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Enhanced Reactivity and Selectivity of Asymmetric oxa-Michael Addition of 2'-Hydroxychalcone in Carbon Confined Space

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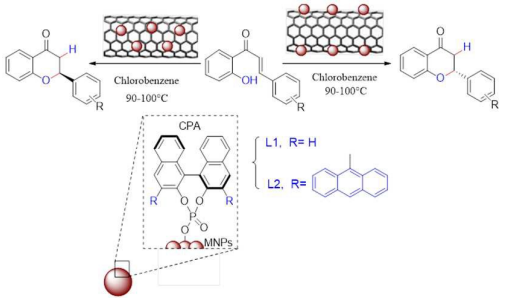
Melad Shaikh[a], Kiran Kumar Atyam[b], Mahendra Sahu[a] and Kalluri V. S. Ranganath[a]*

Carbon nanotubes (CNTs) are employed as nanoscale reaction vessels for the asymmetric oxa-Michael addition of 2'-hydroxychalcones. A systematic comparasion of catalytic activities of chiral phosphoric acid treated ferrite nanoparticles (chiral ferrite) has been studied for the synthesis of flavanones. Higher reactivity, selectivity with switching of enantiomer was observed when these chiral ferrites are inside the CNT channel.

Confinement of molecules inside nanoscale containers provides a powerful strategy for achieving high activity and selectivity.[1,2] The growing demand for enantiopure compounds in the daily life has stimulated an increasing interest in asymmetric catalysis.[3] Homogeneous asymmetric catalysis has proven its usefulness in a number of organic reactions with high enantioselectivity, however only limited number of them have been used in industry because of the intrinsic problems such as recovery of the expensive catalyst.[4-5] Fortunately, asymmetric heterogeneous catalysis has many advantages over homogeneous catalysis, in terms of recyclability.[6] The orientation of the substrate on the catalyst support is crucial in generating the asymmetric heterogeneous catalyst, where choice of the support plays a major role. The change of the support may drastically change the (increase or decrease) enantioselectivity and in some cases reversal of enantiomers can also be observed.[7-8] The inversion of enantioselectivity is due to change of solvent, temperature, heterogeneous support and also by addition of co-solvent.[9] In addition, the switching of isomer is more pronounced on moving from homogeneous to heterogeneous catalytic system.[10]

The utilization of nanomaterials in various directions is exploring rapidly due to the change of properties after surface treatment with various functional groups.[11-12] Recently, we have also contributed to the effect of surface functionalization of ferrite and nano magnesium oxides with dicarboxylic acids and imidazolium salts in the catalytic oxidation and dehydration reactions.[13-16] By introducing the suitable functionality, the properties of CNTs have been explored in various applications, including catalysis.[17-20] The intramolecular oxa-Michael addition has been a significant challenge since the resultant products have important properties of anti-tumor and anti-inflammatory properties. The isomerization of 2'-hydroxychalcones to flavanones belongs to oxa-Michael addition reaction, which produces chromane core that is characteristic of many flavanoids.[21] A significant number of asymmetric catalysts have been reported for the chiral flavanones through the direct asymmetric isomerization of 2'-hydroxychalcone. For instance, the asymmetric isomerization of 2'-hydroxychalcone has been reported by chiral acid and base catalysts in high yields and excellent ee's.[22] In that Hintermann clearly explained that t*he racemization and reversible reactions of flavanone to 2'-hydroxychalcones under particular conditions are major risks to get the enantioriched flavanones*. Recently, Scheidt and Feng groups independently developed a new protocol for the enantioselective synthesis of flavanones using a quinine-derived thiourea catalyst and chiral N,N'-dioxide nickel (II) complex respectively.[23,24] The catalytic asymmetric reactions promoted by chiral phosphoric acids (CPA) and their metal complexes have become powerful methodology to synthesize structurally diverse organic compounds.[25,26]

Herein, we report the highly enantioselective oxa-Michael addition of 2'-hydroxychalcone to flavanones in good yields and ee's using chiral ferrites either inside or outside CNTs (Scheme 1).



Scheme 1 Asymmetric oxa-Michael addition of 2'-hydroxychalcone to flavanone catalyzed by CPA modified MNPs inside and outside CNTs.

The heterogeneous catalyst developed here is the surface modified ferrites, *i.e* magnetite nanoparticles (MNP),[27] and cobalt ferrite nanoparticles (CNP) with a versatile chiral ligands, (*R*)-(−)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate

[a] *Department Of Chemistry, Guru Ghasidas Central University, Bilaspur, India-495009*
E-mail: rangakvs@gmail.com
[b] Dept. of Materials Science and Engineering, RGUKT, Basar India-50401
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(CPA) (L1) and (*R*)-3,3'-Bis(9-anthracenyl)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate (L2). This new class of chiral catalyst is readily formed through the sturdy interaction of MNPs with CPA, and generates a chiral solid. Enhanced enantioselectivity has been observed when these chiral solids are encapsulated either inside CNT or decorated on outside CNT as shown in scheme 1 in the direct oxa-Michael addition of 2'-hydroxychalcone to flavanone (upto 90%). It is well known that CNTs are having strong affinity towards aromatic compounds due to π-π stacking. Therefore chiral ligands L1 and L2 are selected because of expected strong affinity (π-π interactions) of naphthyl and anthracenyl groups with CNTs.

Asymmetric oxa-Michael addition of 2'-hydroxychalcone to flavanone was initially evaluated using homogeneous L1 complexes of Fe(II) and Fe(III), which are prepared by reacting iron (II)/iron (III) chlorides in the presence of base (Fig. 1). Notably, the reaction proceeds quite well and gave the product 64, 68% yields with 24% and 28% ee respectively after 24 h in chlorobenzene at 100°C using both these complexes.

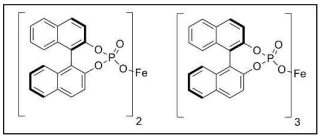

Fig. 1 Fe(II) and Fe(III) complexes of L1.

In continuation of our study for the development of surface modified metal oxides, we synthesized L1 treated ferrites. Since paramagnetic material (MNP) and highly electromagnetic material (CNP) could be easily recovered after the reaction, we selected these two inverse spinels in our present study. As a preliminary experiment, we studied oxa-Michael addition of 2'-hydroxychalcone to flavanone using MNPs, CNPs and the results are shown in the Table S1. Later, L1 treated MNP and CNPs have been evaluated for the synthesis of flavanones at different temperatures. It was found that modified MNPs performed as a versatile nanocatalyst furnishing the chiral flavanone in 79% yield with 20% ee in chlorobenzene at 100°C. The rate of reaction is significantly increased with L1 treated MNPs than naked MNPs and as the concentration of ligand increases, the enantioselectivity increases (Table 1, entry 1 to 4) (up to 24% ee). When L2 treated MNPs used as a catalyst in the cyclization of 2'-hydroxychalcone in chlorobenzene, flavanone was isolated in 52% yield with 38% ee (Table 1, entry 5, 6). Since using of CNTs is enhancing the catalytic activity through confinement in hydrogenation and other reactions, we incorporated surface anchored ferrites into CNTs through a capillary phenomenon. Since the chlorobenzene had turned out to induce high enantioselectivity in the cyclization using MNP-L1, catalyses with all catalysts (MNP-L1/CNT, MNP-L2/CNT, CNP-L1/CNT, CNP-L2/CNT) in that solvent. Indeed, 2'-hydroxychalcone underwent catalytic cyclization to produce chiral flavanones in the presence of ferrite encapsulated CNTs are shown in the Table 1. Surprisingly, the chiral flavanones were isolated in 68% yield with 90% enantioselectivity using carbon confined chiral ferrite (Table 1, entry 7). The enhanced enantioselectivity may be due to the confinement effect of chiral ferries inside CNTs. This result shows the importance of asymmetric catalysis within the nanotubes and channels of CNTs act as highly efficient nano reactors for the asymmetric oxa-Michael addition reactions. Surprisingly, opposite enantiomer of flavanone was observed when MNP-L1 is inside CNT (Fig. 2).

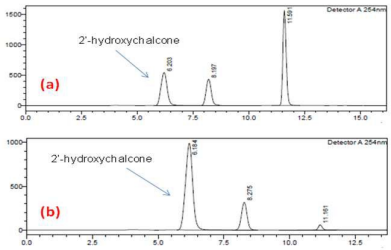

Fig. 2 HPLC traces of flavanones catalyzed by (a) MNP-L1 and (b) MNP-L1/CNT

This may be due to the confinement effect of CNTs inside the channels of nanoreactor and having π- interactions of aromatic groups with CNTs.[30-33] Moreover, the enhanced reactivity and selectivity was observed due to the confinement of CNTs in asymmetric hydrogenations using cinchonidine and in nitroaldol reactions using hetrobimetallic catalyst .[34-36]

Notably, in our present reaction, lowering the temperature did not show the improvement of enantioselectivity (Table 1, entry 8 & 9). Surprisingly, no enantioselectivity was observed when the oxa-Michael addition of 2'-hydroxychalcone was carried out in DMF (Table 1, entry 10). There is a little improvement in the ee (upto 94%) and yield (upto 70%) of flavanone in the presence of MNP-L2/CNT at 100°C in chlorobenzene, however the major enantiomer is same as with that of MNP-L2 catalyzed reaction. This may be due to the bulk anthracenyl groups could not oriented properly inside the channels of CNT and the reaction could takes place on the surface of CNT and thus giving the enantio enriched product in 94%. The higher selectivity of MNP-L2/CNT is due to the steric and electronic effect of the ligand and thus leads to give the product in higher selectivity compared to MNP-L1/CNT. In order to understand better the effect of MNP and CNT, two separate experiments were conducted in the presence of chlorobenzene using CNT and L2. It was observed that there was no reaction in the presence of only CNTs and 15% of flavanone was isolated with 11% ee using L2 (only L2) after 15 h (Table 1, entry 14). An electromagnetic material like CNPs decorated on CNTs showed high catalytic activity in the dehydration of fructose,[19] were used in our asymmetric cyclization reaction, did show the ee after incorporating them into CNTs as like MNPs (Table 1, entry 15-19). A systematic study of asymmetric cyclization of 2'-hydroxychalcone catalyzed by Br∅nsted acids including camphorsulphonic acid, CPA has also been reported earlier with lower yields and ee's.[37] To evaluate the effect of confinement of MNPs on their catalytic performance, we prepared chiral MNPs on outside CNTs and tested in oxa-Michael addition reaction. Notably, flavanones were isolated in 63% yield and 65% ee, which is having the same configuration as that of MNP-L1. This result clearly reveals that the effect of MNPs inside the CNTs and produce opposite enantiomer. Moreover, the turnover frequency (TOF) of M-L1/CNT, 34.3 h^{-1} is much higher than MNP-L1, (2.5 h^{-1}), MNP-L2 (2.7 h^{-1}) and even higher than MNP-L1/CNTs (outside) (27.3 h^{-1}) (Fig. S7). Further, various ratios of MNP-L1 were prepared and encapsulated inside CNT are used in oxa-Michael addition. In all these cases inversion of isomer was observed to that of MNP-L1 (HPLC spectras, SI). The crystallinity and structure of modified ferrites are confirmed by

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powder XRD. The Fig. 3 shows the XRD pattern of the before and after treatment of MNPs with L1. The broadening of the characteristic peak after reacting with L1, indicates that interaction of iron with modifier is preferred than iron-iron interactions. The analysis of the diffraction pattern showed the formation of simple cubic spinel structure due to the strongest reflection from (311) plane at 35.69° using CuKα. In addition, the presence of (220), (311), (422), (511) revealed the cubic spinel phase of L1 modified ferrites either inside or outside CNTs (Fig. 3). The crystallite size was found to be 16.2nm, 12.0 nm, 14.3 nm, 11.4 nms for MNP, MNP-L1, CNP and CNP-L1 respectively. In addition 2θ at 26.2° correspond to reflections of (002) planes of CNTs were observed for both inside and outside MNPs.

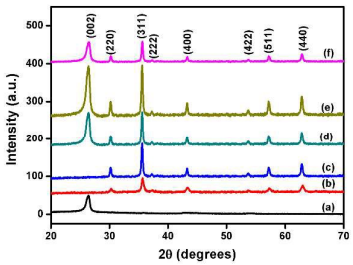

Fig. 3 PXRD pattern of (a) CNT (b) MNP-L1 (10 mol %) (c) CNP-L1 (d) MNP-L1/CNT (e) CNP-L1/CNT (f) MNP-L1 outside of CNT

In addition, MNP-L1/CNT has also been characterized by XPS, which confirm the presence of MNPs decorated in CNTs. The doublet photoelectron profile of Fe_{2p} spectra spin-orbital split into distinct $Fe2p_{3/2}$ and $Fe2p_{1/2}$ orbit at binding energies at 710.75 eV and 724.23 eV respectively (Fig. S1, Supporting Information). The binding energy corresponding to 531.6 eV is attributed for O 1S of Fe_3O_4 (Fig. S1) and it is identified to be the bridge oxygen (O^{2-}) between the octahedral iron (Fe^{3+}) and the tetrahedral (Fe^{2+}) lattice. Along with iron and oxygen, the binding energies at 284.35, 285.12 and 286.55 eV corresponding to C 1s of different carbon atoms of Sp^2 and Sp^3 respectively (Fig. S1). The binding energy at 134.1 and 133.5 eV attributed for phosphorus $2p_{1/2}$ and $2p_{3/2}$ orbitals. The effective decoration of MNPs in CNTs has also been verified by IR spectroscopy (Fig. S2). The mechanism of asymmetric catalysis on chirally anchored materials is complicated and is not yet been well understood. It is generally believed that chiral moiety, (in our case CPA) is adsorbed onto MNP surfaces, and induces enantioselectivity due to the metal-CPA interactions. However, in case of MNP-L1/CNT, MNPs were encapsulated inside the channels of CNTs and thus the asymmetric oxa-Michael addition reaction could take place in a restricted space hence gave the product with inversion of selectivity. Under the optimized reaction conditions, a variety of representative 2'-hydroxychalcones reacted smoothly in the presence of either MNP/L1 or MNP-L1/CNT in moderate to good yields with good enantioselectivity (Table 2). Remarkably, no reaction was observed with aliphatic substituted unsaturated keontes (Table 2, entries 19 & 20). To evaluate the stability of the catalyst, the recycling of MNP-L2/CNT was performed for the asymmetric oxa-Michael addition reaction of 2'-hydroxychalcone in chlorobenzene at 100°C. The chiral solid catalyst was separated by external magnet, washed thoroughly with ethanol and reused for next cycle. A constant conversion of 70% yield with 93% ee was obtained even after five consecutive cycles.

Table 1 Asymmetric oxa-Michael addition of 2'-hydroxychalcone using various catalysts

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)	Selectivity (% of ee)
1	MNP-L1	Chlorobenzene	100	60	15 (*S*)[a]
2	MNP-L1	Chlorobenzene	100	79	20 (*S*)[b]
3	MNP-L1	Chlorobenzene	100	84	22 (*S*)[c]
4	MNP-L1	Chlorobenzene	100	82	24 (*S*)[d]
5	MNP-L2	Chlorobenzene	100	52	38 (*S*)
6	CNP-L2	Chlorobenzene	100	47	30 (*S*)
7	M-L1/CNT	Chlorobenzene	100	68	90 (*R*)
8	M-L1/CNT	Chlorobenzene	80	65	88 (*R*)
9	M-L1/CNT	Chlorobenzene	40	52	90 (*R*)
10	M-L1/CNT	DMF	100	90	- -
11	M-L2/CNT	Chlorobenzene	100	70	94 (S)
12	M-L2/CNT	Chlorobenzene	80	55	65 (S)
13	M-L1/CNT	DMF	100	90	- -
14	L2	Chlorobenzene	100	15	11(*S*)
15	CNP-L2	Chlorobenzene	100	47	30 (*S*)
16	CNP-L2	Chlorobenzene	80	40	20 (*S*)
17	C-L2/CNT	Chlorobenzene	100	70	93 (*R*)
18	C-L1/CNT	Chlorobenzene	100	72	84 (*R*)
19	C-L2/CNT	DMF	100	80	--
20	M-L1/CNT	Chlorobenzene	100	63	65(*S*)[e]

Reaction conditions: 0.5 mmol of reactant, 3.0 mL of solvent, 20.0 mg of the catalyst. [a] 5 mol% of L1 on MNP. [b] 7.5 mol% of L1 on MNP. [c] 10 mol% of L1 on MNP. [d] 15 mol% of L1 on MNP. [e]MNP-L1(10 mol%) outside CNTs

This result indicates that catalyst is stable and active without deterioration in activity or enantioselectivity (Fig. S5). The recovered catalyst was analysed through inductively coupled plasma atomic emission spectroscopy (ICP-AES) and observed that there is no leaching of iron from the catalyst. Apart from other methods, the MNP-L1/CNT catalysts were also characterized by HR-TEM, which indicates the crystallite size, is around 8 nm (Fig. 4). It shows the morphology and size distribution of MNPs inside CNTs.

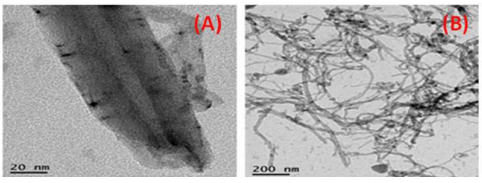

Fig. 4 HR-TEM of (A) MNP-L1/CNT (B) TEM of MNP-L1/CNT

It can see that size of NPs is distributed from 7.8 nm to 16.4 nm, and the mean particle size is around 13.8 nm (Fig. 4).

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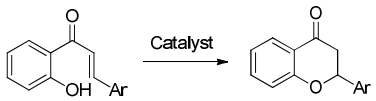
Table 2 Scope of the substrate variation for various flavanones.



Entry	Substrates (Ar)	Catalyst	Yield (%)	Selectivity (% of ee)
1	Ph	MNP-L1/CNT	88	94
2		MNP-L1	79	-39
3		CNP-L1	76	-40
4	4Br-Ph	MNP-L1/CNT	86	50
5		MNP-L1	82	-70
6		CNP-L1	78	-69
7	4MeO-Ph	MNP-L1/CNT	82	80
8		MNP-L1	77	-27
9		CNP-L1	82	19
10	4Me-Ph	MNP-L1/CNT	76	87
11		MNP-L1	80	-46
12		CNP-L1	82	-48
13	4Cl-Ph	MNP-L1/CNT	77	65
14		MNP-L1	65	-45
15	3Cl-Ph	MNP-L1/CNT	72	73
16		MNP-L1	58	-31
17	$3NO_2$-Ph	MNP-L1/CNT	75	64
18		MNP-L1	64	-63
19	CH_2-Ph	MNP-L1	N.R	--
20	C2H5	MNP-L1	N.R	---

Reaction conditions: 0.5 mmol of reactant, 3.0 mL of chlorobenzene and 20.0 mg of the catalyst at 100°C. (no reaction: N.R). The sign "–" indicates opposite enantiomer excess.

The protocol developed in the present case is new and highly environmental concern because the catalyst could be recovered with the help of external magnet. Moreover, the heterogeneous catalyst developed is recyclable and showed excellent activity and selectivity in the asymmetric oxa Michael addition of 2'-hydroxychalcones. No additives or additional substitution in the reactant are required to get the enantioriched products. Catalytic activity and selectivity was unaffected even after repeated use. This process for production of chiral flavanones from direct cyclization is superior from the green and sustainable perspectives and can improve to be commercially viable. This work demonstrates the new dimensions of heterogeneous catalysis and it opens an opportunity for developing a versatile and robust catalyst for chiral molecules.

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