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The One-Pot Wittig Reaction: A Facile Synthesis of α,β-Unsaturated Esters and Nitriles by Using Nanocrystalline Magnesium Oxide

Boyapati M. Choudary,[a,*] Koosam Mahendar ,[b] M. Lakshmi Kantam,[b,*] Kalluri V. S. Ranganath,[b] and Taimur Athar[b]

[a] Ogene Systems (I) Pvt. Ltd, # 11-6-56, GSR Estates, Moosapet, Hyderabad, 500037, India
Fax: (+91)-40-2377-5566; e-mail: bmchoudary@yahoo.com
[b] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax: (+91)-40-27160921or; e-mail: lkmannepalli@yahoo.com

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Abstract: Nanocrystalline magnesium oxide was found to be an effective heterogeneous, solid base catalyst for the one-pot Wittig reaction to afford α,β-unsaturated esters and nitriles in excellent yields with high *E*-stereoselectivity in the presence of triphenylphosphine under mild conditions.

Keywords: α-fluoro-α,β-unsaturated esters; nanocrystalline magnesium oxide; triphenylphosphine; α,β-unsaturated esters; Wittig reaction

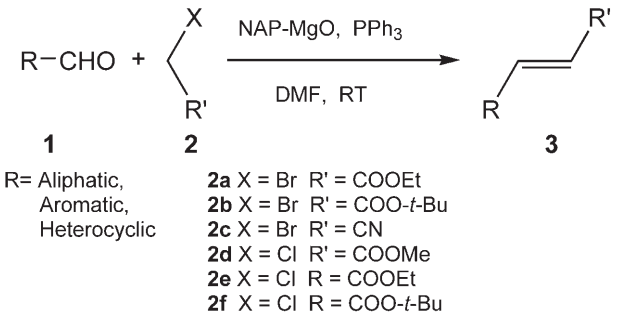
Introduction

The development of methods for the stereoselective formation of C=C double bonds represents one of the most important challenges in organic synthesis.[1] The Wittig reaction and its variants have been acknowledged as powerful and versatile tools in organic synthesis for the formation of C=C double bonds.[2] The most important intermediates for several biologically active molecules[3] ánd fluoro compounds[4] have been synthesized through the Wittig reaction.

The most impressive variant in the Wittig reaction is the replacement of the three step-process, involving the preparation of a phosphonium salt, followed by base treatment to give an ylide, and subsequent reaction with carbonyl compounds to give olefinic products, with a one-pot synthesis. α,β-Unsaturated esters are obtained directly in one pot in good yields by the reaction of an aldehyde with methyl bromoacetae using *n*-Bu_3P/Zn at 100 °C[5] with catalytic amounts of tributylarsine or dibutyl telluride[6] or PEG-supported telluride[7] in the presence of triphenyl phosphite in stoichiometric amounts. Other reports[8] include the use of ethyl diazoacetate (EDA) instead of α-bromo esters in the above protocol by using catalytic amounts of iron, ruthenium, or cobalt porphyrin complexes or ruthenium and rhenium complexes in the presence of PPh_3, $P(OMe)_3$, $P(OEt)_3$ or other PPh_2R ligands. Lebel et al. reported the methylenation of aldehydes by rhodium complexes in the presence of PPh_3 using CH_2N_2 or $TMSCHN_2$ as the diazo precursors.[9] The Wadsworth–Emmons (WWE) reaction is also a widely used method for the preparation of α,β-unsaturated esters as a well established alternative to the Wittig olefination. The phosphonate anions are strongly nucleophilic and react readily with aldehydes to form olefins. Generally, the WWE is performed in the presence of relatively strong bases such as *n*-butyllithium, potassium *tert*-butoxide, sodium hydride, LDA, DBU, Triton B, *N*-ethylpiperidine etc. under homogenous conditions.[2b,10]

Some of the catalysts are expensive, complex or poorly available and reactions are performed in the homogenous conditions, which contaminates the products and restricts use in industry. As a result of the increased environmental consciousness in chemical research and industry, efforts are now directed towards heterogenization. We reported earlier on the WWE reaction by using the heterogeneous solid base catalysts Mg-Al-hydrotalcite-O-*t*-Bu and NAP-MgO.[11]

Nanocrystalline metal oxides[12a,b] have been efficiently used as absorbents for gases and destruction of hazardous chemicals and as catalysts for organic transformations.[11b,12c–g] These high reactivities are due to high surface areas combined with unusually reac-



Scheme 1. NAP-MgO-catalyzed Wittig reaction between aldehydes and α-halo esters or nitriles.

Table 1. Wittig reaction between benzaldehyde and ethyl bromoacetate/PPh_3 with various catalysts[a].

Entry	Catalyst	Time [h]	Yield [%][b]	*E*/*Z*[c]
1.	NAP-MgO	8	96	99:1
2.	NA-MgO	17	95	99:1
3.	CM-MgO	23	94	97:3
4.	Sil-NAP-MgO	18	92	99:1
5.	Sil-NA-MgO	32	90	99:1

[a] *Reaction conditions:* benzaldehyde (1 mmol), ethyl bromoacetate (1 mmol), PPh_3 (1 mmol), catalyst (0.075 g), DMF (5 mL) at room temperature.
[b] Isolated yield.
[c] The ratio of *E:Z* isomers was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 2. Optimization of Wittig reaction of benzaldehyde with ethyl bromoacetate/PPh_3 catalyzed by NAP-MgO[a].

Entry	Solvent	Time [h]	Yield [%][b]	*E*/*Z*[c]
1.	Toluene	2[d]	–	–
2.	Toluene/DMF (1:1)	15	74	99:1
3.	DMF	8	96	99:1
4.	Acetonitrile	17	90	99:1
5.	THF	18	86	98:2
6.	1,4-Dioxane	20	84	99:1
7.	Methanol	8	94	84:16

[a] *Reaction conditions:* benzaldehyde (1 mmol), ethyl bromoacetate (1 mmol), PPh_3 (1 mmol), catalyst NAP-MgO (0.075 g), solvent (5 mL) at room temperature.
[b] Isolated yield.
[c] The ratio of *E:Z* isomers was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[d] In toluene after 2 h, the catalyst sticks to the flask walls.

tive morphologies. Herein, we report an effective one-pot Wittig reaction to afford α,β-unsaturated esters and nitriles in excellent yields with high *E*-stereoselectivity by using nanocrystalline magnesium oxide catalyst (NAP-MgO) (Scheme 1).

Results and Discussion

Various magnesium oxide crystals [commercial MgO, CM-MgO (SSA: 30 $m^2 g^{-1}$), conventionally prepared MgO, NA-MgO (SSA: 250 $m^2 g^{-1}$), aerogel prepared MgO, NAP-MgO (SSA: 590 $m^2 g^{-1}$)] were initially evaluated in the Wittig reaction with benzaldehyde, ethyl bromoacetate and PPh_3 at room temperature in order to understand the relationship between structure and reactivity. All these MgO crystals catalyze the Wittig reaction in quantitative yields. However, the nanocrystalline MgO (NAP-MgO) was found to be more active than NA-MgO and CM-MgO in the Wittig reaction (Table 1).

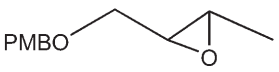
In the studies regarding the effect of various solvents, the reaction was conducted between benzaldehyde and ethyl bromoacetate, in the presence of triphenylphosphine and NAP-MgO with different solvents like toluene, acetonitrile, THF, 1,4-dioxane, toluene/DMF (1:1), methanol and DMF (Table 2). When we take DMF alone as a solvent at room temperature, the desired olefin could be obtained in quantitative yields with excellent stereoselectivity. In all the other solvents, the olefinated product was isolated in low yields. In methanol, the olefinated product was obtained quantitatively, but with poor stereoselectivity compared to the reaction conducted in DMF (Table 2, entry7). Therefore, we conclude that DMF is a suitable solvent for this reaction. We have also tested different organic [$P(OPh_3)$, $P(OMe_3)$] and inorganic [$NaHSO_3$, Na_2SO_3] reducing agents under the same reaction conditions, but all are inactive.

To determine the generality of this reaction, a variety of structurally different aldehydes with different α-halo esters including methyl, ethyl, *tert*-butyl substituted ones and α-bromoacetonitrile were employed and the results are summarized in Table 3. It was found that aliphatic, aromatic and heterocyclic aldehydes afforded good to excellent yields with high stereoselectivity. As expected the rate of the reaction is

Table 3. Wittig reaction of different aldehydes with various α-halo esters and bromoacetonitrile catalyzed by NAP-MgO[a].

Entry	Aldehyde **1**	Substrate **2**	Time [h]	Yield of **3** [%][b]	*E*/*Z*[c]
1	C_6H_5-	**2a**	8	96	99:1
2		**2b**	10	94	99:1
3		**2c**	14	96	50:50
4		**2d**	26	92	98:2
5		**2e**	28	90	99:1

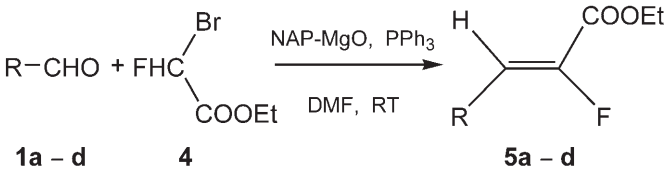
Table 3. (Continued)

Entry	Aldehyde **1**	Substrate **2**	Time [h]	Yield of **3** [%][b]	*E*/*Z*[c]
6	C_6H_5	**2f**	32	90	96:4
7	4-$NO_2C_6H_4$-	**2a**	3, 3[d], 3[e]	98, 95[d], 98[e]	99:1
8		**2b**	4	97	99:1
9		**2c**	9	97	36:74
10		**2d**	20	96	96:4
11	4-ClC_6H_4-	**2a**	4	95	99:1
12		**2b**	9	92	99:1
13	2-$NO_2C_6H_4$-	**2a**	3	96	96:4
14	2-ClC_6H_4-	**2a**	4	94	96:4
15	3-CNC_6H_4-	**2a**	4	98	99:1
16		**2b**	4	96	99:1
17		**2c**	9	96	23:77
18	4-$COOHC_6H_4$-	**2a**	7	94	99:1
19		**2b**	9	94	99:1
20	4-$CH_3C_6H_4$-	**2a**	12	89	99:1
21		**2b**	12	86	99:1
22	4-$CH_3OC_6H_4$-	**2a**	14	88	99:1
23		**2b**	16	86	99:1
24		**2c**	18	89	44:56
25		**2d**	32	88	98:2
26	3,4-$Cl_2C_6H_3$-	**2a**	6	92	99:1
27		**2b**	5	94	99:1
28	4-$CF_3C_6H_4$-	**2a**	3	94	99:1
29		**2b**	3	96	99:1
30	4-BnO,3-$MeOC_6H_3$-	**2a**	16	76	99:1
31		**2b**	20	79	99:1
32	2-naphthyl-	**2a**	10	91	99:1
33		**2b**	8	88	99:1
34		**2c**	12	92	55:45
35	*trans*-$C_6H_4CH{=}CH$-	**2a**	12	82	99:1
36		**2b**	10	86	99:1
37	1-(2-Br)-piperanyl	**2a**	4	93	92:8
38		**2b**	3	94	91:9
39	2-furfuryl-	**2a**	6	90	99:1
40		**2b**	5	93	99:1
41		**2c**	10	95	48:52
42		**2d**	24	92	99:1
43	2-pyridyl	**2a**	8	91	99:1
44		**2b**	6	94	99:1
45	2-(1-Me)-imidazolyl	**2a**	3	90	99:1
46		**2b**	3	96	99:1
47	cyclohexyl-	**2a**	10	83	99:1
48		**2b**	8	88	99:1
49	$CH_3(CH_2)_5$-	**2a**	11	81	99:1
50		**2b**	10	88	99:1
51		**2d**	20	91	95:5
52	$CH_3CH(CH_3)CH_2$-	**2a**	11	82	99:1
53		**2b**	11	86	99:1
54[f]		**2a**	5	90	99:1
55		**2b**	4	86	99:1

[a] *Reaction conditions:* aldehyde (1 mmol), α-halo ester or bromoacetonitrile (1 mmol), PPh_3 (1 mmol), catalyst NAP-MgO (0.075 g), DMF (5 mL) at room temperature.
[b] Isolated yield.
[c] The ratio of *E*:*Z* isomers was determined by ^{1}H NMR spectroscopy of the crude reaction mixtures.
[d] 2nd cycle.
[e] 4th cycle.
[f] PMB = *p*-methoxybenzyl.

faster with benzaldehydes having electron-withdrawing groups than the substrates bearing an electron-donating group. Aromatic aldehydes with electron-withdrawing groups in any position on aromatic ring gave excellent yields (entries 7–19, 26–29). Electron-donating group containing aromatic aldehydes gave good yields (entries 20–25). Highly conjugated aromatics like naphthaldehyde and cinnamaldehyde (entries 32–36), heteroaromatic aldehydes (entries 39–46) and aliphatic aldehydes (entries 47–53) afforded good yields. When we did the reaction with a vanillin derivative (entries 30, 31) moderate yields were obtained, which might be due to bulky and electron-donating groups on the aromatic ring. γ,δ-Epoxy-α,β-unsaturated esters, useful building blocks, could also be synthesized by the current method in good yields with excellent stereoselectivity (entries 54 and 55). In most of these α,β-unsaturated esters, the traditional *E*-stereoselectivity was maintained, compared with typical Wittig reactions of stabilized ylides. But a substituent at the *ortho*-position of an aromatic aldehyde shows little difference in stereoselectivity (entries 13, 14, 37, 38) that might be due to an *ortho* steric effect. In the reaction between aldehyde and α-chloro esters, the olefinated product (entries 4, 5, 6, 10, 25, 42, 51) was obtained quantitatively, with high stereoselectivity in longer reaction times compared to α-bromo esters, which might be due to the difference in electronegativity between chlorine and bromine. We have also prepared α,β-unsaturated nitriles by this method in excellent yields (entries 3, 9, 17, 24, 34, 41) but with poor stereoselectivity. The increase in *Z*-isomer is due to the lower steric requirements of the linear cyano group.

A fluorine atom substitution, adjacent to the ester moiety, increases significantly the biological activity of these compounds, as exemplified in vitamin A and pheromone chemistry.[4a] We have also synthesized α-fluoro-α,β-unsaturated esters (**5**) (Scheme 2, Table 4), a useful class of intermediates in the synthesis of a variety of biologically active fluoro compounds such as retinoids, insect sex pheromones, and pyrethroids[13,4c] through a Wittig reaction under these optimized conditions in moderate yields[14a] with *Z*-selectivity (Scheme 2, Table 4). The rate of the reaction is faster with a benzaldehyde having an electron-withdrawing group than with substrates bearing electron-donating groups.



Scheme 2. Wittig reaction of various benzaldehydes with ethyl bromofluoroacetate by using NAP-MgO.

Table 4. Synthesis of α-fluoro-α,β-unsaturated esters by using NAP-MgO.[a]

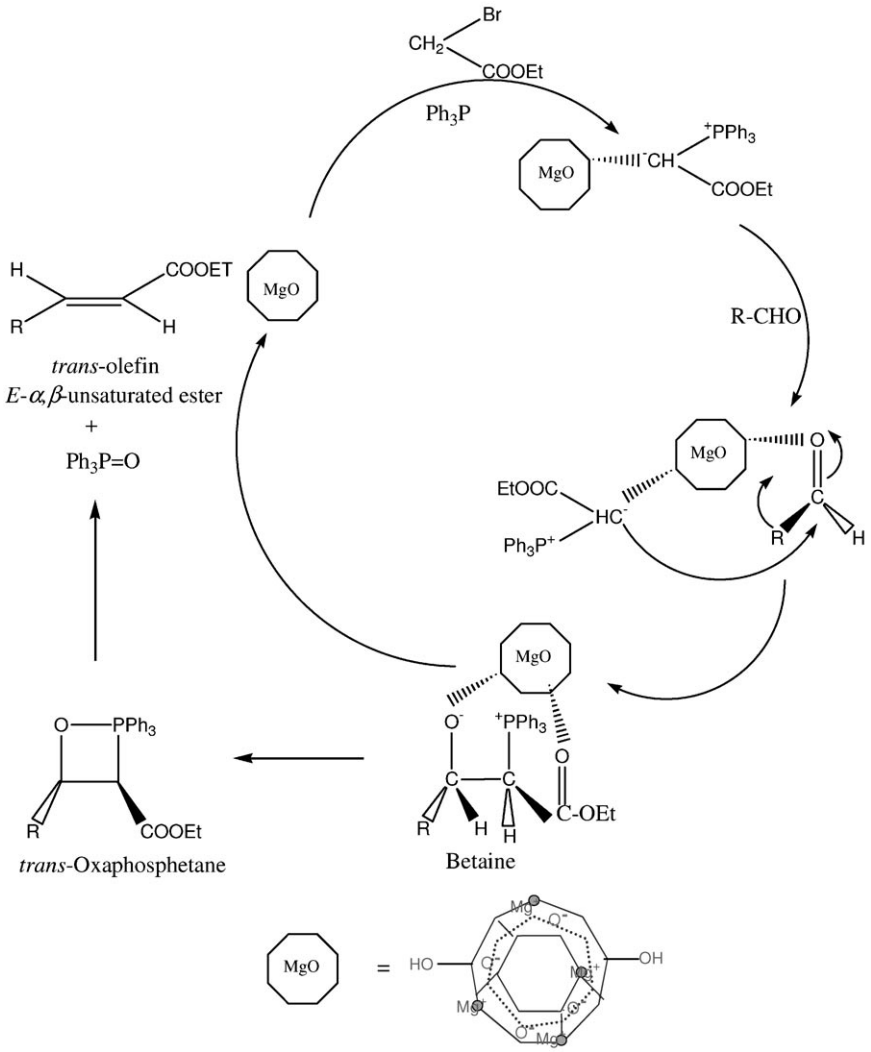
Entry	Aldehyde (R)	Time [h]	Yield [%][b]	*E*/*Z*[c]
1.	C_6H_5- (**a**)	40	56	10:90
2.	4-$NO_2C_6H_4$- (**b**)	36	69	29:71
3.	4-$CH_3OC_6H_4$-(**c**)	48	42	9:91
4.	3-CNC_6H_4- (**d**)	36	67	16:84

[a] *Reaction conditions:* Aldehyde (1 mmol), ethyl bromofluoroacetate (1 mmol), PPh_3 (1 mmol), catalyst NAP-MgO (0.075 g), DMF (5 mL) at room temperature.
[b] Isolated yield.
[c] The ratio of *E:Z* isomers was determined by ^{19}F NMR[14b] spectroscopy of the crude reaction mixtures.

In our mechanistic studies, there was no reaction between benzaldehyde and ethyl bromoacetate on using NAP-MgO in the absence of PPh_3, whereas only 5% conversion was observed in the presence of PPh_3 without NAP-MgO. These results indicate that both PPh_3 and NAP-MgO are essential for this reaction. So, it can be assumed that PPh_3 reacts with ethyl bromoacetate *via* an S_N2 mechanism forming a phosphonium ylide, which immediately attacks the benzaldehyde carbonyl carbon and forms an oxaphosphetane intermediate, then by eliminating the $Ph_3P{=}O$, it forms an olefin (Scheme 3). In these steps, MgO effectively catalyzed and accelerated the formation of the phosphonium ylide and the olefination reactions. To confirm this, ethyl bromoacetate and PPh_3 were stirred with catalyst the NAP-MgO in DMF overnight, and then the catalyst was filtered. To this filtrate, benzaldehyde was added and the misxture was stirred for 20 h but only a 50% yield was obtained. There is only 5% conversion in the reaction between benzaldehyde and ethyl bromoacetate/PPh_3 without using NAP-MgO. In another reaction, the pre-prepared phosphonium salt[26] $Ph_3P^+{-}CH_2{-}COOEtBr^-$ was reacted with benzaldehyde in DMF, and stirred with and without the catalyst. It was observed that in the presence of catalyst, after 20 h, the olefinated product was obtained quantitatively, but in the absence of catalyst, even after 24 h, only 5% product was obtained. Therefore, it can be concluded that MgO catalyzes this reaction.

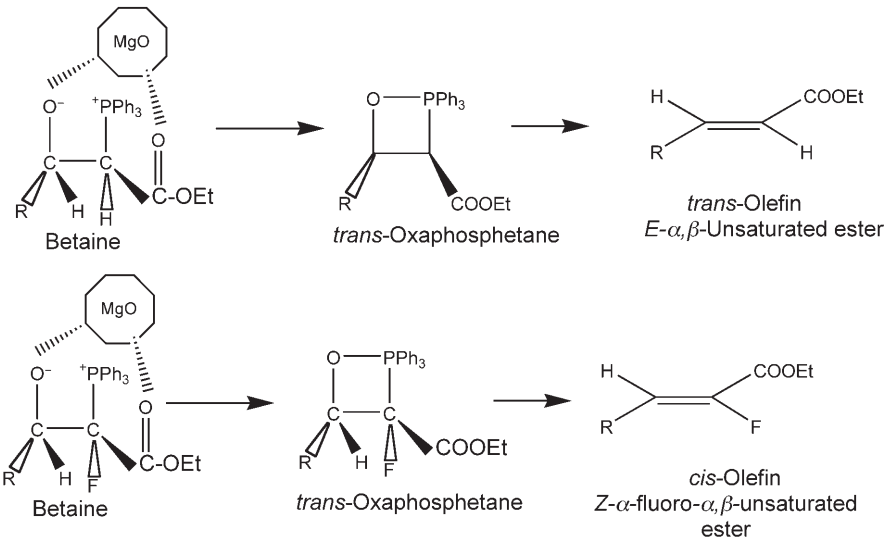
This is further substantiated by ^{31}P NMR studies. In the absence of both aldehyde and catalyst, formation of the phosphonium salt was observed. But when the same reaction was performed without aldehyde but in the presence of catalyst, formation of phosphonium salt and phosphonium ylide were observed. To address this issue, we conducted three experiments.

In the first experiment, ethyl bromoacetate and triphenylphosphine were stirred in DMF without alde-



Scheme 3. The plausible mechanism for the Wittig reaction catalyzed by NAP-MgO.

hyde and catalyst. Within 30 min, triphenylphosphine had completely disappeared (followed by TLC) and formation of phosphonium salt $Ph_3P^+CH_2COOEtBr^-$ was observed *via* S_N2 mechanism. This was confirmed by the observed peak at $\delta = 20.987$ (lit.[15] $\delta = 20.5$) in the ^{31}P NMR spectrum shown in Figure 1 of the Supporting Information. In the second experiment, ethyl bromoacetate and triphenylphosphine were stirred in DMF without aldehyde but in the presence of the catalyst, NAP-MgO, after 1 h there is no phosponium ylide peak; instead we observed the phosphonium salt peak at $\delta = 20.88$ and another peak at $\delta = 22.23$ in ^{31}P NMR spectrum. The reaction was continued and samples were withdrawn periodically after 2 h, 6 h, 9 h, 12 h, 15 h and they showed peaks in the regions $\delta = 17.8$–17.9 and 20.8–20.9 corresponding to phosphonium ylide, $Ph_3P=CHCOOEt$ {lit.[15]: δ17.9} and the phosphonium salt, $Ph_3P^+CH_2COOEtBr^-$ (lit.[15] $\delta = 20.5$}, respectively (see Figures 3–7 in the Supporting Information). On increasing the reaction time, i.e., 2–15 h there is a decrease in the intensity of the phosphonium salt peak and a simultaneous increase in the intensity of phosphonium ylide peak in the ^{31}P NMR spectra. The phosphonium salt was not completely converted into the phosphonium ylide even after 24 h, so there may be an equilibrium between phosphonium salt and ylide. Along with these phosphonium salt and ylide peaks, two more peaks are observed at $\delta =$ 22.1–22.4 and $\delta = 16.1$–16.3. We assume that these peaks also could be due to the salt ($\delta = 22.1$–22.4) and the ylide ($\delta = 16.1$–16.3), which are co-ordinated with the catalyst.[15,16] This is further confirmed by the addition of the aldehyde (4-nitrobenzaldehyde) to the reaction mixture after 24 h, which gave the desired product and the phosphine oxide at $\delta = 29.26$ (lit.[17] $\delta = 30.2$), as observed in ^1H and ^{31}P NMR spectra, respectively, and those two peaks at $\delta = 22.1$–22.4 and $\delta = 16.1$–16.3 had disappeared in ^{31}P NMR spectrum (see Figure 9 in the Supporting Information). Thus, the entire phosphonium salt was completely convert-



Scheme 4. The plausible mechanism for the stereoselective *E*-α,β-unsaturated esters and *Z*-α-fluoro,α,β-unsaturated esters in Wittig reaction catalyzed by NAP-MgO.

ed into the phosphonium ylide which, on interaction with the aldehyde, gave the product and phosphine oxide. In the third experiment, ethyl bromoacetate and triphenylphosphine were stirred in DMF with 4-nitrobenzaldehyde in the presence of the catalyst, NAP-MgO, and after 3 h, we observed only one peak[18] at $\delta = 29.67$ (lit.[17] $\delta = 30.2$) corresponding to triphenylphosphine oxide in the ^{31}P NMR spectrum and the product in the ^{1}H NMR spectrum while there are no peaks at $\delta = 22.1$–22.4 and $\delta = 16.1$–16.3 in the ^{31}P NMR spectrum (see Figure 10 in the Supporting Information).

The phosphonium ylide peak appears at a higher magnetic field than that of the phosphonium salt in the ^{31}P NMR spectrum. This fact may be attributed to a lower positive charge on the phosphorus atom in the ylide than that in the phosphonium salt.

The carbanionoid carbon of the ylide attacks the electrophilic carbon of the carbonyl group of aldehyde with the formation of a betaine, which in turn drives the formation of a very strong phosphorus-oxygen bond, a four-membered cyclic transition state "oxaphosphetane", which collapses into the olefin and $Ph_3P{=}O$ (Scheme 3).

Generally, the stereochemistry of the Wittig reaction is influenced by the presence of π-acceptor groups at the α-carbon. Resonance-stabilized ylides, bearing a π-acceptor group at the α-carbon, react with aldehydes to give almost exclusively *E*-olefins, where as non-stabilized ylides, bearing an α-alkyl group afford *Z*-olefins.[2a] In the Wittig reaction using NAP-MgO, olefins are obtained with high selectivity towards the *E*-isomer which is due to the surface of the catalyst and its highly reactive sites.[12c,19] Here we assume that the formed intermediate "betaine" forms a complex with the unsaturated Mg^+ site (Lewis acid type) of NAP-MgO. The Lewis acid moiety (Mg^{2+}/Mg^+) of the catalyst co-ordinates with O^- of the aldehyde carbonyl oxygen and carbonyl oxygen of ylide ester moiety of the betaine intermediate[20,21] (Scheme 3 and Scheme 4). In the betaine, thealdehyde R group and the ylide COOEt group should be in different planes for minimizing their steric interactions.[22] Therefore, a *trans*-oxaphosphetane will be formed by the planar four-centered transition state to relieve a dominating 1,2 interaction between the R group on the aldehyde and the COOEt group on the ylide, which predominates to give *E*-α,β-unsaturated esters[2a,23] (Scheme 3 and Scheme 4). When the hydrogen is substituted by a fluorine atom in the same *E*-form of the α,β-unsaturated ester, the product α-fluoro-α,β-unsaturated ester is considered as the *Z*-form according to the atomic number priority and the same *Z*-isomer of the fluoro compound was predominantly obtained under our optimized conditions (Scheme 2 and Scheme 4, Table 4) (see Figures 11–14 in the Supporting Information). Thus, a similar condensation holds good for α,β-unsaturated esters (*E*-form) and α-fluoro-α,β-unsaturated esters (*Z*-form), as their basic structure is unaltered except for the fluorine substitution as can be seen in Scheme 4. In contrast, in α,β-unsaturated nitriles, the increase in *Z*-isomer is due to the lower steric requirement of the linear cyano group. Due to the above described reasons, i.e., the formation of a "betaine" intermediate which forms a complex with the unsaturated Mg^+ site (Lewis acid type) of MgO, we obtained almost the same selectivity of α,β-unsaturated esters in various reactions with different MgO crystallites CM-MgO, NA-MgO, Sil-NA-MgO and Sil-NAP MgO (Table 1).

To understand the relationship between structure and reactivity of the catalyst in detail, we need to know the structure and nature of the reactive sites of NAP-MgO. NAP-MgO has a single-crystallite, three-dimensional polyhedral structure, which shows the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001, 111), which leads to an inherently high surface reactivity per unit area. Thus, NAP-MgO indeed displayed the highest activity compared to NA-MgO and CM-MgO. Besides this, the NAP-MgO has Lewis acid sites, Mg^{2+}, Lewis basic sites O^{2-} and O^{-}, lattice-bound and isolated Brønsted hydroxy groups and anionic and cationic vacancies.[12c,19] Wittig reactions are known to be driven by base catalysts[23,24] and, accordingly, the surface -OH, O^{2-} sites of these oxide crystals are expected to trigger these reactions. To examine the role of -OH, Sil-NA-MgO and Sil-NAP-MgO,[12c] devoid of free -OH, were tested in Wittig reactions. It is found that the silylated MgO samples had longer reaction times than the corresponding MgO samples in the Wittig reaction (Table 1). Although both NAP-MgO and NA-MgO possess defined shapes and the same average concentrations of surface -OH groups, a possible rationale for higher reactivity to α,β-unsaturated esters and nitriles by the NAP-MgO is that -OH groups present on the edge and corner sites on the NAP-MgO, which are stretched in three-dimensional space, are more isolated and accessible for the reactants. NAP-MgO has a single crystallite polyhedral structure with the presence of 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 displayed the highest activity compared to NA-MgO and CM-MgO. In the Wittig reaction, O^{2-}/O^{-} sites of NAP-MgO abstract an acidic proton of the Ph_3P^{+}-CH_2-$COOEtBr^{-}$ (PPh_3 reacts with ethyl bromoacetate *via* an S_N2 mechanism), giving a carbanion, which forms a complex with the unsaturated Mg^{+} site (Lewis acid type) of NAP-MgO. The Wittig reaction proceeds *via* dual activation of both substrates (nucleophiles and electophiles) by NAP-MgO. Thus, the Lewis base (O^{2-}/O^{-}) of the catalyst activates Ph_3P^{+}-CH_2-$COOEtBr^{-}$, and the Lewis acid moiety (Mg^{2+}/Mg^{+}) activates the carbonyls of the aldehyde and the ylide ester (Scheme 3 and Scheme 4).[20]

The catalyst was reused for 4 cycles without loss of activity (entry 7, Table 3). In the 2nd cycle, a 95% yield was obtained. After the 3rd cycle, the catalyst was calcined at 250 °C for 1 h under a nitrogen flow and reused and the desired product was obtained in 98% yield. Sychev et al. reported that hydrotalcites efficiently catalyzed the liquid phase synthesis of alkenes in the Wittig reaction, but they did not specify the reusability of the catalyst.[25] Yong Tong et al., reported soluble PEG-supported telluride as an effective catalyst for the Wittig-type reaction to give a variety of α,β-unsaturated esters. The catalyst was recovered quantitatively, but in the second run only a 69% yield was obtained.[7] Sun and Kühn reported the olefination of aldehydes with ethyl diazoacetate in the presence of PPh_3 catalyzed by a ClFeTPP porphyrin complex in an ionic liquid [bmim] PF_6. The catalyst was reusable with an 88% yield in the 2nd cycle.[8a]

Conclusions

In summary, nanocrystalline MgO was found to be an effective heterogeneous catalyst for the one-pot Wittig reaction to afford α,β-unsaturated esters and nitriles in excellent yields with high *E*-stereoselectivity in the presence of triphenylphosphine. To conclude, the simplicity of our procedure, the mildness of the reaction conditions, the excellent yields, the high stereoselectivity, together with capacity for easy separation of reaction mixture, especially the reusability of the catalyst, demonstrates our method to be practical for the synthesis of α,β-unsaturated esters and nitriles.

Experimental Section

General Remarks

Nanocrystalline MgO samples were obtained from Nano-Scale Materials Inc., Manhattan, Kansas, USA. All catalysts are calcined at 400 °C for 4 h before use. All chemicals were purchased from Aldrich Chemicals and S.D Fine Chemicals, Pvt. Ltd. India and used as received. All LR grade solvents were used as received from S.D Fine Chemicals, Pvt. Ltd. India. 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. The ^{1}H NMR spectra were recorded on a Varian-Gemini 200 MHz or a Bruker-Avance 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in $CDCl_3$. ^{31}P NMR spectra were recorded on a Varian-Unity 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, using 85% H_3PO_4 as an external standard in $CDCl_3$. The ^{19}F NMR spectra were recorded on a Varian-Unity 400 MHz spectrometer. The *E*/*Z* ratio was determined from ^{1}H NMR and ^{19}F NMR spectra using coupling constant (*J*) values. All the liquid secondary ion mass spectrometric (LSI-MS) experiments were carried out using an Autospec M (Micromass, Manchester, UK) mass spectrometer of EBE geometry, equipped with an OPUS V3.1X data system. A 2.2 mA primary beam of cesium ions accelerated to 25 keV and the ion source was operated at an acceleration voltage of 8 kV to effect ionization.

Typical Procedure for the One-Pot Wittig Reaction for Synthesis of α,β-Unsaturated Esters and Nitriles

NAP-MgO (0.075 g) was added to a mixture of aldehyde (1 mmol), α-halo ester or bromoacetonitrile (1 mmol), triphenylphosphine (1 mmol) in 5 mL of DMF and the mixture was stirred at room temperature. After completion of the reaction (as monitored by TLC), the catalyst was centrifuged, washed with ethyl acetate, water was added to the filtrate, and then the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The protocol involving addition of water followed by extraction with ethyl acetate is required to remove DMF from reaction mixture. The solvent was removed under reduced pressure, and crude product was purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate/hexane as an eluent to afford the pure product.

Supporting Information

^{31}P NMR of reaction mixtures after various times and ^{19}F NMR spectra of the crude reaction mixtures of **5a–d** are shown.

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