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Reaction of ω-Nitrostyrene with Diethyl Malonate in the Presence of Chiral Nickel(II) Complexes

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Abstract—Single-ligand complexes of nickel(II) with chiral diamines based on L-proline and (*S*)-camphor efficiently catalyze addition of diethyl malonate to ω-nitrostyrene in the presence of 1 equiv of triethylamine as co-catalyst. The reaction enantioselectivity depends on the chiral ligand structure.

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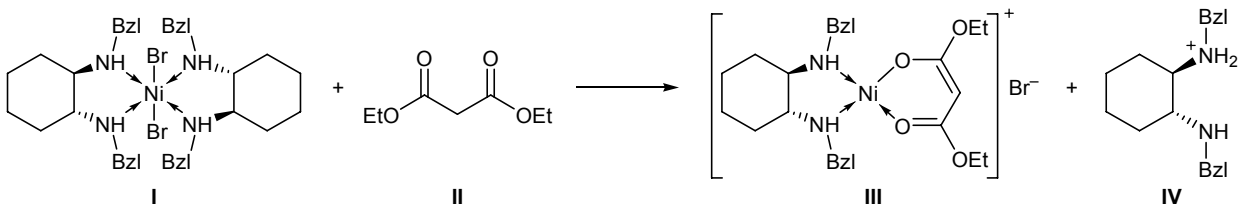
Addition of diethyl malonate to nitroalkenes underlies procedures for the synthesis of a number of neurotropic agents, specifically γ-aminobutyric acid derivatives, and provides a convenient synthetic approach to five-membered nitrogen-containing heterocycles via subsequent reduction and cyclization of the addition products [1–3]. Enantioselectivity of the addition is achieved by the use of organocatalysts (mainly difunctional thiourea derivatives) [4] or chiral transition metal complexes [5]. However, the required metal catalysts have a complex structure and are therefore difficultly accessible, whereas high concentrations (5 mol % and more) of organocatalysts are necessary.

It is known that the nickel(II) complex with (*R*,*R*)-*trans*-*N*,*N*′-dibenzylcyclohexane-1,2-diamine as catalyst ensures high enantioselectivity in the addition of some 1,3-dicarbonyl compounds to nitroalkenes [6, 7]. It was shown that Ni(II) complexes like **I** having two chiral ligands exhibit a high catalytic activity in the above reaction and that single-ligand complexes are weakly active. The authors presumed that the second ligand deprotonates 1,3-dicarbonyl compounds (e.g., **II**) with simultaneous removal of one of the two chiral ligands from the coordination sphere as onium cation **IV** and formation of acetylacetonate-type mixed-ligand complex **III** (Scheme 1). Thus one diamine ligand acts as a base. With a view to reduce consumption of a chiral ligand it seemed promising to use an achiral base as co-catalyst in enantioselective Michael addition. In the present work we examined the catalytic activity of nickel(II) complexes with diamine ligands **V**, **VII**, and **IX** based on accessible natural compounds [L-proline and (*S*)-camphor] in order to verify the above assumption and elucidate the effect of ligand environment on the catalytic properties.

Nickel(II) complexes **VI**, **VIII**, and **X** were synthesized by reactions of chiral diamines **V**, **VII**, and **IX** with $NiCl_2$ or $NiBr_2$ (Scheme 2). The catalytic activity of complexes **VI**, **VIII**, and **X** was assessed using the reaction of ω-nitrostyrene (**XI**) with diethyl malonate (**II**) as model process (see table; Scheme 3). This reaction was selected taking into account that it may be regarded as the key step in the synthesis of such pharmaceuticals as (*R*)-phenibut and (*R*)-phenotropil [7] and that the use of substituted ω-nitrostyrene derivatives in analogous reaction ensures preparation of intermediate products for the synthesis of (*R*)-rolipram [1] and (*R*)-baclofen [2].

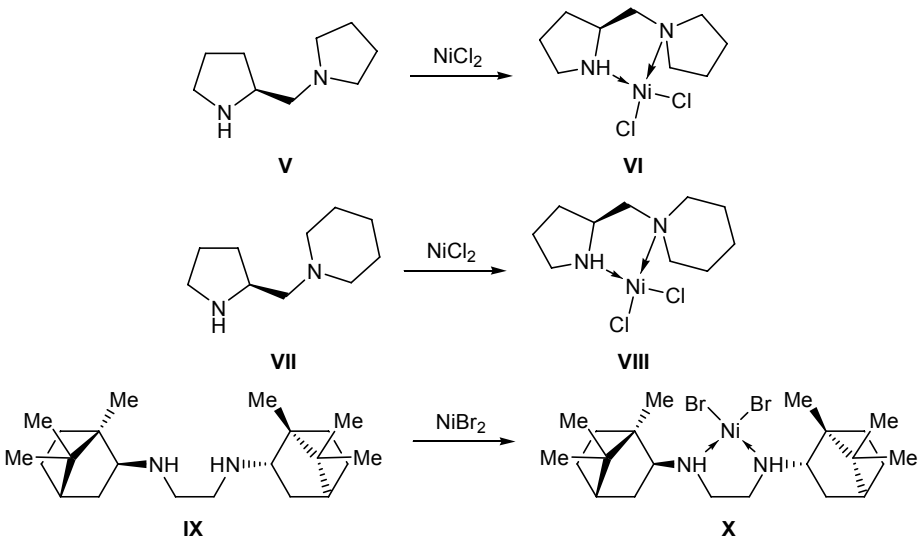
All the examined complexes turned out to be inactive in the Michael addition of diethyl malonate to

Scheme 1.



I **II** **III** **IV**

Scheme 2.

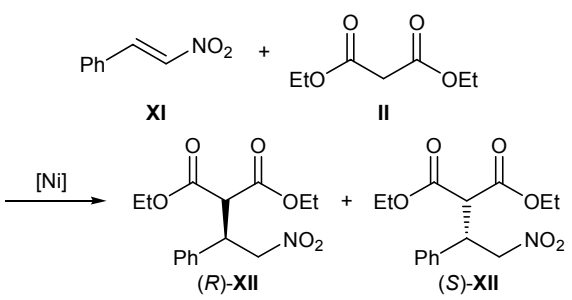


ω-nitrostyrene. However, addition to the reaction mixture of 1 equiv of an achiral base (triethylamine) sharply enhanced the catalytic activity of complexes **VI**, **VIII**, and **X**. In a control experiment, i.e., in the reaction of ω-nitrostyrene with diethyl malonate in the presence of 2 mol % of triethylamine, the conversion of ω-nitrostyrene was less than 5%. This means that the contribution of base catalysis to the overall process is small. The use of the catalytic system magnesium bisoxazoline complex–*N*-methylmorpholine showed that coordination of dicarbonyl compound to the metal complex (which is a Lewis acid) increases acidity of the former, thus facilitating its deprotonation with amine (co-catalyst) with formation of the corresponding enolate [1]. Activation of Ni(II) complexes with triethylamine may be rationalized by the action of the latter as enolizing agent in the formation of acetylacetonate-type coordination compounds that are the true catalysts in the addition of ω-nitrostyrene to diethyl malonate according to the mechanism proposed previously [7].

Addition of diethyl malonate to ω-nitrostyrene, catalyzed by Ni(II) complexes **VI**, **VIII**, and **X**, leads to predominant formation of (*S*)-enantiomer (*S*)-**XII**. Its enantiomeric excess (*ee*) depends on the chiral ligand nature. The highest *ee* value was obtained using complexes with L-proline-based ligands **V** and **VII**, while the size of the second nitrogen-containing ring in the ligand (pyrrolidine or piperidine) was insignificant. The reaction catalyzed by complex **X** with (*S*)-camphor ligand **IX** was characterized by lower enantioselectivity. Presumably, the reduction of *ee* in going from ligands **V** and **VII** to **IX** is related to lower conformational rigidity of the chelate ring in Ni(II) complexes with a longer linker connecting the coordination centers in the diamine ligand.

To conclude, we have demonstrated that nickel(II) complexes with chiral diamine ligands based on accessible natural compounds [L-proline and (*S*)-camphor] effectively catalyze Michael addition of diethyl malonate to ω-nitrostyrene; in this reaction, activation of

Scheme 3.



Catalytic activity of Ni(II) complexes in the reaction of ω-nitrostyrene with diethyl malonate (20°C, 72 h, 2 mol % of the catalyst with respect to ω-nitrostyrene)

Catalyst	Conversion, %	Yield,[a] %	*ee* (*S*)-**XII**, %
VI	<5	0	–
VI + Et_3N	100	90	64.6
VIII	<5	0	–
VIII + Et_3N	100	87	65.0
X	<5	0	–
X + Et_3N	100	88	30.4
Et_3N	<5	0	–

[a] After isolation by flash chromatography.

single-ligand Ni(II) complexes via addition of 1 equiv of an achiral base (triethylamine) is required. The reaction enantioselectivity is determined by the chiral diamine ligand nature, and conformational rigidity of the resulting chelates is a necessary condition ensuring high enantioselectivity.

EXPERIMENTAL

The enantiomeric composition of the addition products was determined by HPLC using a Waters chromatograph equipped with a Waters 2487 UV detector and a Waters 2414 refractive index detector (stationary chiral phase Chiralcel AD; analysis conditions for compound **XII**: eluent hexane–propan-2-ol, 95:5, flow rate 1.0 ml/min). The elemental compositions were determined on a EuroVector EA 3000 analyzer. The IR spectra were measured on a Shimadzu IR Affinity-1 instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECX400 spectrometer at 399.78 and 100.53 MHz, respectively, using $CDCl_3$ as solvent and reference. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan Trace DCQ GC–MS system (SGE BPX-5 capillary column, 30 m×0.32 mm). The optical rotations were determined on a Rudolph Research Analytical polarimeter.

Compounds **V**, **VII**, and **IX** were prepared according to the procedures described in [8–10].

Dichloro{1-[(2*S*)-pyrrolidin-2-ylmethyl]pyrrolidine}nickel(II) (VI). A solution of 51.2 mg (0.33 mmol) of compound **V** and 69.0 mg (0.29 mmol) of nickel(II) chloride hexahydrate in 5 ml of acetonitrile was heated for 30 min under reflux. The mixture was evaporated under reduced pressure, the residue was dissolved in 25 ml of methylene chloride, the solution was filtered from a small amount of undissolved material, and the filtrate was evaporated. The residue was ground with 20 ml of diethyl ether, and the bright yellow precipitate was filtered off, washed with 10 ml of diethyl ether, and dried. Yield 50 mg (39%). IR spectrum (KBr), ν, cm^{-1}: 3250, 2950, 2866, 2780, 1460, 1400, 1345, 1310, 1290, 1140, 870. Found, %: C 38.27; H 6.80; N 9.72. $C_9H_{18}Cl_2N_2Ni$. Calculated, %: C 38.08; H 6.39; N 9.87.

Dichloro{1-[(2*S*)-pyrrolidin-2-ylmethyl]piperidine}nickel(II) (VIII) was synthesized in a similar way from 160 mg (0.95 mmol) of compound **VII** and 197 mg (0.83 mmol) of nickel(II) chloride hexahydrate. Yield 110 mg (45%). IR spectrum (KBr), ν, cm^{-1}: 3300, 2940, 2850, 2800, 1440, 1300, 1155, 1120, 1040, 860, 780. Found, %: C 40.49; H 7.24; N 9.21. $C_{10}H_{20}Cl_2N_2Ni$. Calculated, %: C 40.32; H 6.77; N 9.40.

Dibromo{*N*,*N*′-bis[(1*S*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]ethane-1,2-diamine}nickel(II) (X) was synthesized in a similar way from 103 mg (0.31 mmol) of compound **IX** and 60 mg (0.27 mmol) of nickel(II) bromide. Yield 50 mg (34%), violet crystals. IR spectrum (KBr), ν, cm^{-1}: 3435, 3032, 2920, 1552, 1379, 1066. Found, %: C 48.01; H 7.44; N 5.01. $C_{22}H_{40}Br_2N_2Ni$. Calculated, %: C 47.95; H 7.32; N 5.08.

Catalytic addition of diethyl malonate to ω-nitrostyrene. Nickel(II) complex **VI**, **VIII**, or **X**, 4.42×10^{-2} mol, and triethylamine, 4.5 mg (4.42×10^{-2} mmol), were added to a solution of 0.33 g (2.21 mmol) of ω-nitrostyrene and 0.4 ml (0.42 g, 2.63 mmol) of diethyl malonate in 1 ml of toluene. The mixture was kept for 72 h at 20°C, the solvent was distilled off under reduced pressure, and the residue was subjected to flash chromatography on silica gel (Kieselgel 60, 0.04–0.063 mm) using methylene chloride as eluent. The results of control experiment with triethylamine are given in table.

Diethyl 2-(2-nitro-1-phenylethyl)malonate (XII). The ^{1}H and ^{13}C NMR spectra of **XII** were consistent with those reported in [7]. Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$, 263 (12), 218 (12), 190 (13), 189 (100), 171 (58), 161 (56), 145 (30), 133 (22), 131 (20), 117 (28), 115 (70), 105 (15), 104 (55), 103 (34), 91 (26), 78 (15), 77 (20). Retention time, min: (*R*)-**XII**), 18.5; (*S*)-**XII**, 43.1.

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