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Enantioselective Michael Addition Reaction Catalysed by Enantiopure Binuclear Nickel(II) Close-Ended Helicates

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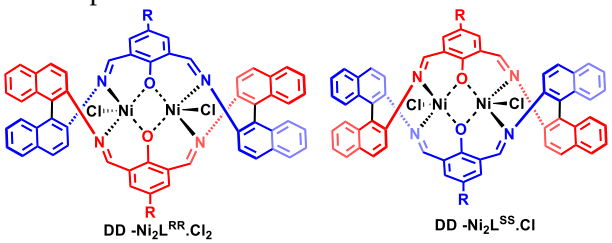
Abstract. The enantiopure Ni(II) helicates $[Ni_2L_1^{RR}.Cl_2]$ **(1),** $[Ni_2L_1^{SS}.Cl_2]$ **(1'),** $[Ni_2L_2^{RR}.Cl_2]$ **(2),** $[Ni_2L_2^{SS}.Cl_2]$ **(2')** were synthesized by one-pot self-assembly technique from *R*-(+)- or *S*-(-)-1,1'-binaphthyl-2,2'-diamine, with 4-methyl-2,6-diformyl phenol or 4-*tert*-butyl-2,6-diformyl phenol and nickel salts. This binuclear double stranded Ni(II) helicates were characterized by ESI-MS, IR and single crystal x-ray structure wherever applicable. The extensive chiroptical studies suggest that the complexes are enantiopure in nature. The chirality transfer from ligand $\mathbf{L_1}^{RR}$ & $\mathbf{L_2}^{RR}$ to Ni(II) metal centre produced ΔΔ geometrical chirality, while their enantiomeric counterpart $\mathbf{L_1}^{SS}$ & $\mathbf{L_2}^{SS}$ produced ΛΛ chirality in their respective complexes.These enantiopure helicates were applied as catalysts in asymmetric Michael addition of 1,3-dicorbonyl compounds with β-nitrostyrene to produce nitroalkanes in good yield (96-98%) and ee (78-90%).

Keywords: Asymmetric catalysis; Binuclear nickel(II) complexes; Chiroptical properties; Enantiopure helicate; Michael addition reaction

Introduction

Asymmetric catalysis[1] is one of the most powerful and economical method to achieve enantiorich compounds compared to kinetic resolution. In such reaction although metal catalysts,[2] organocatalysts[3] and enzymatic catalysts[4] are used, the metal catalysts continue to be a potential player owing to its high efficiency, stability and broad substrate scope. Conventionally, such metal catalysts are generally monometallic with in-built chiral component.[5] Tethering two such catalytic units through covalent or non-covalent bond was found to enhance their cooperative catalytic function. In this direction, compared to monometallic, the bimetallic catalysts are considered superior because of such existence in enzyme based biocatalysts e.g., superoxide dismutase,[6] urease[7] etc. Inspired by such dimeric system in various biocatalysts, there have been a growing interest to develop various homo and hetero binuclear catalysts as evidenced from the literature.[8] Binuclear catalysts thus emerging as a powerful tool, their applications in asymmetric transformation reactions[9] has gained significance.

Similarly, BINOL a well-known compound for its axial chirality is of extensive investigation adapting in various binuclear metal complexes to control the conformation of the catalysts.[10] With in-built enantiopure BINOL, Shibasaki has constructed various binuclear metal catalysts with N_2O_4 chromophores for diverse reactions.



R	*R*-BNDA	*S*-BNDA
-CH_3	$[Ni_2L_1^{RR}.Cl_2]$ (1)	$[Ni_2L_1^{SS}.Cl_2]$ (1')
-$C(CH_3)_3$	$[Ni_2L_2^{RR}.Cl_2]$ (2)	$[Ni_2L_2^{SS}.Cl_2]$ (2')

Scheme 1. Enantiomeric **[2+2]** close-ended macrocyclic Ni(II)-helicates.

Various homo-(Ni_2, Mn_2, Co_2)[11] and hetero-bimetallic catalysts (La-Yb, Ga-Yb, Cu-La, Cu-Pr, Cu-Sm, Cu-Eu, Cu-Dy, Zn-Sm, Mg-Sm and Ni-Sm)[12] were studied for their catalytic applications in Nitroaldol,[13] Michael addition,[14] and Mannich reaction[15] etc. Michael addition reaction thus known for its stereo-controlled C-C bond formation, its influence on total synthesis of optically active natural

10.1002/adsc.201901350

products e.g., hexahydropyrrolo-indole alkaloids, (+)-chimonanthine, (+)-folicanthine, and (-)-calycanthine) pharmaceuticals and materials are well documented in the literature.[16-18]

In this series, the Ni_2-schiff base complex with open ended N_2O_4 chromophore containing endogenous naptholate phenolic oxygen treated with Li, Na, K, or Cs has been extensively investigated.[19] The incremental enantioselectivity obtained upon introduction of metal ions with napthoxide hydroxide salts were correlated with increased atomic radius and polarizability of the napthoxide-Cs pair.[20] In such system the introduction of large sized Cesium enhancing the selectivity, the consequent change in the twist angle associated with conformational change may not be ignored. In this direction, we in the present study report binuclear double-stranded close-ended helicates where the twist angle between the N_2O_2 chromophore is locked by their helical architecture.

Ever since the term helicate was coined by Lehn[21] (1987), the subsequent reports on helicate has increased tremendously for its various applications on sensors,[22] biological applications[23] and catalysis[24] etc. Thus, the double helical structure in the helicate inspired us to implement them as catalyst.[25] Although the enantiopure helicates are known for their appealing architecture and chiral properties, their catalytic application in asymmetric catalysis was less explored. The combined effect of helical chirality and metal centred chirality on enantioselective catalysis has been of keen interest.[26] In this series recently, we have reported a series of binuclear double-stranded Cu_2 and Zn_2 helicates and their catalysis in asymmetric reactions.[27] With that encouragements, we here report the synthesis of few important close-ended nickel(II) helicates and their catalytic application in Michael addition reaction. In this endeavour, this report demonstrate the synthesis of series of chiral nitroalkane from β-nitroalkene and 1,3-dicarbonyl compounds. In addition to investigating the enantioselective catalytic role of this Ni_2 helicate for wide variety of substrates, we also tested them for the enantioselective synthesis of a pharmaceutically important chiral drug (S)-Warfarin.

Results and Discussion

We report here the synthesis of series of binuclear double-stranded helicates **1, 1', 2,** and **2'** using nickel(II) chloride and enantiopure ligands L_1 and L_2. These ligands were obtained using (*R*)-(+)-1,1'-BNDA or (*S*)-(-)-1,1'-BNDA with 4-methyl-2,6-diformylphenol or 4-*tert*-butyl-2,6-diformylphenol following our recent report.[27] As a result we produced four different hexadentate helical ligands L_1^{RR}, L_1^{SS}, L_2^{RR} & L_2^{SS} as shown in scheme 1. These enantiomeric helical ligands efficiently formed a series of binuclear double-stranded Ni(II) helicates (scheme 1).

The ESI-MS spectra (S1) depict a peak at m/Z = 973.43 of monocationic species $[Ni_2L_1^{RR}Cl]^+$ matching with the calculated value 973.14 along with an intense peak at m/z = 991.46 correspond to $[Ni_2L_1^{RR}Cl.H_2O]^+$ (calc. m/Z = 991.15) is appeared with isotopic peaks as depicted in Figure 1.

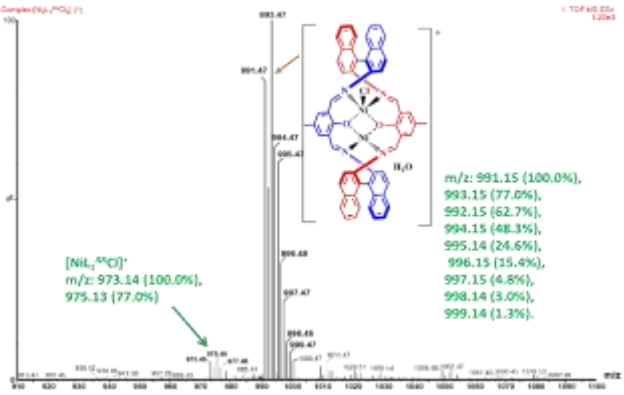


Figure 1. ESI-MS spectra of **$[Ni_2L_1^{RR}.Cl_2]$ (1)** helicate.

Similarly, the m/Z peak at 1027.24 (Calc.1027.13) attributed to the monocationic species to this enantiomeric counterpart **[1'**.$H_2O]H^+$ confirms the formation of binuclear double-stranded helicate. Similarly the complexation of L_2 with nickel(II)chloride provide an intense peak at m/Z = 1111.29 and 1111.31 (Calc: 1111.22) correspond to [**2**.$H_2O.H^+]^+$, [**2'**.$H_2O.H^+]^+$ respectively and confirms their dimeric association (Figure S1-Figure S4).

The IR spectra (S2) recorded for these complexes depict an intense band in the range 1630-1638 cm^{-1} are attributed to νC=N stretching frequencies in all four double stranded-helicates (Figure S5). Electronic spectra of the Ni(II) helicates recorded in THF reveals three set of bands as shown in Figure 2. The two intense and a narrow band in the Uv region 257±5nm and 290±5 nm represents σ-π*, π-π* type intraligand transitions. The prominent band at 419 ± 2 nm attributable to LMCT (ligand centred charge transfer) unveils the coordination of phenolate oxygen to the nickel(II) centre. The additional *d-d* band at 616±3 nm matching well with various reported *d-d* transitions of similar nickel(II) complexes supports a five-coordinated square-pyramidal geometry around the nickel centre in all these complexes.

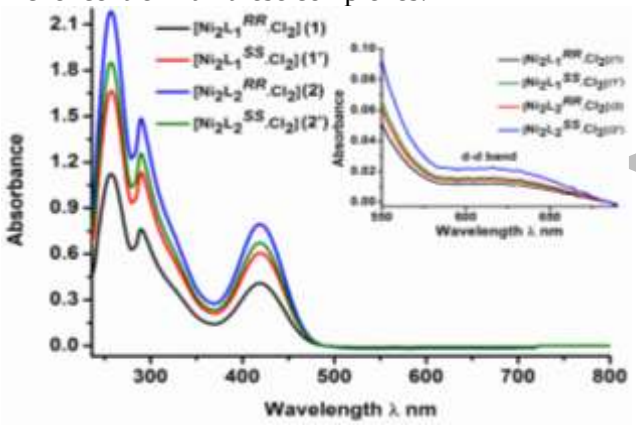


Figure 2. UV-Visible spectra of all the nickel helicates recorded in THF ($1x10^{-5}$M). The inset shows d-d band ($1x\ 10^{-3}$M).

10.1002/adsc.201901350

Chiroptical studies

Since these complexes are composed with enantiopure BNDA, we inspired to investigate their chiroptical properties. Accordingly, the CD spectra recorded for all these complexes in THF are presented in Figure 3. The CD spectra for **1** in Figure 3 revealed ligand centred transitions at 271±4 (-ve cotton), 299±3 (+ve cotton) nm and a broad band at 416±3 (+ve cotton) nm attributable to LMCT matching to the electronic spectra. A similar spectra for $[Ni_2L_1^{ss}Cl_2]$ depicting an opposite optical pattern the opposite optical signature obtained for these enantiomeric counterparts unambiguously attributed to the retention of chirality of the ligand in the respective Ni(II) helicates. A similar trend has been observed in **2** and **2'** helicates (Figure S6). The retention of the chirality, thus infers that the chirality of the ligand is transferred to the metal centre resulting *ΔΔ* geometrical chirality in **1** and **2,** while in the respective enantiomeric counterparts **1'**, **2',** the nickel(II) metal center gains *ΛΛ* chirality as revealed from their d-d band shown in Figure 3.

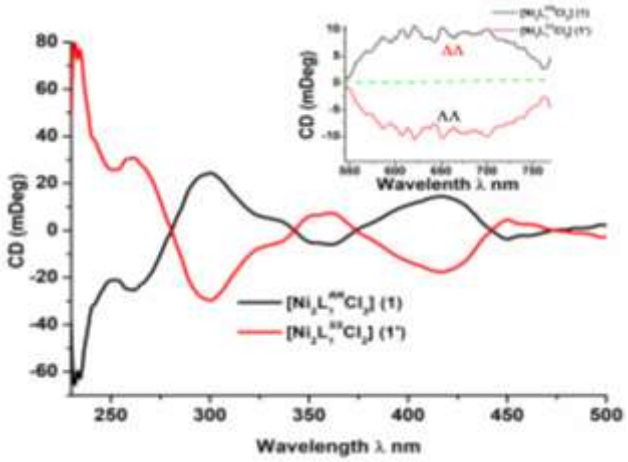


Figure 3. CD spectra of **1** & **1'** recorded in THF (1 x 10^{-5}M). Inset shows d-d band (1 x 10^{-3}M)

Single Crystal X-ray structure analysis

Acetonitrile solution of complex **1'** upon slow evaporation at room temperature yield a dark brownish crystal suitable for single crystal x-ray analysis (S4) in two weeks (Table 1). The crystal structure was solved in a $P2_1$ space group. The structural analysis shows a neutral binuclear double-stranded Ni(II) helicate complex **1'**, which possesses two binaphthyl diamine and two 4-MDFP units that incorporate two Ni(II)–Cl centers (Figure 4). The helically twisted macrocycle-type ligand ($\mathbf{L_1}^{SS}$) in **1'** possesses two metal binding domains, each consisting of an N_2O_2 chromophoric compartments with two azomethine nitrogens, N1 and N2, [*d*(Ni1–N1) = 1.96(2)Å, *d*(Ni1–N2) = 2.03(3)Å] and two phenolate oxygens, O1 and O2 [*d*(Ni1–O1) = 1.952(18) Å and *d*(Ni1–O2) = 2.04(3) Å]. The selected bond distances and bond angles are presented in table S1. These central phenolate oxygens bridge the Ni(II) centers and form a planar Ni_2O_2 core as shown in Figure 4 (Figure S7- Figure S9). Thus, each Ni(II) ion adapts an identical distorted square pyramidal geometry by coordinating to two azomethine nitrogens and two phenolate oxygens with the Ni atom sitting 0.416 Å above the square base and a chloride ion at the apex. The relevant bond distances and angles are presented in Table S1. The axially chiral BNDA units, incorporated in the ($\mathbf{L_1}^{SS}$) backbone coordinate to the Ni-atoms *via* their azomethine nitrogens and are twisted in an angle of *ca*. 71.38 and 69.29° in respect to the biphenyl planes. The unit cell contains two molecules of enantiopure nickel helicate (Figure S10) consisting of *S*-BNDA in both sides confirm that chiral self-sorting[28] persist in the chirality. The Flack parameter 0.14(4) obtained for this complex indicates the chiral nature of the complex.

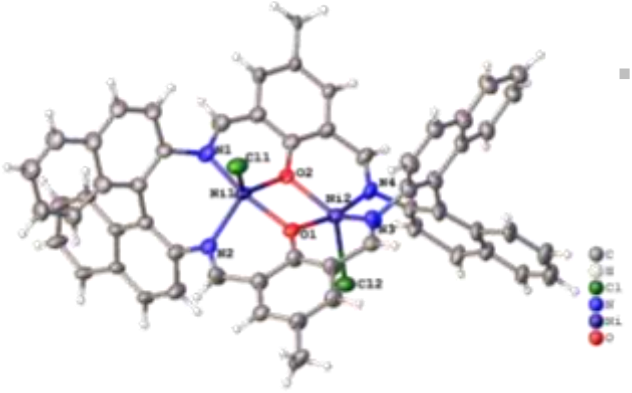


Figure 4. Thermal ellipsoid plot with partial atom labelling depicting the neutral dimeric complex **1'** (50% probability factor for the thermal ellipsoids).

As indicated in the CD spectra (Figure 3), each dimeric unit in the complex containing two enantiomeric BNDA units, the RR isomers in the dimer promotes ΔΔ metal centred chirality around the Ni(II) metal center is witnessed from their chromophoric rotation. This observation in the crystallographic analysis gives confidence that the opposite complex would certainly have ΛΛ from the respective *SS*–BNDA unit is understandable from their CD spectra as stated above. The ΔΔ and ΛΛ in the respective helicate is shown below in Figure 5.

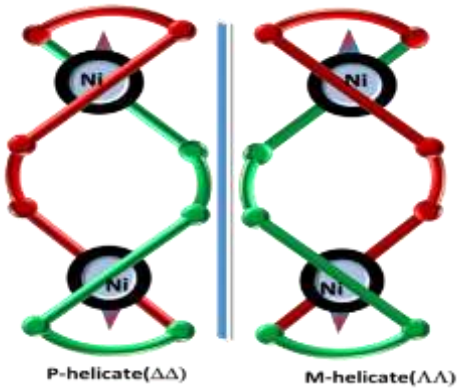


Figure 5. Schematic representation of P and M close-ended [**2+2**]-helicates.

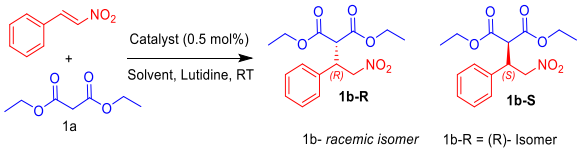
Table 1. Summary of the crystal data for **1'.**

Identification code	**[$Ni_2L_1^{SS}Cl_2$] 1'**
Empirical formula	C_{58} H_{38} Cl_2 N_4 Ni_2 O_2
Formula weight	1011.24
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	17.5098(17)
b/Å	10.6620(9)
c/Å	17.5153(16)
α/°	90
β/°	105.807(5)
γ/°	90
Volume/Å^3	3146.27
Z	2
ρ_{calc}g/cm^3	1.067
μ/mm^{-1}	0.720
F(000)	1040
Crystal size/mm^3	0.21 X 0.13X 0.11
Radiation	Mo-Kα (λ = 0.71073)
2Θ range for data collection/°	2.26 to 23.588
Reflections collected	48356
Independent reflections	14249 [R_{int} = 0. 1478, R_{sigma} = 0.1967]
Data/restraints/parameters	14249/3110/1184
Goodness-of-fit on F^2	0.926
Final R indexes [I>=2σ (I)]	R_1 = 0.0915, wR_2 = 0.2273
Final R indexes [all data]	R_1 = 0.1860, wR_2 = 0.2891
Largest diff. peak/hole / e Å^{-3}	0.68/-0.60
Flack parameter	0.14(4)
CCDC	1957380

Catalysis

The successful synthesis of these enantiopure Ni(II) helicates and their detailed chiroptical studies, encouraged us to apply them as catalysts for enantioselective Michael addition reactions of nitroalkenes to nitroalkanes using 1,3-dicarbonyl compounds. Initially, we have screened all four complexes as catalysts for this reaction with various solvents. We first checked the reaction without catalyst, but in the presence of lutidine as a base, toluene as solvent, diethyl malonate as nucleophile and β-nitrostyrene as electrophile. This reaction produced racemic **1b** with 42% yield (Table 2, entry 1). Following the progress of the reaction, we inspired to use all these enantiopure helicates as catalysts aiming to achieve high enantioselectivity. Accordingly all these enantiopure nickel(II) double stranded - helicates **1**, **1'**, **2** and **2'** were adapted as catalysts (Table 2, entry 2-5). Interestingly all these complexes have produced **1b** with good yield ranging 77-81% and moderate ee with a range of 55-60%. All these catalysts producing almost similar catalytic results, the products differ in their stereoisomer. Among all, the catalyst **1**, has produced good yield (81%) and ee (60%). Hence **1** has been chosen as catalyst for further screening of reaction conditions (Table 2, entry 2). Then we screened the reaction with different solvents for the better homogeneous mixing. Accordingly, the solvent variation like dichloromethane (Table 2, entry 6), acetonitrile (Table 2, entry 7), chloroform (Table 2, entry 8), methanol (Table 2, entry 9), tetrahydofuran (Table 2, entry 10) and dichloroethane (Table 2, entry 11) are carried out. All these reactions were monitored by TLC for complete consumption of substrate. This systematic observation suggests that the reaction takes 14 h for complete conversion. All the solvents are giving yield in the range of 65 - 85% and a moderate ee upto 40-75% range. However among them DCM giving best results than the other solvents *i.e.*, 85 yield and 75% ee, we have chosen DCM as suitable solvent for this catalyst system and moved ahead for further optimisation (Table 2, entry 6).

Table 2. Screening of catalyst and solvent[a]



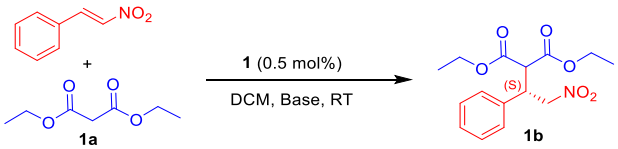
1b- *racemic isomer* 1b-R = (R)- Isomer 1b-S = (S)- Isomer

Entry	Catalyst	Solvent	Yield[b] (%)	ee[c](%)
1	Blank	Toluene	42	---
2	**1**	Toluene	81	60(*S*)
3	**1'**	Toluene	80	59(*R*)
4	**2**	Toluene	78	56(*S*)
5	**2'**	Toluene	77	55(*R*)
6	**1**	CH_2Cl_2	85	75(*S*)
7	**1**	CH_3CN	78	50(*S*)
8	**1**	$CHCl_3$	79	65(*S*)
9	**1**	Methanol	70	50(*S*)
10	**1**	THF	65	40(*S*)
11	**1**	CH_3CHCl_2	76	64(*S*)

[a] All the reactions were carried out by 0.5mmol of β–nitrostyrene, 1 equivalant of diethylmalonate, 1 mmol of DIPEA and 3mL solvent used and the reaction time is 14h, [b] isolated yield, [c] calculated by using UFLC phenomenox Lux cellulose-1 column.

Then we checked the reaction without base but we did not get better results (Table 3, entry 1) suggesting that the external base is necessary to facilitate the deprotonation of active methylene group of the substrate. Hence, we moved to screening of various bases, the tributylamine produced **1b** with 80% yield and 55% ee (Table 3, entry 2), triethylamine (Table 3, entry 3) gave 90% yield & 40% ee, tertamethylethylene diamine (TMEDA) gave 85% yield & 56% ee (Table 3, entry 4), 4-dimethylaminopyridine (4-DMAP) gave 85% yield & 45% ee (Table 3, entry 5), diisopropylethylamine (DIPEA) gives good yield 93% and 80% ee (Table 3, entry 6). Use of some inorganic base such as $CaCO_3$ (Table 3, entry 7), K_2CO_3 (Table 3, entry 8) gave moderate yields 65 & 50 % and ee 33 & 25% respectively. Amongst all, DIPEA (Table 3, entry 6) giving best results (93% yield and 80% ee), it has been chosen as a best deprotonating agent for this reaction with the catalyst **1**.

Table 3. Screening of base[a]

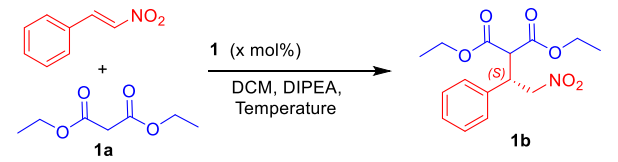


Entry	Base	Yield[b] (%)	ee[c] (%)(*S*)
1	--	10	40
2	Tributylamine	80	55
3	Triethylamine	90	40
4	TMEDA	85	56
5	4-DMAP	85	45
6	DIPEA	93	80
7	$CaCO_3$	65	33
8	K_2CO_3	50	25

[a] All the reactions were carried out by 0.5mmol of β-nitrostyrene, 1mmol of diethylmalonate, 1mmol of base and 3mL solvent used and the reaction time is 14h. [b]isolated yield, [c] calculated by using UFLC phenomenox Lux cellulose-1 column.

Next in order to optimise the catalyst amount, we varied different amount of catalyst from 1 – 10 mol%. In our first attempt, we increased the loading from 0.5 to 1 mol% which gave better yield 94% & ee 83% (Table 4, entry 1). Then 1.5 mol% (Table 4, entry 2) gave 96% yield and 85% ee. Similarly, 2 mol% (Table 4, entry 3) gave 98% yield and 90% ee. Thus the increase in the catalyst load was found to increase the yield and ee of **1b**. Hence, we thought to increase further like 2.5 mol% gave 98% yield, 89% ee (Table 4, entry 4), 3 mol% produce 95% yield, 87% ee (Table 4, entry 5), 4 mol% produce 92% yield, 86% ee (Table 4, entry 6). In this series, the 10 mol% catalyst load produced 88% yield, 85% ee (Table 4, entry 7). From this series of experiments, it is concluded that the increasing of the catalyst amount in the range 1 mol% to 2mol% show an increasing trend of yield and ee. But beyond 2.5 mol% upto 4 mol% reveals a gradual decline in the yield cum ee is visible (Table 4, entries 4-6). A further increase in the catalyst load upto 10 mol% depict a dramatic fall in the yield and ee. Hence the 2 mol% was chosen as an optimum amount of catalyst for this reaction (Table 4, entry 3).

Table 4. Screening of Catalyst loading and temperature[a]



Entry	Catalyst load (mol%)	Temp °C	Yield[b] %	ee[c](*S*) %
1	1	RT	94	83
2	1.5	RT	96	85
3	2	RT	98	90
4	2.5	RT	98	89
5	3	RT	95	87
6	4	RT	92	86
7	10	RT	88	85
8	2	60	90	75
9	2	40	95	85
10	2	20	96	88
11	2	10	80	87
12	2	0	70	86

[a] All the reactions were carried out by 0.5mmol of β–nitrostyrene, 1mmol of diethylmalonate, 1mmol of DIPEA and 3mL solvent used and the reaction time is 14h all the substrate were monitored by TLC and completely consumed, [b] isolated yield, [c] calculated by using UFLC phenomenox Lux cellulose-1 column.

Temperature being one of the important parameter on such enantioselective reaction, next we optimised the reaction temperature. Accordingly, we screened the reaction varying temperatures from 60 to 0ºC and the respective data are presented in Table 4 (entry 8-12). The rise in temperature from RT to 40°C and 60°C (Table 4, entry 8, 9) showed significant loss in ee (85 & 75% respectively) yield (95 & 90% respectively). While reducing the temperature from RT to 20 ºC (Table 4, entry 10), 10 ºC (Table 4, entry 11), and 0 ºC (Table 4, entry 12), the yield falling 96%, 80% and 70% respectively, the ee is maintained to remain 87-88%. Hence, we have chosen RT (25±2°C) as optimized temperature as both on higher as well as lowering from RT caused significant loss of yield and ee. Finally, the optimised conditions derived from the above systematic experiments suggests that DCM as solvent, DIPEA as base, 2mol% catalyst load and RT as optimised temperature.

Upon succeeding the optimisation of reaction conditions, then we have screened scope of the substrates of Michael donors containing different active methylene groups by keeping the β-nitro styrene as shown in chart-1 (**1a** - **9a**). Consequently, we have screened various active methylene substrates covering diethylmalonate **1a**, malonyl chloride **2a**, malononitrile **3a**, adapting the above optimised conditions. The diethyl substituted active-methylene group in diethylmalonate **1a** gave product **1b** with good yield 98% and ee 90% (Chart-1, **1b**). The malonyl chloride **2a** gave **2b** with 96% yield and 89% ee (Chart-1, **2b**). Then the malononitrile **3a** produced **3b** with yield of 98%, generated ee 78% (Chart-1, **3b**). Using ethyl cyanoacetate, (**4a)** ethyl bromoacetate(**5a**) as substrates produced **4b** & **5b** in 90 & 92% yield and 80 & 78% ee respectively. The methyl 2-pyridylacetate (**6a**) and ethyl 2-pyridylacetate (**7a**) produced **6b** & **7b** in 88, 86% yield and 74, 76% ee respectively. Then we extended our substrate scope to barbituric acid (**8a**) and dimedone (**9a**) which produced (**8b)** and (**9b)** with good yield (78 & 90%) and ee (72 & 86%). The screening of substrates thus suggested that the catalyst **1** is catalysing all the substrates almost equally, but provide the best results in the case of diethylmalonate (Chart-1, **1b**) than the other substrates.

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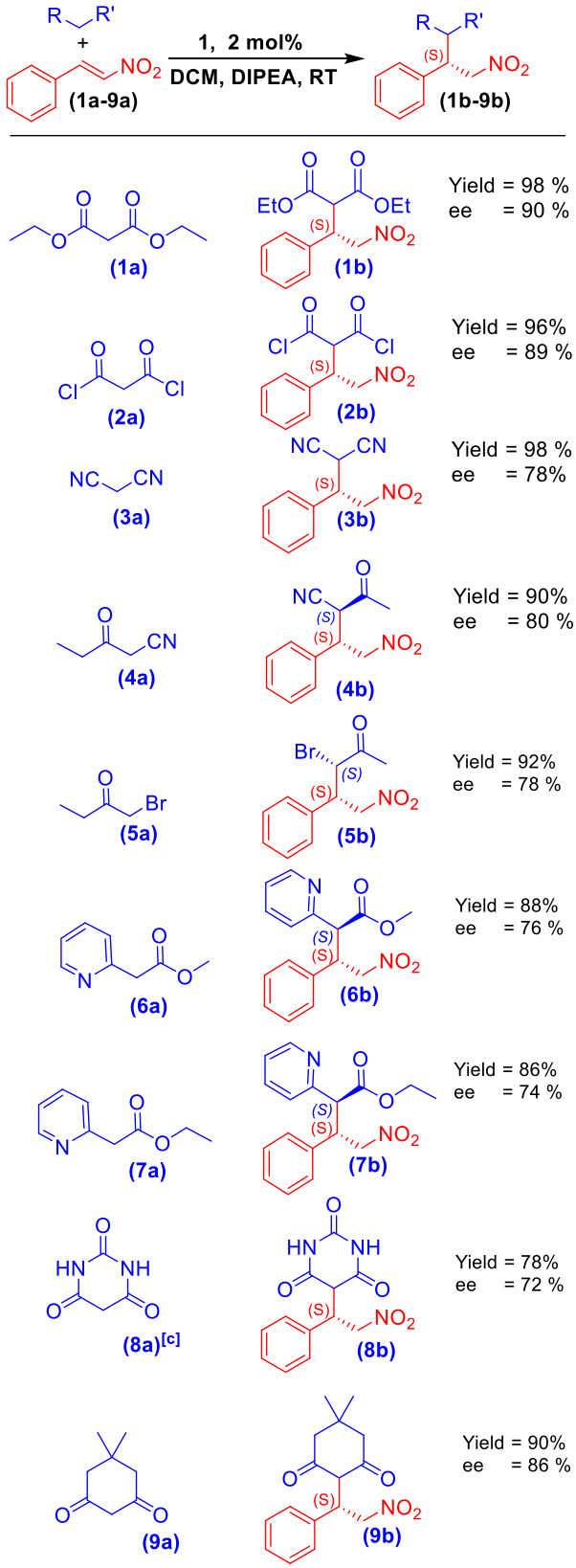
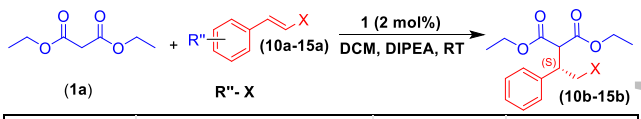
Chart 1. Screening of substrate[a]

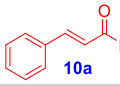
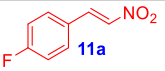
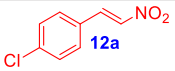
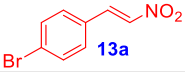
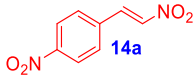
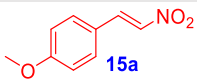
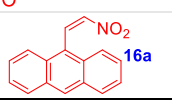


[a]All the reactions were carried out by 0.5mmol of β–nitrostyrene, 1mmol of dialkylmalonate, 1mmol of DIPEA and 3mL solvent used and the reaction time is 14h all the substrate were monitored by TLC and completely consumed. [b](1:2) ratio of DCM:Toluene used. Yield shown here is isolated yield, ee calculated by using UFLC phenomenox Lux cellulose-1 column & amylose-2 column.

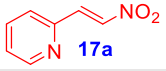
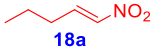
Then we moved to screen the Michael acceptors and the results are depicted in Table 5 (entry 1-10). Initally, we used chalcone (**10a**) as a Michael acceptor with diethylmalonate (**1a**) leads to **10b** (Table 5, entry 1) in better yield (95%) and moderate ee (76%) which is lesser than the β-nitrostyrene product (**1b**). Hence we have screened different substituted β-nitrostyrenes (**11a-19a**) as shown in Table 5. The electron withdrawing (**11a-14a**), donating (**15a**), different aromatic (**16a-17a**) and aliphatic nitroalkenes (**18a-19a**) were adapted. The electron withdrawing group at the nitrostyrene provides (Table 5, entry 2-5) better yield in the range of 90-98% and ee in 86-94%. While the electron donating methoxy substituted nitrostyrene **15a** leads to produce **15b** in 88% yield and 80 % ee (Table 5, entry 6). Then the use of 9-(2-nitrovinyl)anthracene (**16a**) and 2-(2-nitrovinyl)pyridine (**17a**) as Michael acceptors (Table 5, entry 7-8) leads to **16b** & **17b** in 92 & 93 % yield and 88 & 85 % ee respectively. We also used aliphatic olefins (Table 5, entry 9-10) such as 1-nitropent-1-ene (**18a**) and 1-nitrohept-1-ene (**19a**) leading to **18b** and **19b** in 82 & 80% yield and 66 & 60 ee respectively. As a result of screening different Michael acceptors, the 4-flouro substitued β-nitrostyrene (**11a**) produced **11b** in good yield (98%) and ee (94%) suggesting that electron withdrawing group in the phenyl ring of niitrostyrene supporting the formation of carbocation which further facilitates the interaction of carbanion of diethylamalonate. However, the aromatic Michael acceptors are found to give better results than the aliphatics suggesting the possible strong π- π interaction between the aromatic nitrostyrenes and catalyst matching to our earlier observation derived in our earlier work.[27]

Table 5. Screening of Michael acceptor[a]

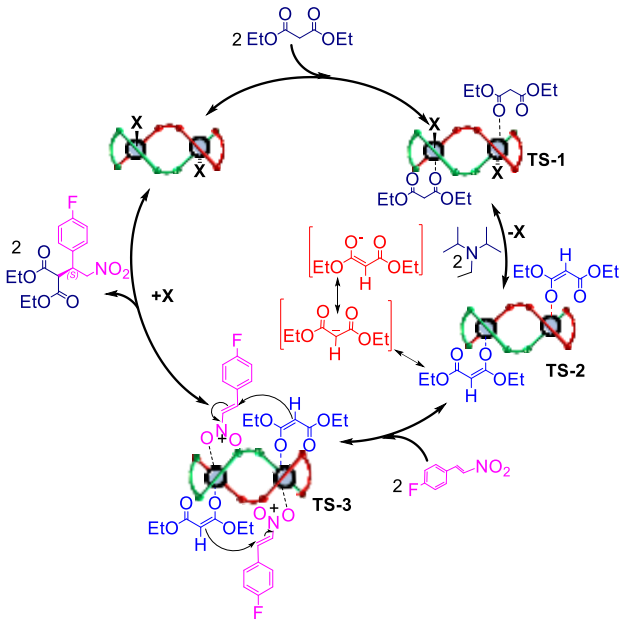


Entry	R''-X	Yield[b]	ee[c] (*S*)
1		95 (**10b**)	76
2		98 (**11b**)	94
3		95(**12b**)	92
4		90 (**13b**)	90
5		92(**14b**)	86
6		88(**15b**)	80
7		92(**16b**)	88

10.1002/adsc.201901350

8	 17a	93(**17b**)	85
9	 18a	82(**18b**)	66
10	 19a	80(**19b**)	60

[a] All the reactions were carried out by 0.5mmol of β–Michael acceptor, 1mmol of diethylmalonate, 1mmol of DIPEA and 3mL solvent used and the reaction time is 14h all the substrate were monitored by TLC and completely consumed, [b] isolated yield, [c] calculated by using UFLC phenomenox Lux cellulose-1 column & amylose-2 column.



Scheme 2. Probable mechanism for asymmetric Michael addition reaction catalysed by nickel helicate.

Based on the results and the literature studies we propose here a probable mechanism for the Michael addition reaction [29] in scheme 2. The Ni-complex initially interact with diethyl malonate *via* carbonyl group as shown in **TS-1**. Following this, the organic base DIPEA remove the hydrogen ion from active methylene compound as shown in **TS-2** (Figure S11). The deprotonated diethyl malonate in its resonance structures existing in both carbanion and enolate forms are known to associate with the delocalisation of electron pair. On the other hand, the nitrostyrene approaches to Ni(II) center simultaneously weakening the Ni-Cl bond. Upon establishing the strong interaction of nitrostyrene, the chloride ion is detached from the Ni(II) center (**TS-3**). The carbanion attacks the β-carbon of nitrostyrene through *Si* face attack as illustrated in the Figure 6a which lead to ***S*-11b** while on the other hand the opposite isomer catalyst **1'** leads to *Re* face attack leads to ***R*-11b** (Figure 6a). The crystal structure of catalyst **1'** is used for depicting the stereochemical induction model shown in figure 6b. This clearly suggest that the *Re* face attack favoured the formation of ***R*-11b.**

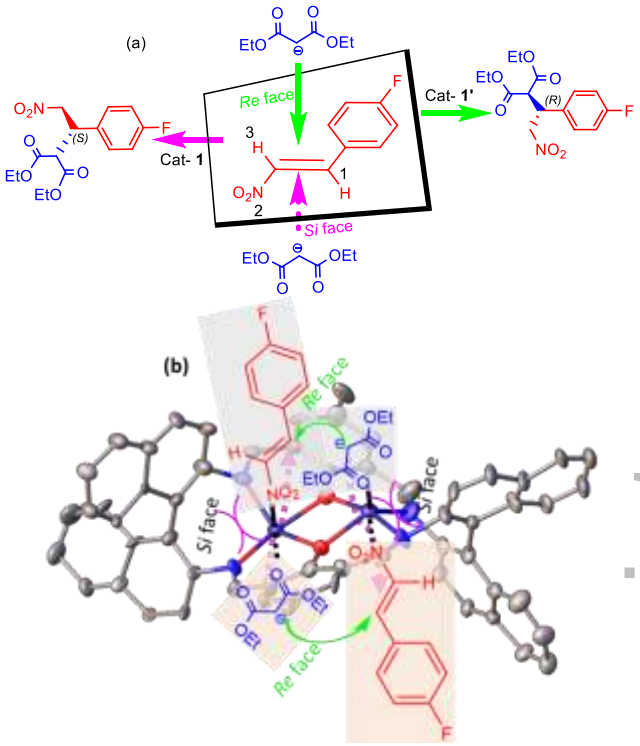


Figure 6. Stereochemical model of catalyst-substrate interactions, (a) Catalyst **1** and **1'** involve in the favour of *Re* and *Si* face attack respectively, (b) Catalyst **1'** favoured *Re* face stereo induction to *R*-Product.

At this juncture, a comparative analysis was carried out in view of gaining better understanding about the efficiency of the present catalyst. In this regard we have screened few important catalysts **3-7** comprising both Ni(II)-bimetallic and monometallic complexes incorporating the respective ligands,[26,30] L_a, L_b, L_c, L_d and L_e (Figure S12). Incorporating Ni(II), the complexes **3-5** are monometallic while **6 &7** are obtained as bimetallic. Adapting the above optimized reaction condition, the catalytic reaction between the substrates **1a** &**12a**, produce **12b** as product. All the bimetallic complexes (**5-7**) provides yield 80-85% with ee ranging 70-86%, while the monomeric complexes (**3** & **4**) are giving yield 90, 75% with ee 80,85% respectively. This detailed comparative catalytic study again re-establish that the present bimetallic helicate catalyst **1** is superior. Thus the encouraging yield and ee, and the comparative study together inspired us to undertake the recyclability test for the catalyst **1**. Accordingly, the catalyst **1** was tested for its catalytic stability adapting 4-Fluoro-β-nitrostyrene and diethylmalonate as standard substrates adapting the above optimised conditions. The catalyst was recycled upto nine times, where significant retention of yield and ee were maintained as shown in Figure 7. The recovered catalyst was analysed by FT-IR studies and was found to match with fresh catalyst (Figure S13) at the end of the 9th cycle.

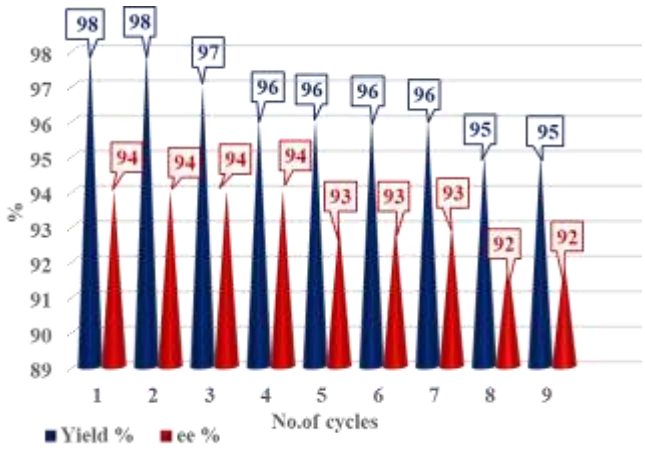
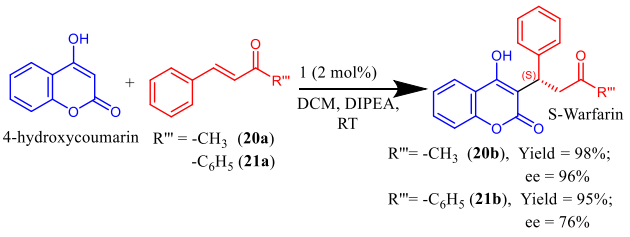


Figure 7. Recyclability of the catalyst **1**

Synthesis of *S*-Warfarin and its derivatives

In a view to understand the impact of the present catalyst, we inspired to investigate the efficiency of the catalyst **1** on the synthesis of enantioselective warfarin. In addition the enantioselective Michael addition of 4-hydroxy coumarin and 4-phenylbut-3-en-2-one was adapted to achieve (S)-Warfarin (Scheme 3) which is an effective anticoagulnt for preventing thrombosis and embolism. The literature survey suggests that there are various organcatalyts mainly functionalized with amine and imine motiefs[31] and metal[32] complex. Adapting catalyst **1** and using the above optimized reaction condition, the substrate benzylideneacetone (**20a**) and chalcone (**21a**) with 4-hydroxycoumarin, we could achieve the respective warfarin derivates with excellent enantioselectivity shown in scheme 3. The (**20b)** was obtained in good yield (98%) and ee (96%), and the (**21b)** with 95% yield and 76% ee.

Scheme 3. Enantioselective synthesis of (*S*)-warfarins[a]



[a] All the reactions were carried out by 0.5mmol of 4–hydroxycoumarin, 0.55mmol of enone, 0.5mmol of DIPEA and 3mL solvent used and the reaction time is 16h all the substrate were monitored by TLC and completely consumed, Yield presented here are isolated yield and the ee calculated by using UFLC phenomenox amylose-2 column.

Conclusion

In conclusion a series of enantiopure Ni(II) helicates were successfully synthesised by simple one pot metal template method. This helically structured dinuclear double-stranded Ni(II) complexes were characterised by ESI-MS, FT-IR and CD. The detailed chiroptical spectral investigation suggest that these helicates retains the chirality of the ligand in its complexes; A transfer of chirality from ligand to metal center has also been established without any ambiguity. This detailed study shows that the chirality transfer from ligand to metal produced ΔΔ in the case of **1, 2** where the ligand is in *RR* form. A similar approach in the case of **1', 2'** complexes has produced ΛΛ metal centered chirality. This chirally active binuclear helicates were further applied as catalysts in asymmetric Michael addition of 1,3-dicorabonyl compound with 4-Fluoro-β-nitrostyrene and was found to produce maximum yield of 98% and 94% ee in the case of diethylmalonate. Further, the catalyst **1** giving better result the respective recyclability experiment has proven to run upto nine cycles without any significant loss in the yield and ee. The catalytic system also been applied to synthesis of *S*-warfarin an anti-coagulant drug in good yield (98%) and ee (96%).

Experimental Section

Materials and methods

2-hydroxy-5-methyl-1,3-benzenedicarboxaldehyde, 4-*tert*-Butyl-2,6-diformylphenol, (R)-(+)-1,1'-Binaphyl-2,2'-diamine, (S)-(-)-1,1'-Binaphyl-2,2'-diamine Nickel(II) chloride hexahydrate were purchased from Aldrich & Co. All these chemicals were used as received without any further purification. IR spectra were recorded using KBr pellets (1% w/w) on a Perkin-Elmer Spectrum GX FT-IR spectrophotometer. Electronic spectra were recorded on a Shimadzu UV 3101 PC spectrophotometer. Mass analyses were performed using the positive electron spray ionization (ESI^+) technique on a waters Q TOF-micro mass spectrometer. ^1H, ^{13}C NMR spectra were recorded on a Bruker *Avance* DPX 200 and 500 MHz FT-NMR spectrometer. Chemical shifts for proton resonances are reported in ppm (δ) relative to tetramethylsilane (TMS). The CD spectra were recorded on a JASCO 815 Spectrometer. The enantioselectivity of the monobenzoylated product was determined by UFLC (Shimadzu SCL-10AVP) and ThermoFisher Scientific ultimate 3000 UHPLC using chiral columns (Phenomenox Lux cellulose-1 and Amylose-2 column).

Synthesis of Ni(II) helicate: The 5-methyl-2-hydroxyisophthalaldehyde (16.4mg, 0.1mmol) in acetonitrile (5mL), then 0.1mmol of triethylamine (13.9µl) and Nickel(II) chloride hexahydrate (0.1mmol, 23.8mg) were added to the solution with constant stirring at room temperature for 30mniutes. To this *R*-(+)-1, 1'-Binaphthyl-2, 2'-diamine (28.4 mg, 0.1mmol) was added drop by drop. After the complete addition of amine, the mixture has refluxed for 36 h. The solvent was removed by rotavapour, and the resulting solid material dissolved with dichloromethane, was washed with water (3x10ml), the organic layer separated and dried. **$[Ni_2(L_1^{RR})Cl_2]$** (**1**). $C_{58}H_{38}Cl_2Ni_2N_4O_2$, Yield 80 %. UV vis. λ (ε, cm^{-1}) = 256 (11,229), 289 (7,553), 419(4,072), 617(14) nm. FT-IR (KBr) ν = 3148, 1632, 1538, 1503, 1401, 1343, 1327, 1269, 1218, 1202, 1146, 1055, 999, 980, 941, 870, 824, 771, 747, 696, 665, 621, 577, 530, 513, 482, 437 cm^{-1}. $[ESI\text{-}MS]^+$ Chemical formula for **$[Ni_2(L_1^{RR})Cl]^+$** $C_{58}H_{38}ClN_4Ni_2O_2$ m/z Cal(found): 973.13(973.45) and **$[Ni_2(L_1^{RR})Cl.H_2O]^+$** $C_{58}H_{40}ClN_4Ni_2O_3$ m/z Cal(found): 991.15(991.47). Elemental Analysis: Mol. Formula. $C_{58}H_{44}Cl_2N_4$ Ni_2O_5.

Calc(found) C, 65.39(65.02), H, 4.16(4.32), N, 5.26(5.45) %.

[$Ni_2(L_1^{SS})Cl_2$], (1'). Similar procedure followed from above procedure except *S*-BNDA used instead of *R*-BNDA. The single crystal obtained by room temperature slow evaporation of acetonitrile solution of **[$Ni_2(L_1^{SS})Cl_2$]** to yield dark brown needle type crystals suitable for X-ray analysis. $C_{58}H_{38}Cl_2Ni_2N_4O_2$, Yield 82 %. UV vis. λ (ε, cm^{-1}) = 256 (16,650), 290 (11,333), 420 (6038), 615 (15) nm. FT-IR (KBr) ν =3420, 3148, 1631, 1542, 1507, 1404, 1326, 1222, 1202, 1120, 1066, 1005, 870, 822, 773, 751, 701, 658, 625, 568, 486 cm^{-1}. $[ESI\text{-}MS]^+$ Chemical formula for **[$Ni_2(L_1^{SS})Cl_2$.$H_2O.H^+$]**$^+$ $C_{58}H_{41}Cl_2N_4Ni_2O_3^+$ m/z Cal(found): 1027.13(1027.24. Elemental Analysis: Mol. Formula. $C_{60}H_{42}Cl_6N_4Ni_2O_2$. Calc(found) C, 61.02(61.26), H, 3.58(3.74), N, 4.74(4.89) %.

[$Ni_2(L_2^{RR})Cl_2$] (**2**). Similar procedure followed from above procedure except 4-*tert*-Butyl-2,6-diformylphenol. $C_{58}H_{38}Cl_2Ni_2N_4O_2$, Yield 80 %. UV vis. λ (ε, cm^{-1}) = 257(18,440), 289(12,533), 418(6716), 616 (16) nm. FT-IR (KBr) ν = 3441, 3143, 1630, 1542, 1504, 1403, 1327, 1224, 1203, 1165, 1146, 1061, 1025, 974, 946, 891, 865, 830, 802, 774, 747, 692, 668, 619, 576, 510, 481 cm^{-1}. $[ESI\text{-}MS]^+$ Chemical formula for **[$Ni_2(L_2^{RR})Cl_2(H_2O)H^+$]** $C_{64}H_{53}Cl_2N_4Ni_2O_3^+$ m/z Cal(found): 1111.22(1111.2981). Elemental Analysis: Mol. Formula. $C_{64}H_{52}Cl_2N_4Ni_2O_3$. Calc(found) C, 69.04(69.35), H, 4.71(4.54), N, 5.03(4.95) %.

[$Ni_2(L_2^{SS})Cl_2$] (2'). Similar procedure followed from above procedure except 4-*tert*-Butyl-2,6-diformylphenol and *S*-BNDA used instead of *R*-BNDA. $C_{58}H_{38}Cl_2Ni_2N_4O_2$, Yield 80 %. UV vis. λ (ε, cm^{-1}) = 256 (21,874), 290 (14,816), 419 (7,986), 617 (23) nm. FT-IR (KBr) ν = 3442, 3148, 1626, 1590, 1539, 1507, 1404, 1327, 1287, 1224, 1203, 1163, 1145, 1059, 1025, 974, 946, 891, 867, 828, 804, 773, 748, 692, 324, 574, 510, 477 cm^{-1}. $[ESI\text{-}MS]^+$ Chemical formula for **[$Ni_2(L_2^{SS})Cl_2(H_2O)H^+$]** $C_{64}H_{53}Cl_2N_4Ni_2O_3^+$ m/z Cal(found): 1111.22(1111.3111). Elemental Analysis: Mol. Formula. $C_{64}H_{54}Cl_2N_4Ni_2O_4$. Calc(found) C, 67.94(68.02), H, 4.81(4.72), N, 4.95(4.68) %.

General procedure for Asymmetric Michael Addition reaction.

A dry 5 mL flask, equipped with a magnetic stirring bar, was charged with catalyst (2 mol %) and freshly distilled dry DCM (3mL) at RT (25±2 ºC). Corresponding malonate (1 mmol), was then added, and the resulting mixture was stirred at RT. Then the β-nitrostyrene (0.5mmol) and DIPEA (1mmol) were successively added to a mixture. The mixture was stirred at the same temperature until the 14 h or complete consumption of substrate through monitoring by TLC. After completion of reaction, the solvent was evaporated by rotavapour and the resulting solid mixture was washed with ethyl acetate: hexane (20:80, 8-10 times) to separate catalyst from the mixture. Finally the crude product was purified by column chromatography (silica gel: 100-200 mesh using ethyl acetate and hexanes) to give corresponding product. Enantiomeric excess was determined by HPLC using Phenomenox Lux cellulose-1 column and Amylose-2 column using isopropanol and hexanes (10% and 90%) as eluting agent. The absolute configuration of the product were assigned by comparison HPLC profile with reported literature. [33]

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FULL PAPER

Enantioselective Michael Addition Reaction Catalysed by Enantiopure Binuclear Nickel(II) Close-Ended Helicates

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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