0 mL, 15mmol), NAP-MgO (0.200 g), Toluene (10 mL), (+)-Diethyl tartrate (0.047l g). Enantiomeric excess was measured by Diacel Chiralcel HPLC using OJ column with 10% isopropanol in hexane.

We studied Claisen-Schmidt condensation and AE reactions with different solvents and the reaction in toluene afforded higher yields than other solvents (Table S5 & S6). Although THF showed same influence in terms of yields as that toluene in epoxidation reaction, we used toluene primarily, because it is the best solvent for both the AE and CSC reactions. However, a mixture of Toluene-THF was used for the AE reaction as the substituted chalcones have low solubility in toluene**.**

Table S5: Effect of solvents on the Claisen-Schmidt condensation of benzaldehyde and acetophenone catalyzed by NAP-MgO**.**

Entry	Solvent	Time (h)	Yield (%)
1	Toluene	12	98
2	THF	12	25
3	DMF	22	90
4	Benzene	18	97
5	1,2 dichloroethane	12	50
6	Heptane	16	96
7	Acetonitrile	16	92
8	Dioxane	24	No reaction
9	Ethanol	24	No reaction

Conditions: ketone (3mmol), aldehyde (2.5 mmol) and catalyst (0.175 g), dry solvent (10 mL)

Table S6**:** Effect of solvents on the epoxidation of chalcone catalyzed by NAP-MgO at 25 ºC

entry	Solvent	Time (h)	Yield (%)[a]
1	Toluene	36	70
2	THF	36	70
3	Heptane	36	65
4	Methanol	48	55
5	Acetonitrile	36	50

[a] Isolated yields. Conditions: Chalcone (0.500 g, 2.5 mmol), TBHP (3.7 M in toluene, 4.0 mL, 15mmol), NAP-MgO (0.200 g), dry solvent (10 mL)

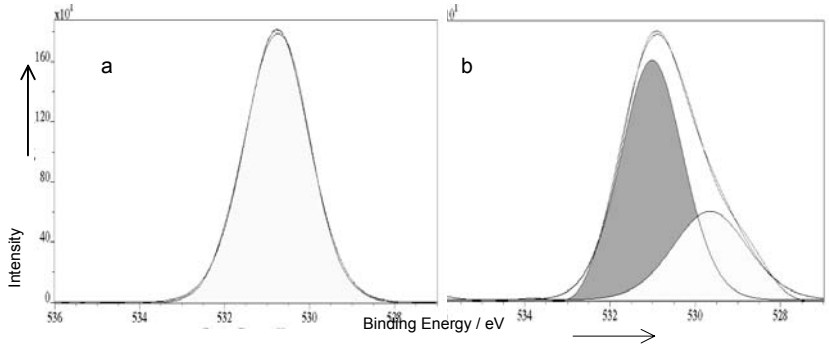

***Figure** 2:*XPS of O1s for a) fresh NAP-MgO b) TBHP-treated NAP-MgO

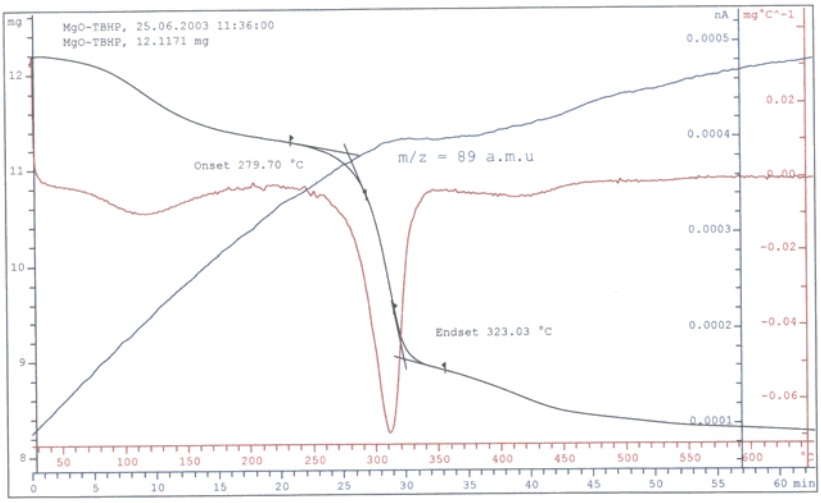

Figure 3: DTA-TGA-MS of TBHP treated NAP-MgO

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