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Nitroalkenes in the Ni(II) catalyzed asymmetric Michael addition. Convenient route to the key intermediate of brivaracetam

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A series of Ni(II) complexes with novel chiral ligands derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine were synthesized. The catalytic activity of these complexes in the asymmetric Michael reaction is demonstrated. Asymmetric addition of diethyl malonate to ω-nitrostyrene and 1-nitropent-1-ene in the presence of these complexes leads to the enantiomerically enriched diethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate (up to 96 % *ee*) and (*R*)-diethyl 2-(1-nitropenthan-2-yl)malonate (up to 91 % *ee*). (4*R*)-4-Propylpyrrolidin-2-one, the key intermediate of antiepileptic drug brivaracetam, was obtained from corresponding nitroester.

Keywords: Michael addition • Asymmetric catalysis • Neurological agents • N Ligands • Nickel

Introduction

Metal catalyzed asymmetric *Michael* addition is an effective strategy for the total synthesis of natural compounds [1] and is used as the initial stage of a series of cascade transformations [2-5]. The reaction of 1,3-dicarbonyl compounds with nitroalkenes attracts the greatest attention, since the resulting adducts suggest a wide range of possible further applications, the most important of which is the reductive cyclization as the way to pyrrolidine-2-ones and gamma-amino acids [6, 7]. A number of these compounds are used as drugs for the treatment of CNS disorders ((*R*)-baclofen **1** [8-10], (*R*)-rolipram **2** [11, 12], (*S*)-pregabalin **3** [13-18] (Figure 1)).

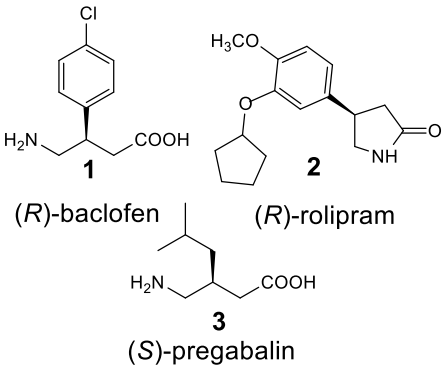

Figure 1. Pyrrolidine-2-ones and gamma-amino acids for the treatment of CNS disorders.

The strategy for the synthesis of chiral *Michael* adducts [19-26], based on the use of nickel complexes with chiral ligands, was applied to obtain non-racemic GABA derivatives [27], polysubstituted cyclohexanes [28], piperidin-2-ones [29]. We have also shown that Ni(II) complexes with chiral diamines are active catalysts in asymmetric conjugate addition of other *Michael* donors, such as β-oxo phosphonates [30] and β-oxo sulfoxides [31]. However, enantioselectivity strongly depends on the nature of the unsaturated substrate. Therefore, research in this area remains relevant. Brivaracetam ((2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl] butanamide) **4** (Figure 2) is a novel high-affinity ligand of synaptic vesicle protein 2A (SV2A) [32, 33], that is marketed by UCB and used to treat partial-onset seizures with or without secondary generalisation [34].

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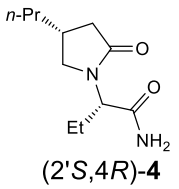
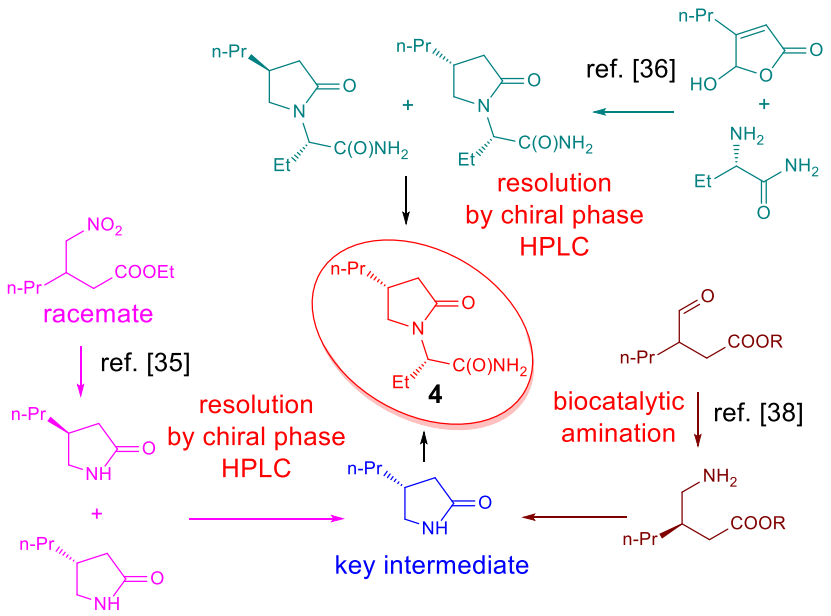


(2'*S*,4*R*)-**4**

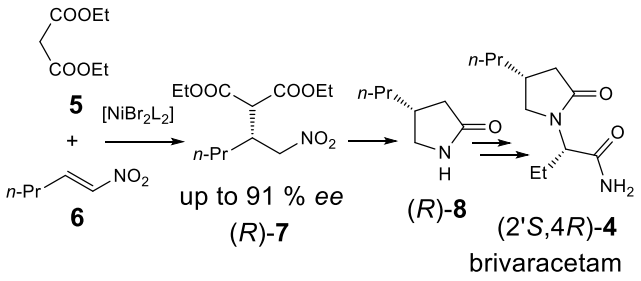
Figure 2. Brivaracetam **4**

The known procedures for the preparation of brivaracetam usually include generation of two or more stereoisomers of synthetic intermediates and thus one or more separation steps of these stereoisomers are required in order to obtain the desired compound. These separation steps may lower the overall yield and are generally time- and cost-consuming. The existing methods of the synthesis of brivaracetam are multistage and involves using of chromatography with a chiral stationary phase and the chiral starting reagents (Scheme 1) [35-38].



Scheme 1. The existing methods of the synthesis of brivaracetam **4**.

In the present work we report on the synthesis of a number of Ni(II) complexes with N,N´-disubstituted derivatives of (*R*,*R*)-1,2-diphenylethane-1,2-diamine (DPEN), (*R*,*R*)-cyclohexane-1,2-diamine (DACH) and (*S*,*S*)-bicyclo[2.2.2]octane-2,3-diamine, screening of their catalytic activity in the reactions of asymmetric addition of diethyl malonate (**5**) to ω-nitrostyrene and 1-nitropent-1-ene (**6**) as a key step in the synthesis of neurotropic drugs - GABA analogues and synthesis of the key intermediate (*R*)-(**8**) of brivaracetam (Scheme 2).



Scheme 2. Synthesis of the key intermediate of brivaracetam (*R*)-**8**

The advantage of the proposed method consists in asymmetric *Michael* addition as a key step. This allows to create the asymmetric center of desired configuration which remains unchanged in the later steps of the synthesis. Thus, the main objective is to ensure a high enantiomeric excess of the (*R*)-isomer by searching for effective chiral catalysts of the *Michael* addition.

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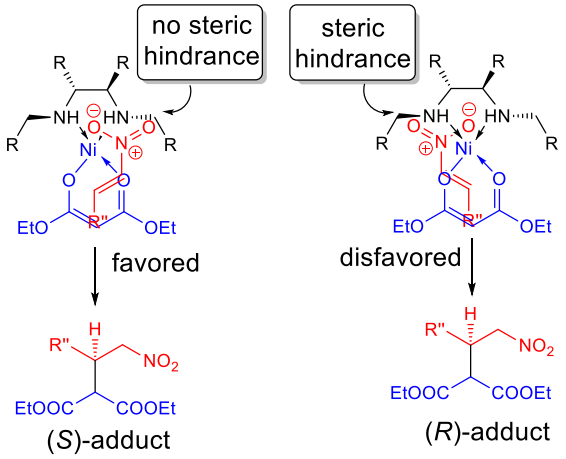
Results and Discussion

As shown by the authors [19], asymmetric induction in the reaction of 1,3-dicarbonyl compounds with nitroalkenes is caused by steric hindrance of substituents at the nitrogen atoms of the chiral ligands (Scheme 3). Therefore the use of a Ni(II) complex with unsubstituted DACH as a catalyst leads to a product with a low yield and enantioselectivity (6 %) [20].

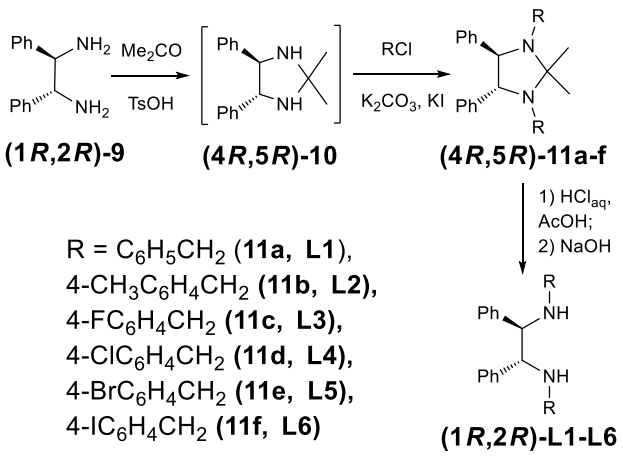


Scheme 3. Proposed transition state for the Ni-catalyzed Michael addition of 1,3-dicarbonyl compounds to nitroalkenes [19].

However, the reaction catalyzed by a complex of similar structure but with a ligand containing tertiary amino groups (N, N'-dibenzyl-N, N'-dimethylcyclohexane-1,2-diamine) also leads to a decrease in the rate and enantioselectivity of the reaction [19]. This fact shows that the possible formation of hydrogen bond between secondary amino group of the ligand and the nitro group of the substrate in the favored transition state can also make a certain contribution to the difference in the energies of favored and disfavored transition states. Consequently, it can be assumed that the condition for achieving high enantioselectivity of Michael addition is a combination of the secondary amino group and the bulky substituent at the nitrogen atom in the ligand structure.

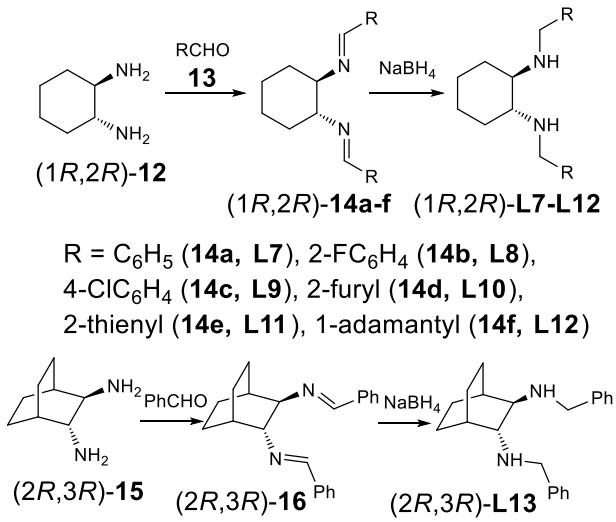
Therefore we should expect that the nature of the substituents in the chiral diamines will significantly affect the enantioselectivity of the reaction. To achieve an asymmetric induction in the reaction of diethyl malonate with 1-nitropent-1-ene we used ligands that provide the conformational rigidity of resulting chelate with varied aromatic and heteroaromatic substituents.

Initially, we obtained N,N´-dibenzylated (1*R*,2*R*)-DPEN derivatives **L1-L6** through successive treatment of diamine **9** with acetone to form imidazolidine **10** and following reaction with substituted benzyl chlorides in the presence of K_2CO_3. Acid hydrolysis of imidazolidines **11a-f** leads to DPEN derivatives (1*R*,2*R*)-**L1-L6** (Scheme 4).



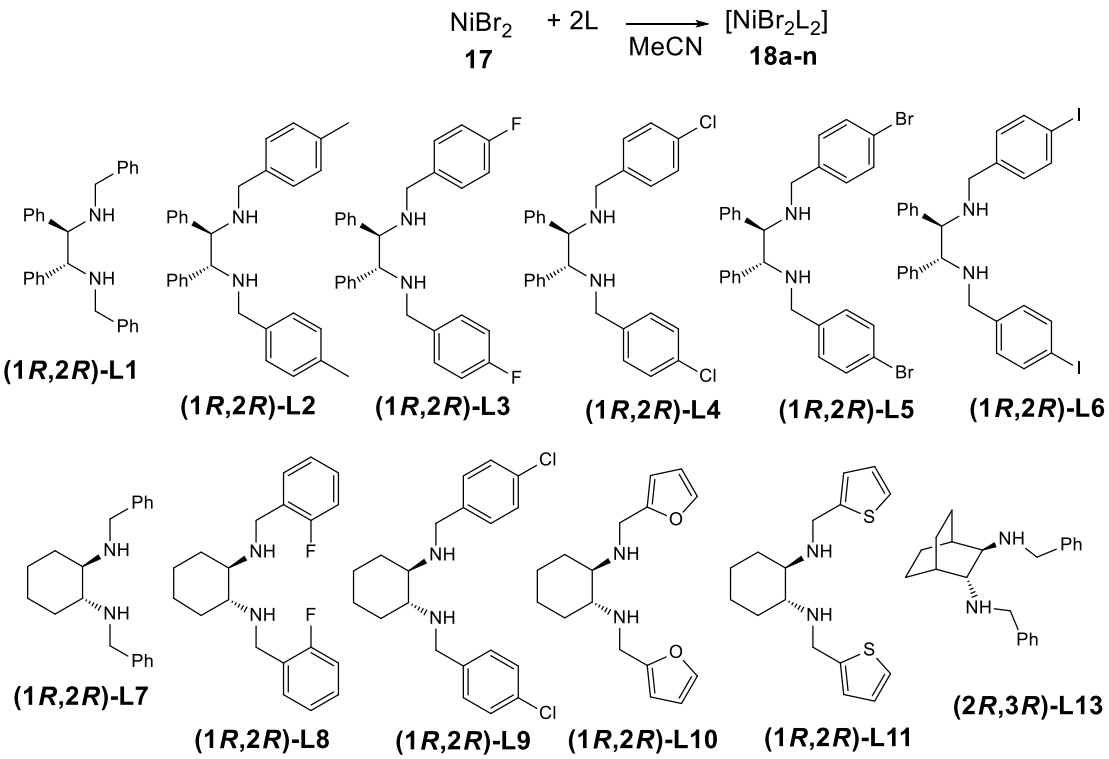
Scheme 4. Synthesis of N,N´-disubstituted derivatives of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **L1-L6**.

Other previously described chiral ligands - derivatives of (1*R*,2*R*)-DACH **L7-L12** [39-43] and (2*R*,3*R*)-bycyclo[2.2.2]octane-2,3-diamine **L13** [44] were synthesized to compare the catalytic properties of their complexes (Scheme 5).



Scheme 5. Synthesis of N,N´-disubstituted derivatives of (1*R*,2*R*)-cyclohexane-1,2-diamine **L7-L12** and (2*R*,3*R*)-bycyclo[2.2.2]octane-2,3-diamine **L13**

Ni(II) complexes with chiral ligands (1*R*,2*R*)-**L1-L11** and (2*R*,3*R*)-**L13** were obtained by the reaction of anhydrous nickel(II) bromide **17** with chiral vicinal diamines in acetonitrile (Scheme 6).



Scheme 6. Synthesis of Ni(II) complexes **18a-n**

According to the elemental analysis, the composition of complexes **18a-n** corresponds to formula $[NiBr_2L_2]$ (L = **L1-L11**, **L13**). In the IR spectra of **18a-n** the *ν*(NH) is shifted towards lower wave numbers by 40-100 cm^{-1} in comparison with *ν*(NH) for the free ligand. Other absorption bands basically correspond to those in the IR spectra of free ligands.

The single crystal X-ray diffraction study of compound **18b (L** = **L2)** proved *trans*-configuration of octahedral Ni(II) complex (Figure 3).

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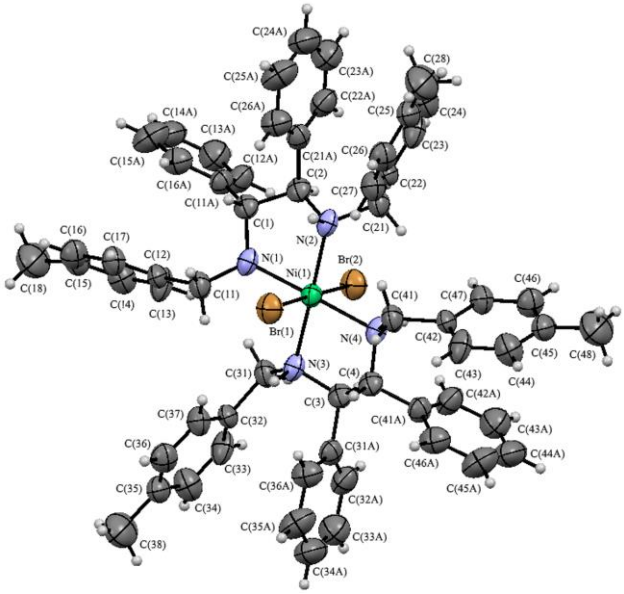
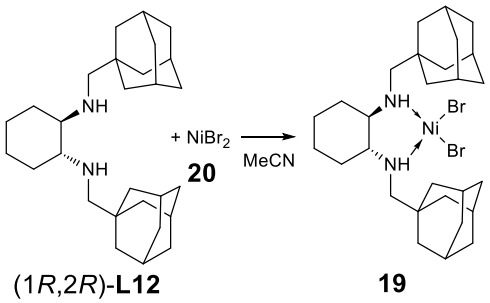


Figure 3. General view of compound **18b** molecule in the crystal.

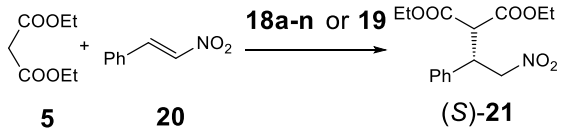
In the case of a ligand with adamantylmethyl substituent **L12**, the complex **19** containing only one coordinated diamine is formed (Scheme 7):



Scheme 7. Synthesis of Ni(II) complexes with ligand **L12**.

To study the catalytic activity of the complexes **18a-n**, **19** and the enantioselectivity of *Michael* addition, we have performed a screening of this complexes in the reaction of diethylmalonate with *ω*-nitrostyrene and 1-nitropent-1-ene.

Initially, we screened the obtained complexes in the model reaction of diethyl malonate **5** with ω-nitrostyrene **20** (Scheme 8, Table 1). Toluene was chosen as a solvent, because previously we found the best results in the reactions of nitrostyrene with *Michael* donors [30].



Scheme 8. Asymmetric addition of diethyl malonate **5** to *ω*-nitrostyrene **20**.

Table 1. Asymmetric addition of diethyl malonate **5** to *ω*-nitrostyrene **20** in the presence of complexes **18a-n** and **19**.

Entry[a]	Catalyst	Additive	Conversion, %[b]	Yield, %[c]	*ee*, %[d]
1	[$NiBr_2$(**L1**)$_2$] **18a**	-	>99	87	95
2	[$NiBr_2$(**L2**)$_2$] **18b**	-	>99	85	95

3	[$NiBr_2$(**L3**)$_2$] **18c**	-	>99	83	96
4	[$NiBr_2$(**L4**)$_2$] **18d**	-	>99	89	96
5	[$NiBr_2$(**L5**)$_2$] **18e**	-	>99	86	95
6	[$NiBr_2$(**L6**)$_2$] **18f**	-	>99	87	94
7	[$NiBr_2$(**L7**)$_2$] **18g**	-	>99	87	95
8	[$NiBr_2$(**L8**)$_2$] **18h**	-	>99	85	94
9	[$NiBr_2$(**L9**)$_2$] **18j**	-	**>99**	**87**	**97**
10	[$NiBr_2$(**L10**)$_2$] **18k**	-	>99	86	93
11	[$NiBr_2$(**L11**)$_2$] **18m**	-	>99	86	93
12	[$NiBr_2$(**L13**)$_2$] **18n**	-	>99	85	93
13	[$NiBr_2$(**L12**)$_2$] **19**	-	50	32	10
14	[$NiBr_2$(**L12**)$_2$] **19**	Et_3N	>99	81	42

[a] Reaction conditions: 1.10 mmol of ω-nitrostyrene, 1.00 mmol of diethyl malonate, 0.02 mmol (2 mol. %) of Ni(II) catalyst in toluene (1 ml), 25 °C, 72 h. [b] Determined by NMR. [c] Isolated yield after flash chromatography. [d]Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD column; the absolute configuration of **21** was determined by comparison with the literature data [19].

As seen from the data given in the table, all the studied octahedral complexes showed high catalytic activity in this reaction. The enantioselectivity of the reaction is 94-97% and depends weakly on the presence of substituents in the aromatic ring. Similar enantiomeric excesses of the (*S*)-isomer of nitroester **21** (entries 1 and 7) are achieved in the presence of complexes with N,N'-dibenzylated derivatives of DPEN and DACH. The highest enantioselectivity (97%) was achieved with the complex **18j (**entry 9**)**, in which the chlorine atom is in the para position. On the oppose, ortho-fluorobenzyl substituents at the nitrogen atom of the ligand lead to a certain decrease in enantioselectivity (entry 8). The complex **19** with one diamine containing adamantyl substituent showed low activity in the studied reaction (entry 13). Addition of one equivalent of triethylamine leads to an increase in catalytic activity. However, even in this case, the enantiomeric excess of the (*S*)-isomer is only 42% (entry 14).

The use of the less electrophilic 1-nitropent-1-ene as an unsaturated substrate (Scheme 9, Table 2) leads to a significant decrease in the reaction rate. Reaction at room temperature is slow (entry 1). Therefore, further reaction was carried out at 50 °C (entries 2-9).

Optimization of the reaction conditions in the presence of complexes **18a**, **18m**, **18n** and **19** (Table 2) showed that highest reaction rates are achieved in the absence of solvent, however, the enantioselectivity of the reaction is lower in this case (entries 2, 4, 6).

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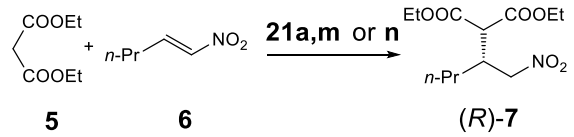


5 **6** (*R*)-**7**

Scheme 9. Asymmetric addition of diethyl malonate **5** to 1-nitropent-1-ene **6**.

Table 2. Optimization of reaction condition for asymmetric addition of diethyl malonate **5** to 1-nitropent-1-ene **6** [a].

Entry[a]	Catalyst	Solvent	t, °C	Time, h	Conversion, %[b]	Yield, %[c]	*ee*, %[d]
1	[$NiBr_2$(**L1**)$_2$] **18a**	-	25	72	16	ND	ND
2	[$NiBr_2$(**L1**)$_2$] **18a**	-	50	12	76	62	86
3	[$NiBr_2$(**L1**)$_2$] **18a**	**CCl_4**	**50**	**72**	**33**	**24**	**91**
4	[$NiBr_2$(**L11**)$_2$] **18m**	-	50	12	83	68	84
5	[$NiBr_2$(**L11**)$_2$] **18m**	CCl_4	50	72	>99	82	86
6	[$NiBr_2$(**L12**)$_2$] **18n**	-	50	12	>99	81	82
7	[$NiBr_2$(**L12**)$_2$] **18n**	EtOAc	50	12	>99	83	83
8	[$NiBr_2$(**L12**)$_2$] **18n**	toluene	50	12	>99	83	85
9	[$NiBr_2$(**L12**)$_2$] **18n**	CCl_4	50	12	>99	82	87

[a] Reaction conditions: 1.10 mmol of 1-nitropent-1-ene, 1.00 mmol of diethyl malonate, 0.02 mmol (2 mol. %) of Ni(II) catalyst. [b] Determined by NMR. [c] Isolated yield after flash chromatography [d] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD column; the absolute configuration of **7** assigned by analogy to the known product **21**.

The enantioselectivity of the addition of diethyl malonate **5** to 1-nitropent-1-ene **6** is also lower than the reaction with ω-nitrostyrene. This fact can be explained by conformational flexibility of the propyl substituent, which reduces the difference in the energy of the transition states in accordance with the adopted stereochemical model for catalysis by chiral *Lewis* acids [19].

The highest enantioselectivity in the reaction of diethyl malonate with 1-nitropent-1-ene was achieved for the complexes **18a** and **18b** with the ligands **L1** and **L2** - diphenylethanediamine derivatives (Table 3, entries 1, 2). However, the reaction rate in this case was lower than for complexes based on ligands - cyclohexane-1,2-diamine derivatives **L7** - **L12** (entries 7-12). Complex **19** is the least active in the catalysis of the Michael reaction (entry 13), as in the case with nitrostyrene (see Table 1). The enantiomeric excess in the presence of **19** is 16 %, but it increases to 63 % when **19** is used in combination with triethylamine.

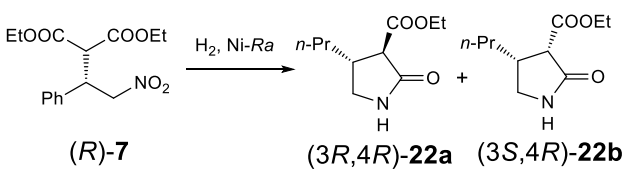
Table 3. Asymmetric addition of diethyl malonate **5** to 1-nitropent-1-ene **6** [a].

Entry[a]	Catalyst	Additive	Time, h	Conversion, %[b]	Yield, %[c]	*ee*, %[d]
1	[$NiBr_2$(**L1**)$_2$] **18a**	-	**72**	**33**	**24**	**91**

2	[$NiBr_2$(**L2**)$_2$] **18b**	-	**72**	**40**	**29**	**91**
3	[$NiBr_2$(**L3**)$_2$] **18c**	-	72	50	41	89
4	[$NiBr_2$(**L4**)$_2$] **18d**	-	72	43	32	87
5	[$NiBr_2$(**L5**)$_2$] **18e**	-	72	50	40	90
6	[$NiBr_2$(**L6**)$_2$] **18f**	-	72	50	39	86
7	[$NiBr_2$(**L7**)$_2$] **18g**	-	72	>99	87	87
8	[$NiBr_2$(**L8**)$_2$] **18h**	-	72	88	65	84
9	[$NiBr_2$(**L9**)$_2$] **18j**	-	72	>99	86	85
10	[$NiBr_2$(**L10**)$_2$] **18k**	-	12	85	64	81
11	[$NiBr_2$(**L11**)$_2$] **18m**	-	72	>99	82	86
12	[$NiBr_2$(**L12**)$_2$] **18n**	-	12	>99	82	87
13	[$NiBr_2$(**L13**)$_2$] **19**	-	72	53	42	16
14	[$NiBr_2$(**L13**)$_2$] **19**	Et_3N	72	87	62	63

[a] Reaction conditions: 1.10 mmol of 1-nitropent-1-ene, 1.00 mmol of diethyl malonate, 0.02 mmol (2 mol. %) of Ni(II) catalyst in CCl_4 (1ml), 50 °C. [b] Determined by NMR. [c] Isolated yield after flash chromatography. [d]Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD column.

The resulting *Michael* adduct was used to synthesize the key intermediate of brivaracetam. Hydrogenation of nitroester **7** in isopropanol in the presence of *Ra*-Ni leads to the (4*R*)-4-propylpyrrolidine-2-one-3-carboxylic acid ester **22** as a mixture of *trans*- and *cis*-isomers (9 : 1 according NMR ^1H) (Scheme 10).

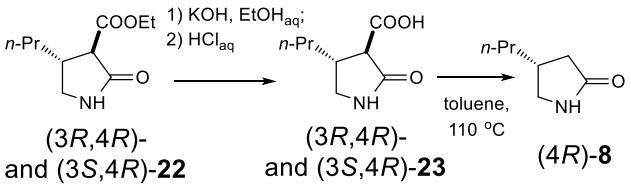


(*R*)-**7** (3*R*,4*R*)-**22a** (3*S*,4*R*)-**22b**

Scheme 10. Synthesis of 4-propylpyrrolidine-2-one-3-carboxylic acid ester **22**.

The NOESY experiment showed no interaction between H3 and H4 of the pyrrolidine moiety of **22a** (see *Supporting information*). Based on these data, it can be concluded that major stereoisomer of **22** is a *trans* isomer.

Subsequent hydrolysis of this ester in the presence of a base in an aqueous organic medium gave (3*R*,4*R*)- and (3*S*,4*S*)-4-propylpyrrolidine-2-one-3-carboxylic acid **23**. Decarboxylation of the acid **23** by refluxing in toluene gives (4*R*)-4-propyl pyrrolidin-2-one **8** (Scheme 11).



Scheme 11. Synthesis of (4*R*)-4-propylpyrrolidine-2-one **8**.

Optical rotatory power of **8** corresponds to sign and absolute value of known data for (4*R*)-4-propyl pyrrolidin-2-one [35].

Conclusions

In conclusion, new Ni(II) complexes, effective for Michael addition catalysis, were synthesized and described. The enantioselectivity of addition of diethyl malonate to ω-nitrostyrene in the presence of these complexes is 94 - 97 % and to 1-nitropent-1-ene is 82 - 91 %. We have shown that nickel complexes with 1,2-diphenylethane-1,2-diamine derivatives provide the greatest enantioselectivity in the reaction of diethyl malonate with 1-nitropent-1-ene, but have less catalytic activity compared to analogous complexes with cyclohexane-1,2-diamine.
An effective approach to the key intermediate of the antiepileptic drug brivaracetam is proposed.

Experimental Section

General information

^{1}H, ^{13}C NMR spectra were recorded on JEOL JNM-ECX400 (^{1}H NMR - 399.78 MHz, ^{13}C NMR 100.53 MHz). All signals were expressed as ppm using residual solvent peak as an internal standard. FTIR spectra were recorded on a Shimadzu IRAffinity-1 spectrophotometer with Specac® Quest ATR. Melting points were determined on an electrothermal melting point apparatus OptiMelt and are uncorrected. Elemental analysis was performed on EuroVector EA-3000 analyzer. Optical rotatory power was measured on Rudolph Research Analytical (Autopol V Plus Automatic Polarimeter) at 589 nm. The enantiomeric purity of the products was determined by HPLC analysis on Waters LC equipped with a chiral stationary phase column Chiralcel AD-3 with hexane/2-propanol 82:18 as eluent, 1.2 ml/min, λ = 210 nm. Column chromatography was performed on Silica gel 60, Merck (230 – 400 mesh). X-Ray crystallographic data was collected using a Stoe STADI-VARI Pilatus-100K diffractometer. CCDC-1841633 contains the supplementary crystallographic data for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif. Ligands **L1** [43], **L7-L12** [38-42], **L13** [43] and complexes **18a** [43], **18g** [19], **18k-n** [43] were obtained in accordance with previously described procedures.

*General procedure for the synthesis of imidazolidines **11b-f**.*

To (1*R*,2*R*)-1.2-diphenylethane-1,2-diamine **9** (4.87 mmol) acetone (45 ml) and TsOH (25 mg) were added, and the resulting mixture was refluxed for 3 h. Then, to resulting solution of **10** anhydrous K_2CO_3 (14.6 mmol), KI (0.983 mmol) and substituted benzyl chloride (9.83 mmol) were added and the mixture was refluxed with vigorous stirring for 12 h. Reaction mixture was filtered, the precipitate washed with boiling acetone, filtrate was evaporated. The residue was recrystallized from acetone.

(4*R*,5*R*)-2,2-Dimethyl-1,3-Bis(4-methylbenzyl)-4,5-diphenylimidazolidine (11b). Yield: 0.42 g (32 %). M.p. 113 – 115 °C. $[\alpha]_D^{20}$ = +88.0 (*c* 0.5, acetone). IR (neat/cm^{-1}): 3026 (w), 2974 (w), 2922 (w), 2843 (w), 2793 (w), 1603 (w), 1514 (m), 1489 (w), 1452(w), 1371 (m), 1356 (m), 1315 (m)., 1252 (m), 1207 (m), 1179 (m), 1082 (w), 1070 (w), 1020 (w), 961 (w), 831 (w), 799 (s), 752 (s), 696 (vs), 617 (w), 559 (w), 509 (w), 490 (s), 478 (m). ^{1}H NMR (400 MHz, C_6D_6) δ: 1.19 (s, 6H, CH_3), 2.05 (s, 6H, CH_3), 3.56 (s, 4H, CH_2), 3.82 (s, 2H, CH), 6.89-6.91 (m, 4H), 6.97-7.01 (m, 2H), 7.02-7.07 (m, 4H), 7.17-7.19 (m, 4H), 7.24-7.27 (m, 4H). ^{13}C NMR (100.5 MHz, C_6D_6) δ: 20.81 (CH_3), 26.04 (CH_3), 51.53 (CH_2), 75.89 (CH), 79.59 (**C**(CH_3)$_2$), 127.38 (CH), 128.01 (CH), 128.57 (CH), 128.62 (CH), 128.95 (CH), 135.70 (C), 138.04 (C), 140.65 (C). Anal. calc. for $C_{33}H_{36}N_2$ (460.66): C 86.04, H 7.88, N 6.08; found: C 86.14, H 7.81, N 6.01.

(4*R*,5*R*)-1,3-Bis(4-fluorobenzyl)-2,2-dimethyl-4,5-diphenylimidazolidine (11c). Yield: 0.60 g (41 %). M.p. 119 – 121 °C. $[\alpha]_D^{20}$ = +97.2 (*c* 0.5, acetone). IR (neat/cm^{-1}): 3028 (w), 2970 (w), 2795 (w), 1603 (m), 1506 (vs), 1454 (m), 1373 (m), 1360 (m), 1254 (m), 1217 (vs), 1152 (s), 1015 (m), 926 (w), 916 (w), 837 (s), 812 (vs), 754 (vs), 690 (vs), 631 (w), 617 (m), 561 (m). ^{1}H NMR (400 MHz, C_6D_6) *δ*: 1.03 (s, 6H, CH_3), 3.34 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.42 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.70 (s, 2H, CH), 6.67-6.73 (m, 4H), 6.93-7.03 (m, 10H), 7.09-7.14 (m, 4H). ^{13}C NMR (100.5 MHz, C_6D_6) *δ*: 25.80 (s, CH_3), 51.12 (s, CH_2), 75.82 (s, CH), 79.45 (s, **C**$(CH_3)_2$), 114.56 (d, CH, $^2J_{CF}$ 22.0 Гц), 127.51 (s, CH), 128.02 (s, CH), 128.50 (s, CH), 130.30 (d, CH, $^3J_{CF}$ 7.7 Гц), 136.52 (d, C, $^4J_{CF}$ 2.9 Гц), 140.13 (s, C), 161.85 (d, **C**-F, $^1J_{CF}$ 244.4 Гц). Anal. calc. for $C_{31}H_{30}F_2N_2$ (468.59): C 79.46, H 6.45, N 5.98; found: C 79.52, H 6.40, N 5.91.

(4*R*,5*R*)-1,3-Bis(4-chlorobenzyl)-2,2-dimethyl-4,5-diphenylimidazolidine (11d). Yield: 1.42 g (41 %). M.p. 166 – 167 °C. $[\alpha]_D^{20}$ = +109.2 (*c* 0.5, acetone). IR (neat/cm^{-1}): 3030 (w), 2980 (w), 2845 (w), 2793 (w), 1601 (w), 1489 (s), 1452 (m), 1369 (m), 1315 (m), 1238 (w), 1256 (m), 1215 (m), 1186 (m), 1171 (m), 1088 (s), 1015 (s), 962 (w), 862 (w), 835 (m), 808 (m), 794 (vs), 758 (s), 698 (vs), 671 (m), 631 (m), 610 (m), 554 (m), 511 (s). ^{1}H NMR (400 MHz, C_6D_6) *δ*: 0.98 (s, 6H, CH_3), 3.29 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.37 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.68 (s, 2H, CH), 6.80-7.12 (m, 18H). ^{13}C NMR (100.5 MHz, C_6D_6) *δ*: 25.81 (CH_3), 51.17 (CH_2), 75.73 (CH), 79.46 (**C**$(CH_3)_2$), 127.55 (CH), 127.97 (CH), 128.03 (CH), 128.49 (CH), 130.17 (CH), 132.21 (**C**-Cl), 139.40 (C), 139.94 (C). Anal. calc. for $C_{31}H_{30}Cl_2N_2$ (501.50): C 74.25, H 6.03, N 5.59; found: C 74.31, H 5.96, N 5.52.

(4*R*,5*R*)-1,3-Bis(4-bromobenzyl)-2,2-dimethyl-4,5-diphenylimidazolidine (11e). Yield: 1.57 g (55 %). M.p. 179 – 181 °C. $[\alpha]_D^{20}$ = +102.2 (*c* 0.5, acetone). IR (neat/cm^{-1}): 3030 (w), 2980 (w), 2845 (w), 2793 (w), 1601 (w), 1485 (s), 1452 (m), 1369 (m), 1357 (m), 1315 (m), 1256 (m), 1213 (m), 1186 (m), 1171 (m), 1069 (s), 1011 (vs), 962 (w), 862 (w), 831 (s), 804 (m), 791 (vs), 758 (vs), 698 (vs), 658 (m), 635 (m), 602 (w), 552 (w). ^{1}H NMR (400 MHz, C_6D_6) *δ*: 0.96 (s, 6H, CH_3), 3.26 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.34 (d, 2H, CH_2, $^2J_{HH}$ 14.6 Hz), 3.67 (s, 2H, CH), 6.84 (d, 4H, $^3J_{HH}$ 8.2 Hz), 6.98 (d, 4H, $^3J_{HH}$ 8.2 Hz), 7.07-7.17 (m, 10H). ^{13}C NMR (100.5 MHz, C_6D_6) *δ*: 25.82 (CH_3), 51.20 (CH_2), 75.70 (CH), 79.46 (**C**$(CH_3)_2$), 120.31 (**C**-Br), 127.56 (CH), 128.04 (CH), 128.48 (CH), 130.53 (CH), 130.93 (CH), 139.89 (C). Anal. calc. for $C_{31}H_{30}Br_2N_2$ (590.40): C 63.07, H 5.12, N 4.74; found: C 63.14, H 5.07, N 4.69.

(4*R*,5*R*)-1,3-Bis(4-iodobenzyl)-2,2-dimethyl-4,5-diphenylimidazolidine (11f). Yield: 0.52 g (59 %). M.p. 189 – 191 °C. $[\alpha]_D^{20}$ = +86.6 (*c* 0.5, acetone). IR (neat/cm^{-1}): 3030 (w), 2982 (w), 2791 (w), 1600 (w), 1585 (w), 1566 (w), 1481 (m), 1452 (m), 1398 (w), 1367 (m), 1315 (m), 1256 (s), 1213 (s), 1184 (s), 1070 (m), 1057 (m), 1026 (m), 1004 (vs), 962 (w), 947 (w), 914 (w), 831 (s), 787 (vs), 758 (vs), 698 (vs), 653 (m), 629 (m), 503 (m). ^{1}H NMR (400 MHz, C_6D_6) *δ*: 0.95 (s, 6H, CH_3), 3.25 (d, 2H, CH_2, $^2J_{HH}$ 14.7 Hz), 3.32 (d, 2H, CH_2, $^2J_{HH}$ 14.7 Hz), 3.66 (s, 2H, CH), 6.72 (d, 4H, $^3J_{HH}$ 8.0 Hz), 6.98 (d, 4H, $^3J_{HH}$ 8.0 Hz), 7.07-7.10 (m, 6H), 7.34-7.37 (m, 4H). ^{13}C NMR (100.5 MHz, C_6D_6) *δ*: 25.84 (CH_3), 51.27 (CH_2), 75.68 (CH), 79.47 (**C**$(CH_3)_2$), 91.68 (**C**-I), 127.54 (CH), 128.04 (CH), 128.48 (CH), 130.81 (CH), 136.93 (CH), 139.89 (C), 140.56 (C). Anal. calc. for $C_{31}H_{30}I_2N_2$ (684.40): C 54.40, H 4.42, N 4.09; found: C 54.47, H 4.37, N 4.02.

*General procedure for synthesis of diamines **L2-L6.***

To imidazolidine **11b-f** (2.65 mmol) 10% hydrochloric acid (13 ml) and acetic acid (26 ml) were added. The mixture was refluxed for 6 h. Reaction mixture was cooled, filtered, and the precipitate of the diamine dihydrochloride was treated with saturated aqueous solution of NaOH. Diamine was extracted with CH_2Cl_2 (3×25 ml). The extract was dried over K_2CO_3 and solvent was evaporated.

(1*R*,2*R*)-N,N´-Bis(4-methylbenzyl)-1,2-diphenylethane-1,2-diamine (L2). Yield: 0.24 g (89 %). M.p. 67 – 70 °C. $[\alpha]_D^{20}$ = -29.4 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3313 (w), 3024 (w), 2920 (w), 1514 (w), 1490 (w), 1452 (s), 1217 (w), 1199 (w), 1103 (m), 1072 (w), 1020 (w), 914 (w), 870 (w), 849 (w), 802 (m), 750 (vs), 696 (vs), 608 (m), 590 (m), 567 (m), 480 (s). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.28 (broad s, 2H, NH), 2.34 (s, 6H, CH_3), 3.44 (d, 2H, CH_2, $^2J_{HH}$ 13.1 Hz), 3.62 (d, 2H, CH_2, $^2J_{HH}$ 13.1 Hz), 3.70 (s, 2H, CH), 7.03-7.06 (m, 4H), 7.09-7.18 (m, 14H). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 21.21 (s, CH_3), 51.14 (s, CH_2), 68.41 (s, CH), 126.94 (s, CH), 128.02 (s, CH), 128.10 (s, CH), 128.14 (s, CH), 129.08 (s, CH), 136.37 (C), 137.67 (C), 141.37 (C). Anal. calc. for $C_{30}H_{32}N_2$ (420.60): C 85.67, H 7.67, N 6.66; found: C 85.75, H 7.61, N 6.61.

(1*R*,2*R*)-N,N´-Bis(4-fluorobenzyl)-1,2-diphenylethane-1,2-diamine (L3). Yield: 0.40 g (73 %). M.p. 65 – 67 °C. $[\alpha]_D^{20}$ = -29.1 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3345 (w), 3327 (w), 3028 (w), 2882 (w), 2828 (w), 2760 (w), 1601 (m), 1508 (vs), 1454 (m), 1433 (m), 1346 (w), 1308 (w), 1219 (vs), 1155 (m), 1113 (m), 1072 (m), 1063 (m), 1028 (w), 1016 (w), 978 (w), 916 (w), 856 (m), 841 (m), 833 (m), 820 (vs), 756 (vs), 694 (vs), 648 (m), 600 (vs), 554 (m), 544 (m). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.47 (broad s, 2H, NH), 3.46 (d, 2H, CH_2, $^2J_{HH}$ 13.3 Hz), 3.64 (d, 2H, CH_2, $^2J_{HH}$ 13.3 Hz), 3.70 (s, 2H, CH), 6.93-6.99 (m, 4H), 7.04-7.07 (m, 4H), 7.14-7.20 (m, 10H). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 50.64 (s, CH_2), 68.21 (s, CH), 115.19 (d, CH, $^2J_{CF}$

21.1 Hz), 127.18 (s, CH), 127.99 (s, CH), 128.17 (s, CH), 129.73 (d, CH, $^3J_{CF}$ 7.7 Hz), 136.11 (s, C), 140.85 (s, C), 161.95 (d, **C**-F, $^1J_{CF}$ 244.4 Hz). Anal. calc. for $C_{28}H_{26}F_2N_2$ (428.52): C 78.48, H 6.12, N 6.54; found: C 78.54, H 6.08, N 6.49.

(1*R*,2*R*)-N,N´-Bis(4-chlorobenzyl)-1,2-diphenylethane-1,2-diamine (L4). Yield: 0.84 g (65 %), pale yelow oil. $[\alpha]_D^{20}$ = -44.1 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3312 (w), 3026 (w), 2974 (w), 2897 (w), 2826 (w), 1599 (w), 1489 (s), 1452 (s), 1406 (m), 1362 (w), 1263 (w), 1233 (w)., 1200 (m), 1088 (s), 1015 (s), 978 (w), 914 (w), 870 (w), 847 (m), 831 (m), 806 (s), 795 (s), 758 (s), 738 (m), 696 (vs), 673 (m), 633 (m), 609 (w), 578 (m), 551 (w), 521 (m). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.36 (broad s, 2H, NH), 3.45 (d, 2H, CH_2, $^2J_{HH}$ 13.7 Hz), 3.64 (d, 2H, CH_2, $^2J_{HH}$ 13.7 Hz), 3.68 (s, 2H, CH), 7.02-7.06 (m, 4H), 7.11-7.18 (m, 10H), 7.23-7.27 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 50.66 (CH_2), 68.20 (CH), 127.20 (CH), 127.99 (CH), 128.19 (CH), 128.53 (CH), 129.53 (CH), 132.58 (**C**-Cl), 139.03 (C), 140.87 (C). Anal. calc. for $C_{28}H_{26}Cl_2N_2$ (461.43): C 72.88, H 5.68, N 6.07; found: C 72.93, H 5.62, N 6.01.

(1*R*,2*R*)-N,N´-Bis(4-bromobenzyl)-1,2-diphenylethane-1,2-diamine (L5). Yield: 1.17 g (82 %), pale yelow oil. $[\alpha]_D^{20}$ = -38.6 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3312 (w), 3026 (w), 2918 (w), 2826 (w), 1591 (w), 1485 (s), 1452 (s), 1402 (m), 1346 (w), 1198 (w), 1103 (s), 1069 (s), 1011 (vs), 912 (w), 868 (w), 802 (m), 791 (m), 758 (m), 696 (vs), 656 (m), 625 (w), 573 (s), 542 (w), 515 (m). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.46 (broad s, 2H, NH), 3.43 (d, 2H, CH_2, $^2J_{HH}$ 13.5 Hz), 3.63 (d, 2H, CH_2, $^2J_{HH}$ 13.5 Hz), 3.68 (s, 2H, CH), 7.03 (d, 4H, $^3J_{HH}$ 8.2 Hz), 7.07 (d, 4H, $^3J_{HH}$ 8.2 Hz), 7.14-7.19 (m, 6H), 7.38-7.41 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 50.63 (CH_2), 68.07 (CH), 120.75 (**C**-Br), 127.27 (CH), 127.99 (CH), 128.22 (CH), 129.95 (CH), 131.50 (CH), 139.30 (C), 140.57 (C). Anal. calc. for $C_{28}H_{26}Br_2N_2$ (550.34): C 61.11, H 4.76, N 5.09; found: C 61.18, H 4.69, N 5.02.

(**1*R*,2*R*)-N,N´-Bis(4-iodobenzyl)-1,2-diphenylethane-1,2-diamine (L6).** Yield: 0.37 g (75 %). M.p. 47 – 49 °C. $[\alpha]_D^{20}$ = -34.7 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3304 (w), 3024 (w), 2918 (w), 2820 (w), 1601 (w), 1585 (w), 1481 (s), 1450 (s), 1398 (m), 1346 (w), 1196 (w), 1101 (s), 1072 (m), 1059 (m), 1026 (w), 1005 (vs), 912 (w), 868 (w), 802 (m), 787 (s), 758 (s), 696 (vs), 646 (w), 605 (w), 592 (w), 569 (s), 538 (w), 511 (m). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.49 (broad s, 2H, NH), 3.42 (d, 2H, CH_2, $^2J_{HH}$ 13.5 Hz), 3.62 (d, 2H, CH_2, $^2J_{HH}$ 13.5 Hz), 3.68 (s, 2H, CH), 6.95 (d, 4H, $^3J_{HH}$ 8.2 Hz), 7.02 (d, 4H, $^3J_{HH}$ 8.2 Hz), 7.13-7.18 (m, 6H), 7.58-7.61 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 50.69 (CH_2), 68.07 (CH), 92.27 (**C**-I), 127.26 (CH), 127.99 (CH), 128.22 (CH), 130.25 (CH), 137.48 (CH), 139.99 (C), 140.56 (C). Found (%): C, 52.26; H, 4.02; N, 4.29. Calc. for $C_{28}H_{26}I_2N_2$ (%): C, 52.19; H 4.07; N, 4.35. Anal. calc. for $C_{28}H_{26}I_2N_2$ (644.34): C 52.19, H 4.07, N 4.35; found: C 52.26, H 4.02, N 4.29.

*General procedure for the synthesis of complexes **18** and **19.***

To a solution of diamine **L1-L13** (0.910 mmol) in 5 ml of acetonitrile anhydrous $NiBr_2$ **17** (0.433 mmol) was added. The resulting mixture was refluxed under argon for 12 h. The acetonitrile was evaporated in vacuo. The residue was dissolved in methyl *tert*-butyl ether (2 ml), and the complex was precipitated by the addition of hexane (10 ml). The precipitate was filtered off and dried in vacuo.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-methylbenzyl)-1,2-diphenylethane-1,2-diamine]nickel(II) (18b). Yield: 0.22 g (72 %). M.p. 175 – 177 °C (decomp.). $[\alpha]_D^{20}$ = +102.9 (*c* 1.0, $CHCl_3$). IR (neat/cm^{-1}): 3263 (w), 3022 (w), 2955 (w), 2918 (w), 1587 (w), 1516 (m), 1495 (m), 1439 (s), 1360 (w), 1315 (w), 1198 (w), 1123 (m), 1076 (m), 1059 (s), 1040 (s), 962 (s), 947 (s), 930 (s), 887 (vs), 816 (s), 797 (vs), 756 (s), 694 (vs), 650 (m), 640 (m), 600 (m), 583 (w), 554 (s), 544 (s), 521 (s). Anal. calc. for $C_{60}H_{64}Br_2N_4Ni$ (1059.70): C 68.01, H 6.09, N 5.29; found: C 68.10, H 6.01, N 5.22.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-fluorobenzyl)-1,2-diphenylethane-1,2-diamine]nickel(II) (18c). Yield: 0.37 g (74 %). M.p. 178 - 180 °C (decomp.). $[\alpha]_D^{20}$ +133.9 (*c* 0.5, $CHCl_3$). IR (neat/cm^{-1}): 3260 (w), 3227 (w), 1603 (m), 1508 (vs), 1454 (m), 1439 (m), 1423 (w), 1300 (w), 1221 (vs), 1157 (m), 1103 (m), 1082 (m), 1057 (m), 1024 (w), 968 (m), 952 (s), 939 (m), 923 (w), 891 (s), 849 (m), 820 (s), 806 (s), 758 (vs), 696 (vs), 646 (m), 594 (m), 554 (m), 554 (m), 527 (m). Anal. calc. for $C_{56}H_{52}Br_2F_4N_4Ni$ (1075.56): C 62.54, H 4.87, N 5.21; found: C 62.61, H 4.82, N 5.16.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-chlorobenzyl)-1,2-diphenylethane-1,2-diamine]nickel(II) (18d). Yield: 0.86 g (83 %). M.p. 173 – 175°C (decomp.). $[\alpha]_D^{20}$ = +166.6 (*c* 0.5, $CHCl_3$). IR (neat/cm^{-1}): 3254 (w), 3238 (w), 3024 (w), 2937 (w), 1599 (w), 1493 (s), 1452 (m), 1435 (m), 1408 (w), 1302 (w), 1273 (w), 1157 (w), 1125 (m), 1090 (s), 1059 (s), 1014 (m), 945 (m), 932 (m), 885 (vs), 814 (s), 789 (vs), 760 (s), 698 (vs), 644 (m), 592 (m), 540 (s), 517 (s). Anal. calc. for $C_{56}H_{52}Br_2Cl_4N_4Ni$ (1141.37): C 58.93, H 4.59, N 4.91; found: C 59.01, H 4.52, N 4.85.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-bromobenzyl)-1,2-diphenylethane-1,2-diamine]nickel(II) (18e). Yield: 1.22 g (87 %). M.p. 165 – 167°C (decomp.). $[\alpha]_D^{20}$ = +102.3 (*c* 0.5, $CHCl_3$). IR (neat/cm^{-1}): 3258 (w), 3238 (w), 3040 (w), 2951 (w), 1591 (w), 1489 (s), 1452 (s), 1435 (s), 1404 (m), 1357 (w), 1304 (w), 1271 (w), 1186 (m), 1155 (w), 1124 (m), 1072 (s), 1059 (s), 1011 (s), 976 (m), 966 (s), 945 (s), 931 (m), 883 (vs), 821 (s), 812 (s), 783 (vs), 760 (s), 698 (vs), 656 (w), 626 (m), 619 (m), 584 (m), 540 (s), 517 (s). Anal. calc. for $C_{56}H_{52}Br_6N_4Ni$ (1319.18): C 50.99, H 3.97, N 4.25; found: C 51.07, H 3.91, N 4.19.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-iodobenzyl)-1,2-diphenylethane-1,2-diamine]nickel(II) (18f). Yield: 0.30 g (69 %). M.p. 173 – 175°C (decomp.). $[\alpha]_D^{20}$ = +74.6 (*c* 0.5, $CHCl_3$). IR (neat/cm^{-1}): 3265 (w), 3256 (w), 1585 (w), 1493 (w), 1479 (m), 1454 (m), 1439 (m), 1396 (m), 1352 (w), 1300 (w), 1269 (w), 1182 (w), 1117 (m), 1080 (m), 1053 (s), 1003 (s), 966 (m), 945 (s), 885 (s), 820 (s), 783 (s), 758 (m), 696 (vs), 679 (vs), 650 (m), 621 (w), 611 (m), 592 (m), 530 (s), 513 (s). Anal. calc. for $C_{56}H_{52}Br_2I_4N_4Ni$ (1507.18): C 44.63, H 3.48, N 3.72; found: C 44.70, H 3.42, N 3.69.

Dibromobis[(1*R*,2*R*)-N,N´-bis(2-fluorobenzyl)cyclohexane-1,2-diamine]nickel(II) (18h). Yield: 0.12 g (79%). M.p. 198–200 °C (decomp.). $[\alpha]_D^{20}$ = -45.1 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 3279 (w), 2936 (m), 2855 (w), 1616 (w), 1585 (w), 1489 (s), 1450 (vs), 1229 (s), 1111 (m), 1090 (m), 1059 (m), 1038 (w), 972 (s), 932 (vs), 889 (s), 878 (vs), 837 (m), 820 (vs), 783 (m), 745 (vs), 696 (m), 434 (s), 419 (s). Anal. calc. for $C_{40}H_{48}Br_2F_4N_4Ni$ (879.33): C, 54.64; H, 5.50; N, 6.37; found: C, 54.69; H, 5.46; N, 6.41.

Dibromobis[(1*R*,2*R*)-N,N´-bis(4-chlorobenzyl)cyclohexane-1,2-diamine]nickel(II) (18j). Yield: 0.15 g (62%). M.p. 158–160 °C (decomp.). $[\alpha]_D^{20}$ = -100.4 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 3264 (w), 2931 (m), 2860 (w), 1597 (w), 1575 (w), 1495 (s), 1450 (vs), 1408 (w), 1094 (vs), 1063 (m), 1013 (s), 976 (s), 937 (s), 895 (s), 880 (vs), 847 (m), 837 (m), 797 (vs), 658 (s), 478 (s), 422 (m), 407 (m), 401 (m). Anal. calc. for $C_{40}H_{48}Br_2Cl_4N_4Ni$ (945.15): C, 50.83; H, 5.12; N, 5.93; found: C, 50.89; H, 5.09; N, 5.98.

Dibromo[(1*R*,2*R*)-N,N´-bis(adamantan-1-ylmethyl)cyclohexane-1,2-diamine]nickel(II) (19). Yield: 0.15 g (37%). M.p. >320 °C (decomp.). $[\alpha]_D^{20}$ = -35.7 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 3264 (w), 3217 (w), 2899 (vs), 2845 (s), 1443 (vs), 1391 (w), 1368 (w), 1344 (w), 1317 (w), 1150 (w), 1092 (m), 1057 (m), 1040 (s), 1015 (s), 978 (s), 912 (m), 895 (m), 885 (m), 878 (m), 571 (w), 509 (w), 463 (w), 414 (s), 407 (m). Anal. calc. for $C_{28}H_{46}Br_2N_2Ni$ (629.18): C, 53.45; H, 7.37; N, 4.45; found: C, 53.52; H, 7.31; N, 4.51.

*General Procedure for Ni(II) Catalyzed Enantioselective Michael Addition of diethyl malonate **5** to ω-nitrostyrene **20**.*

Nickel(II) complex **18a-n** or **19** (0.02 mmol) was added to a solution of 164 mg (1.10 mmol) ω-nitrostyrene **23** and 160 mg (1.00 mmol) diethyl malonate **5** 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 purified by chromatography on silica gel using $CHCl_3$ as eluent.

Diethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate (21). M.p. 45–46 °C. $[\alpha]_D^{20}$ = +7.3 (*c* 1.5, $CHCl_3$). IR (neat/cm^{-1}): 2984 (w), 1728 (vs), 1553 (vs), 1497 (w), 1466 (w), 1456 (w), 1447 (w), 1369 (s), 1329 (m), 1300 (m), 1256 (m), 1231 (m), 1177 (s), 1152 (s), 1096 (m), 1026 (s), 988 (w), 860 (m), 768 (m), 700 (vs), 608 (m). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.03 (t, 3H, CH_3, $^3J_{HH}$ 7.1 Hz), 1.24 (t, 3H, CH_3, $^3J_{HH}$ 7.1 Hz), 3.80 (d, 1H, **C**H(COOEt)$_2$, $^3J_{HH}$ 9.2 Hz), 3.99 (q, 2H, CH_2O, $^3J_{HH}$ 7.1 Hz), 4.15–4.30 (m, 3H, CH_2O, **C**HPh), 4.80–4.95 (m, 2H, **CH_2**NO_2), 7.23–7.30 (m, 5H, Ph). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 13.79 (CH_3), 14.02 (CH_3), 43.06 (**CH**Ph), 55.08 [**CH**(COOEt)$_2$], 61.93 and 62.21 (CH_2O), 78.68 (CH_2NO_2), 128.11 (CH), 128.41 (CH), 128.99 (CH), 136.36 (C), 166.90 and 167.53 (C=O). Anal. calc. for $C_{15}H_{19}NO_6$ (309.32): C 58.25, H 6.19, N 4.53; found: C 58.29, H 6.14, N 4.49. HPLC (Chiralcel AD, hexane/2-propanol = 82/18, 1.2 mL/min, λ = 210 nm, retention times: (*R*) (minor) 9.5 min, (*S*) (major) 23.9 min).

*General Procedure for Ni(II) Catalyzed Enantioselective Michael Addition of diethyl malonate **5** to 1-Nitropent-1-ene **6**.*

To a mixture of diethyl malonate **5** (160 mg, 1.00 mmol) and 1-nitropent-1-ene **6** (127 mg, 1.10 mmol) the catalyst (0.02 mmol) was added and the reaction mixture was stirred at 50 °C for 12 h. Conversion was determined by NMR analysis. The reaction product was isolated by flash chromatography (CCl_4 – 3 % ethyl acetate) to give the product as a pale yellow oil.

(*R*)-Diethyl 2-(1-nitropenthan-2-yl)malonate (7). Yield: 79 %. B.p. 105–110 °C (1×10^{-3} torr). $[\alpha]_D^{20}$ = +8.36 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 2967 (s), 2940 (s), 2877 (m), 1732 (s), 1551 (s), 1466 (s), 1446 (m), 1373 (m), 1304 (m), 1265 (m), 1219 (m), 1180 (m), 1157 (m), 1096 (w), 1026 (s), 864 (w), 810 (w), 737 (w), 698 (w). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.88 (t, 3H, $^3J_{HH}$ = 6.9 Hz), 1.23 (t, 6H, $^3J_{HH}$ = 7.1 Hz), 1.30 – 1.45 (m, 4H), 2.82 – 2.92 (m, 1H), 3.57 (d, 1H, $^3J_{HH}$ = 5.7 Hz), 4.17 (q, 1H, $^3J_{HH}$ = 8.0 Hz), 4.49 (dd, 1H, $^3J_{HH}$ 6.9 Hz, $^2J_{HH}$ 13.3 Hz), 4.66 (dd, 1H, $^3J_{HH}$ 5.0 Hz, $^2J_{HH}$ 13.3 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$) *δ*: 13.79, 14.06, 19.87, 32.22, 36.73, 52.70, 61.80, 61.95, 76.75, 167.85, 168.05. Anal. calc. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09; found, %: C 52.29; H 7.73; N 5.07. HPLC analysis (Chiralcel AD column; hexane / 2-propanol, 98:2; flow rate 1.2 mL/min; wavelength 210 nm); retention times: (*R*) (major) 8.82 min, (*S*) (minor) 10.15 min).

Ethyl 2-oxo-4-propylpyrrolidine-3-carboxylate (mixture of (3*R*,4*R*)- and (3*S*,4*R*)-isomers) (22). The solution of **7** (9.4 g, 34.1 mmol) in 30 ml of *i*-PrOH is transferred to an autoclave and about 1 g of Raney nickel is added. The reaction mixture is allowed to react at 70 °C under 50 bars of hydrogen pressure for 36 h. The catalyst is filtered off and washed with *i*-PrOH. The filtrate was concentrated in vacuo. The residue was purified by silica column chromatography ($CHCl_3$) to give the product as a pale yellow oil. Yield: 5.0 g (74 %). *dr* 9 : 1. $[\alpha]_D^{20}$ = +31.4 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 3198 (w), 3098 (w), 2955 (w), 2930 (w), 2864 (w), 1732 (s), 1697 (vs), 1491 (w), 1456 (m), 1379 (m), 1337 (m), 1298 (m),

1265 (m), 1204 (m), 1175 (s), 1155 (s), 1123 (m), 1092 (m), 1016 (m), 935 (w), 845 (w), 787 (m), 766 (m), 746 (m), 704 (m), 637 (m), 523 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.20–1.30 (m, 5H), 1.36–1.48 (m, 2H), 2.74–2.84 (m, 1H), 2.93 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^2J_{HH}$ = 9.6 Hz), 3.02 (d, 1H, $^3J_{HH}$ = 8.9 Hz), 3.49 (t, 1H, *J* = 8.70 Hz), 4.10 – 4.25 (m, 2H, CH_2O), 7.46 (bs, 1H, NH) (for (3*R*,4*R*)-isomer); 0.86 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.20 – 1.30 (m, 5H), 1.36 – 1.48 (m, 2H), 2.58 – 2.69 (m, 1H), 3.18 (t, 1H, *J* = 9.40 Hz), 3.26 (d, 1H, $^3J_{HH}$ = 9.15 Hz), 3.38 (t, 1H, *J* = 8.47 Hz), 7.35 (bs, 1H, NH) (for (3*S*,4*R*)-isomer). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 14.00, 14.21, 20.42, 36.01, 39.30, 46.79, 54.81, 61.60, 170.16, 174.00 (for (3*R*,4*R*)-isomer); 14.06, 14.27, 20.82, 31.42, 39.10, 47.41, 52.53, 61.21, 169.07, 174.75 (for (3*S*,4*R*)-isomer). Anal. calc. for $C_{10}H_{17}NO_3$ (199.25): C, 60.28; H, 8.60; N, 7.03; found, %: C 60.21; H 8.65; N 7.08.

2-Oxo-4-propylpyrrolidine-3-carboxylic acid (mixture of (3*R*,4*R*)- and (3*S*,4*R*)-isomers) (23). To a solution of **22** (5.22 g, 26.2 mmol) in 110 ml of ethanol 25 ml of the 15 % aqueous solution of KOH was added at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and 30 min at room temperature. Then 50 ml of water was added and the resulting solution was extracted with toluene. The organic layer was separated and the aqueous phase was acidified with hydrochloric acid to pH 2 and extracted with chloroform. The extract was dried over sodium sulfate and evaporated in vacuo to give the product as a pale yellow oil. Yield: 3.63 g (81 %). *dr* 9 : 1. $[\alpha]_D^{20}$ = +52.5 (*c* 1.0, $CHCl_3$). IR (neat, ν/cm^{-1}): 3287 (w), 2957 (w), 2930 (w), 2872 (w), 1682 (vs), 1659 (vs), 1649 (vs), 1489 (w), 1447 (w), 1377 (w), 1281 (m), 1206 (m), 1177 (m), 1121 (w), 1049 (w), 748 (m), 691 (m), 665 (m), 515 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.27 – 1.36 (m, 2H), 1.39 – 1.48 (m, 1H), 1.58 – 1.67 (m, 1H), 2.75 – 2.84 (m, 1H), 3.01 (dd, $^3J_{HH}$ = 7.8 Hz, $^2J_{HH}$ = 9.6 Hz, 1H), 3.08 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 3.55 (t, 1H, *J* = 9.0 Hz), 7.61 (bs, 1H), 10.23 (bs, 1H) (for (3*R*,4*R*)-isomer); 0.90 (t, 3H, $^3J_{HH}$ = 7.3 Hz), 1.27–1.36 (m, 2H), 1.39–1.48 (m, 1H), 1.58–1.67 (m, 1H), 2.65–2.74 (m, 1H), 3.24 (t, 1H, *J* = 8.9 Hz), 3.35 (d, 1H, $^3J_{HH}$ = 8.7 Hz), 3.40–3.48 (m, 1H), 7.61 (bs, 1H), 10.23 (bs, 1H) (for (3*S*,4*R*)-isomer). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 14.03, 20.41, 36.09, 38.75, 47.10, 53.77, 172.38, 175.38 (for (3*R*,4*R*)-isomer); 14.03, 20.75, 31.12, 38.66, 47.38, 52.32, 172.05, 176.11 (for (3*S*,4*R*)-isomer). Anal. calc. for $C_8H_{13}NO_3$ (171.19): C, 56.13; H, 7.65; N, 8.18; found, %: C 56.03; H 7.69; N 8.22.

(4*R*)-4-Propylpyrrolidin-2-one (8). Acid **23** (3.63 g, 21.2 mmol) was dissolved in 40 ml of toluene and refluxed for 6 hours. Then the reaction mixture was evaporated in vacuo. The residue was purified by silica column chromatography ($CHCl_3$) to give the product as a pale yellow oil. Yield: 2.13 g (64 %); pale yellow oil; $[\alpha]_D^{20}$ = +2.3 (*c* 1.0, MeOH); IR (neat, ν/cm^{-1}): 3229 (w), 2957 (w), 2926 (w), 2872 (w), 1686 (vs), 1489 (w), 1456 (w), 1425 (w), 1377 (w), 1285 (m), 1263 (w), 1244 (w), 1065 (w), 742 (w), 690 (w), 673 (w), 500 (m); ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, $^3J_{HH}$ = 7.0 Hz), 1.30 – 1.45 (m, 4H), 1.85–2.00 (m, 1H), 2.30–2.48 (m, 2H), 2.99 (dd, 1H, *J* = 15.13, 10.74 Hz), 3.38–3.48 (m, 1H), 6.90–7.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.07, 20.71, 34.72, 36.86, 48.28, 178.34. Anal. calcd. for $C_7H_{13}NO$, (127.18): C, 66.11; H, 10.30; N, 11.01; Found, %: C 66.04; H 10.36; N 11.07.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

The research was conceived by AR. AS, LK and VI carried out the experiments under the supervision of AR and YK. The discussion of the results and the redaction of the manuscript were made by AR and YK. Experimental data were described by AS and AR. The crystallographic structures were elucidated by VR.

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