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Reaction of β-Nitrostyrene with Diethyl Malonate in the Presence of Bispidines: The Unusual Role of the Organocatalyst

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Abstract: The aim of this work was the investigation of novel organocatalysts for the Michael addition of diethyl malonate to β-nitrostyrene. The methodology of the study included NMR titration, reaction monitoring by NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS), product characterization by MALDI, IR spectroscopy, scanning electron microscopy (SEM), thermal gravimetric analysis (TGA), and elemental analysis. As a result, evidence of supramolecular interactions between two pairs of components of the reaction was found. In addition to the supramolecular complexes, an unusual reaction, i.e., the Michael addition of NH-bispidines to β-nitrostyrene, was found, which led to previously unknown oligomers of β-nitrostyrene. A new mechanism for the catalytic action of NH-bispidine was proposed, which involved catalysis not by the initial organocatalyst but rather by its adduct with β-nitrostyrene. Thus, in this reaction, *N*-benzylbispidine acted as an initiator, and the real catalyst was the betaine formed during the initiation stage.

Keywords: catalysis; bispidines; monoterpenoids; Michael addition; nitroolefins; β-nitrostyrene; NMR spectroscopy; mass-spectrometry; oligomerization

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1. Introduction

Michael conjugate addition is a convenient and widely used method for creating carbon-carbon bonds in organic synthesis [1,2]. In recent years, approaches to conducting the catalytic asymmetric variant of the Michael reaction have been actively developed [3–8]. Such reactions make it possible to obtain optically pure reagents with high selectivity for the synthesis of a wide range of biologically active and natural compounds [9,10]. The implementation of the enantioselective addition of various nucleophiles to nitro-alkenes, or the nitro-Michael reaction, is of great interest. This is because the products formed, in this case, are convenient precursors in the synthesis of modern drugs: derivatives of γ-aminobutyric acid, such as baclofen [11], phenibut [12], tolibut [13], and pregabalin [14]; derivatives based on piracetam, such as phenylpiracetam [15] and rolipram [16,17]. Both chiral metal complexes and chiral organocatalysts are used as catalysts in the asymmetric version of the nitro-Michael reaction. The literature provides examples of the addition of 1,3-dicarbonyl compounds to nitro-alkenes in the presence of palladium [18], scandium [19], copper [20], aluminum [21], nickel [22,23], magnesium [24], iridium [25], ruthenium [26], lanthanum [27], and heterometallic complexes of lithium and aluminum [28]. Among the chiral organocatalysts in the nitro-Michael reaction, derivatives of proline [29,30], urea [31], thiourea [32], squaramide [33], and quinine [34] are most often used (Figure 1).

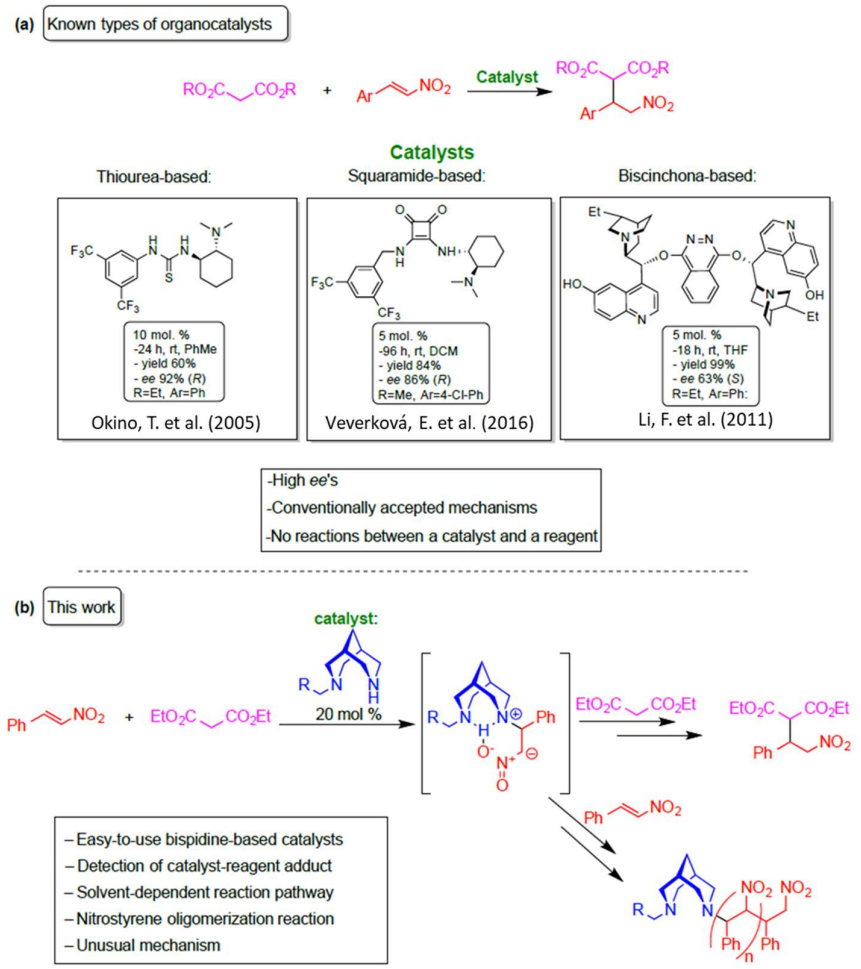
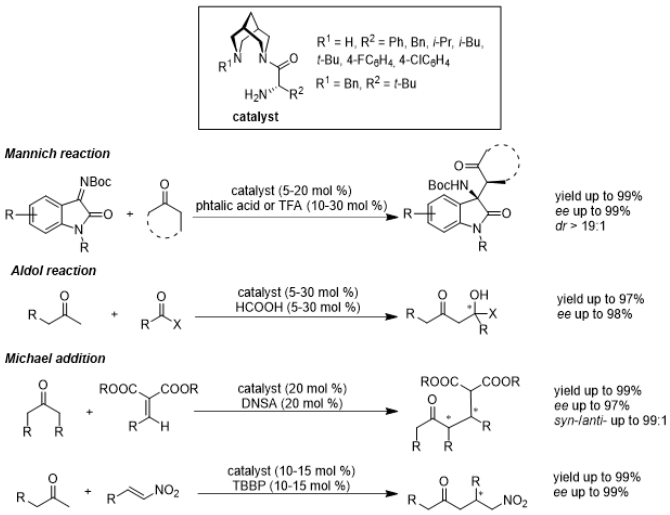


Figure 1. Organocatalysts in the nitro−Michael reaction: reaction scheme and known types of organocatalysts for the nitro−Michael reaction (**a**) [32,34,35]; the nitro−Michael reaction featured in the present study, in the presence of bispidine, and the main features of the study (**b**).

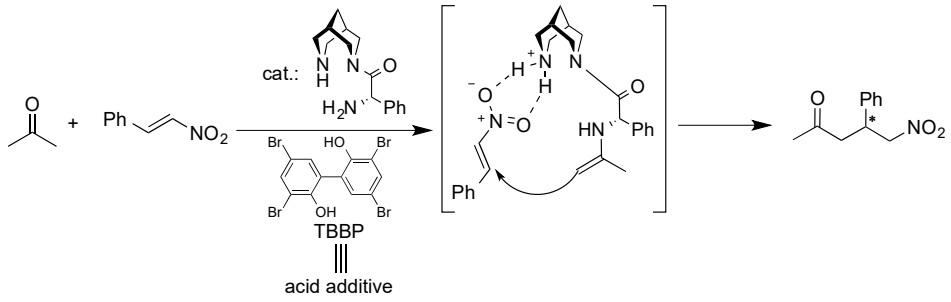
Bispidine, or 3,7-diazabicyclo[3.3.1]nonane, is of great interest as a basis for the creation of catalysts in asymmetric synthesis due to its conformational rigidity and the presence of two nitrogen atoms, which opens up wide possibilities in terms of functionalization and the potential for supramolecular interactions. Indeed, chiral bispidines are used as ligands in metal-complex catalysts of asymmetric variants of Henry reactions [36–38], the addition of diethyl zinc to aldehydes [39,40], chalcones [41,42] and enones [43], the hydrogenation of C=C bonds [44], the oxidative kinetic separation of secondary alcohols [45], deprotonation [46], and cyclopropanation [47].

All currently known bispidine-based chiral organocatalysts have been developed by the research group of Professor X. Feng [48]. They have found their application in carrying out asymmetric variants of Mannich reactions [49,50], the aldol reaction [51], and the Michael addition [52,53] (Scheme 1).

Such catalysts have a secondary or tertiary nitrogen atom and a chiral amino group with a primary nitrogen atom due to the presence of an amino acid fragment in their structure and are, in fact, hybrid bifunctional catalysts. In these catalysts, a secondary or tertiary nitrogen atom participates in the activation of the electrophile due to the formation of hydrogen bonds, and a primary amino acid nitrogen atom activates the nucleophile through the formation of an enamine intermediate. Such a mechanism is proposed, for example, for the Michael addition of ketones to nitroalkenes in the presence of bispidines [53] (Scheme 2). The proposed mechanism also explains the need for an acidic additive for the effective operation of the catalyst.



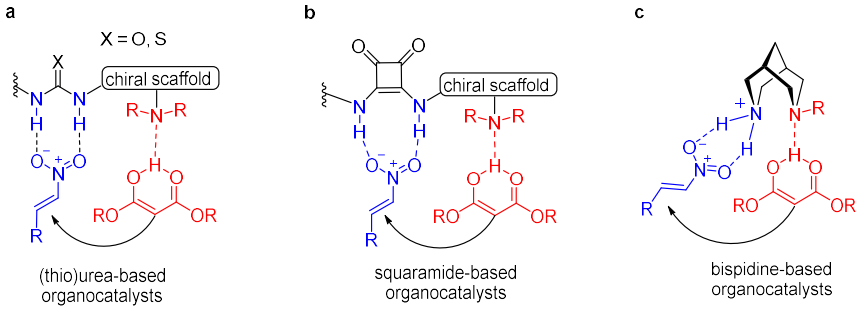
Scheme 1. Reactions catalyzed by bispidine−based chiral organocatalysts. DNSA = 3,5−dinitrosalicylic acid; TBBP = 3,3′,5,5′−tetrabromobiphenol. * indicates the asymmetric carbon atom being created.



Scheme 2. The mechanism of Michael's addition of ketones to nitroalkenes in the presence of bispidines as organocatalysts. * indicates the asymmetric carbon atom being created.

To date, there are no examples of the addition of malonates to nitroalkenes catalyzed by bispidines. At the same time, the bispidine platform appears to be convenient for the development of catalysts similar to derivatives of urea, thiourea, and squaramide. These known compounds also have secondary nitrogen atoms in their structure as hydrogen bond donors for the binding of nitroalkene and tertiary nitrogen atoms as Lewis bases for the enolization of malonate (Scheme 3).

Thus, the aim of this work was to investigate diethyl malonate addition to *β*-nitrostyrene in the presence of *N*-substituted bispidines as organocatalysts.



Scheme 3. The principle of operation of chiral organocatalysts based on (thio)urea (**a**) and squaramide (**b**); the idea of using bispidine in the reactions of Michael addition of malonates to nitroalkenes (**c**).

2. Materials and Methods

2.1. General Information

All reagents and solvents used in the work (purity 90.0–99.9+%) were obtained from commercial sources (Sigma-Aldrich (St. Louis, MA, USA), abcr (Karlsruhe, Germany), Acros Organics (Geel, Belgium), Fisher Scientific (Hampton, NH, USA)) and, if necessary, subjected to additional purification to achieve analytical purity in a standard manner immediately before use. Bispidines **6** and **7** were synthesized according to procedure [54]. Halogen derivatives of monoterpenoids **8a-c** were synthesized according to procedure [55]. Racemic diethyl 2-(2-nitro-1-phenylethyl) malonate **5** was synthesized as a reference sample according to procedure [56].

2.2. Characterization Methods

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (400 and 101 MHz, respectively) and Bruker AM-300 (300 and 75 MHz, respectively) instruments (Karlsruhe, Germany). The monitoring of catalytic reactions in time was carried out by recording ^{1}H NMR spectra on a Bruker Avance 600 (600 MHz) instrument. High-resolution mass spectra were recorded on a Bruker maXis q-TOF instrument equipped with an electrospray ionization source (ESI). The measurements were carried out in the mode of registration of positive ions (the voltage on the capillary was 4500 V). The mass scanning range was m/z 50–3000, and calibration was carried out using a low-concentration calibration solution called 'Tuning mix' (Agilent Technologies, Santa Clara, CA, USA). The samples were injected using a Hamilton RN 1750 500 mL syringe (Reno, NV, USA) in tetrahydrofuran. The flow rate was 3 μL/min. Nitrogen was used as a spray gas (1.0 bar) and desiccant gas (4 l/min), and the interface temperature was 200 °C.

High-resolution mass spectra of **11-7**, **11-8,** and **11-9** were recorded on a SolariX XR FT/ICR mass spectrometer (Karlsruhe, Germany) equipped with a 15 T superconducting magnet, a ParaCell analyzer cell, and an ESI Apollo II and MALDI SmartBeam-II ion source. External calibration of the mass spectrometer was performed using a low-concentration sodium trifluoroacetate solution (0.1 mg/mL in acetonitrile:water, 1:1). The data set size was 4M with 64 scans. All MALDI-FT-ICR-MS measurements were recorded in positive ion mode with MTP 384 ground steel target plate (trans-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) matrix, with a scan range of m/z 150–3000). All data visualization was processed using the Data Analysis 5.1 software package from Bruker Daltonics. For MALDI measurements, 20 μL of sample (10 μg/mL in THF) was mixed with 20 μL of DCTB (saturated solution in THF) using a pipette and placed onto a MTP 384 ground steel target plate (Bruker Daltonics, Bremen, Germany) and allowed to dry at room temperature. The angle of optical rotation was measured using a JASCO P-2000 polarimeter (Tokio, Japan). The HPLC analysis of the reaction mixtures was carried out on a liquid chromatograph, Steyer-M (JSC Acquilon, Podolsk, Moscow Region, Russia), equipped with a DAICEL Chiralpak AD-H column with chiral stationary phase and a UV detector (λ = 220 nm). Retention times for compound **5** (*n*-Hexane: *i*-PrOH 70:30): (*S*) rt = 5.63 min, (*R*) rt = 10.17 min (racemate). The control of the reaction progress and purity of the compounds obtained was performed by TLC on Merck TLC Silica gel 60G F_{254} plates. Carl Roth Silica gel 60 silica gel with particle size 0.04–0.063 mm was used for chromatography. To obtain IR spectra of nitrostyrene and the products of its interaction with bispidine, tablets of the substance with potassium bromide were prepared. Registration of IR spectra was carried out in the region of 4000–400 cm^{-1} (16 scans, resolution 2 cm^{-1}) on a Bruker ALPHA instrument (Karlsruhe, Germany). The spectra were processed using the OPUS Spectroscopic Software (Bruker, Karlsruhe, Germany).

2.3. General Procedure for Synthesis of Compounds **9a-c**

2.2 mmol of Et_3N was added to a solution of 2.2 mmol of *N*-Boc-bispidine **7** and 2.2 mmol of the halogen derivative **8a-c** in 10 mL of MeCN. The reaction mixture was refluxed with stirring for 6 h. The reaction mixture was then diluted with water and extracted with $CHCl_3$. The organic phase was separated, dried over anhydrous Na_2SO_4, and

evaporated in a vacuum. The resulting residue was purified by column chromatography (silica gel; eluent PE:EA 4:1).

2.3.1. *tert*-Butyl 7-(2-oxo-2-(((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)ethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (**9a**)

Yellow oil. Yield: 74% (0.684 g). $[\propto]_D^{20} = -24.1$ (C = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.96 (dd, *J* = 13.7, 3.5 Hz, 1H, CH), 1.18–1.34 (m, 2H, 2CH), 1.44 (s, 9H, $3CH_3$), 1.63–1.84 (m, 6H, CH_2 + 4CH), 1.92 (ddd, *J* = 13.0, 9.3, 4.4 Hz, 1H, CH), 2.30–2.39 (m, 1H, CH), 2.92 (br.s, 4H, $2CH_2$), 2.99–3.10 (m, 2H, CH_2), 3.27 (d, *J* = 6.5 Hz, 2H, CH_2), 4.06–4.22 (m, 2H, CH_2), 4.89 (ddd, *J* = 10.0, 3.5, 2.1 Hz, 1H, CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.2, 18.4, 19.3, 26.9, 27.6, 28.2, 28.6, 30.5, 36.5, 44.5, 47.3, 48.2, 58.7, 78.2, 79.5, 154.9, 170.7. Found $[M + H]^+$: m/z = 421.3067. $C_{24}H_{41}N_2O_4^+$. Calculated $[M + H]^+$: 421.3061. Δ = 1.4 ppm.

2.3.2. *tert*-Butyl 7-(3-oxo-3-(((1S,2R,4S)-1,7,7-trimethylbicyclo [2.2.1]heptan-2-yl)oxy)propyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (**9b**)

Yellow oil. Yield: 67% (0.64 g). $[\propto]_D^{20} = -20.2$ (C = 2.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.87–0.94 (m, 4H, CH_3 + CH), 1.15–1.32 (m, 2H, 2CH), 1.44 (s, 9H, $3CH_3$), 1.55–1.84 (m, 6H, CH_2 + 4CH), 1.91 (ddd, *J* = 12.9, 9.2, 4.5 Hz, 1H, CH), 2.16–2.37 (m, 3H, CH_2 + CH), 2.40–2.65 (m, 4H, $2CH_2$), 2.82–3.12 (m, 4H, $2CH_2$), 4.03–4.19 (m, 2H, CH_2), 4.85 (ddd, *J* = 10.0, 3.5, 2.1 Hz, 1H, CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.0, 18.4, 19.3, 26.7, 27.6, 28.2, 28.7, 28.9, 31.3, 32.2, 36.3, 44.5, 47.3, 48.3, 48.5, 53.6, 57.3, 58.2, 78.2, 79.3, 154.9, 172.8. Found $[M + H]^+$: m/z = 435.3218. $C_{25}H_{43}N_2O_4^+$. Calculated $[M + H]^+$: 435.3217. Δ = 0.2 ppm.

2.3.3. *tert*-Butyl 7-(4-oxo-4-(((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)butyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (**9c**)

Yellow oil. Yield: 44% (0.436 g). $[\propto]_D^{20} = -20.6$ (C = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.94 (dd, *J* = 13.8, 3.6 Hz, 1H, CH), 1.17–1.33 (m, 2H, 2CH), 1.44 (s, 9H, $3CH_3$), 1.52–1.97 (m, 9H, $2CH_2$ + 5CH), 2.05–2.25 (m, 4H, $2CH_2$), 2.26–2.37 (m, 3H, CH_2 + CH), 2.81–3.15 (m, 4H, $2CH_2$), 3.98–4.14 (m, 2H, CH_2), 4.87 (dt, *J* = 9.7, 2.8 Hz, 1H, CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.1, 18.4, 19.3, 22.0, 26.7, 27.6, 28.2, 28.6, 31.0, 32.0, 36.4, 44.5, 47.3, 47.4, 48.3, 57.8, 58.3, 78.2, 79.2, 154.6, 173.9. Found $[M + H]^+$: m/z = 449.3385. $C_{26}H_{45}N_2O_4^+$. Calculated $[M + H]^+$: 449.3374. Δ = 2.5 ppm.

2.4. General Procedure for Synthesis Compounds **10a-c**

1.2 mmol of **9a-c** was dissolved in 2 mL of $CHCl_3$, and 1 mL of TFA was added to the solution. The reaction mixture was stirred for 1 h. The reaction mixture was evaporated to dryness in a vacuum, and the residue was dissolved in water and alkalized to pH 14 with an aqueous KOH solution. The mixture was extracted with $CHCl_3$, the organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated in a vacuum to dryness.

2.4.1. (1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(3,7-diazabicyclo[3.3.1]nonan-3-yl)acetate (**10a**)

Yellow oil. Yield: 88% (0.34 g). $[\propto]_D^{23} = -28.14$ (C = 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.99 (dd, *J* = 13.8, 3.5 Hz, 1H, CH), 1.18–1.40 (m, 2H, CH_2), 1.59–2.00 (m, 7H, CH, CH_2, CH_2, 2CH), 2.32–2.46 (m, 1H, CH), 2.60 (d, *J* = 10.8 Hz, 2H, CH_2), 2.97 (d, *J* = 13.6 Hz, 2H, CH_2), 3.05 (d, *J* = 10.8 Hz, 2H, CH_2), 3.10–3.15 (m, 4H, $2CH_2$), 3.70 (br. s., 1H), 4.95 (ddd, *J* = 9.9, 3.5, 2.1 Hz, 1H, CH). ^{13}C NMR (76 MHz, $CDCl_3$) δ 13.6, 18.8, 19.7, 27.2, 28.1, 29.7, 32.6, 36.9, 44.9, 47.8, 48.8, 52.1, 52.2, 59.1, 60.6, 80.4, and 171.2. Found $[M + H]^+$: m/z = 321.2541. $C_{19}H_{33}N_2O_2^+$. Calculated $[M + H]^+$: 321.2537. Δ = 1.2 ppm.

2.4.2. (1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(3,7-diazabicyclo[3.3.1]nonan-3-yl)propanoate (**10b**)

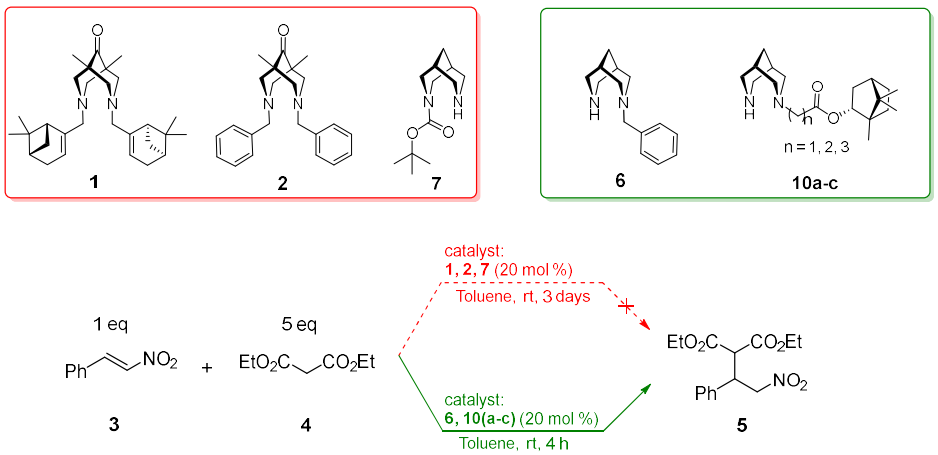
Yellow oil. Yield: 91% (0.367 g). $[\alpha]_D^{23} = -26.53$ (C = 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.95 (dd, *J* = 13.7, 3.5 Hz, 1H, CH), 1.17–1.36 (m, 2H, 2CH), 1.59–1.98 (m, 7H, CH_2 + 5CH), 2.31–2.42 (m, 3H, CH_2 + CH), 2.47–2.60 (m, 4H, $2CH_2$), 2.90 (d, *J* = 13.6 Hz, 2H, CH_2), 2.97–3.10 (m, 4H, $2CH_2$), 3.25 (br.s, 1H, NH), 4.88 (ddd, *J* = 10.0, 3.5, 2.1 Hz, 1H, CH). ^{13}C NMR (76 MHz, $CDCl_3$) δ 13.6, 18.9, 19.7, 27.2, 28.1, 29.9, 33.1, 36.9, 44.9, 47.8, 48.8, 52.2, 54.9, 59.3, 59.4, 80.0, and 172.8. Found $[M + H]^+$: *m*/*z* = 335.2690. $C_{20}H_{35}N_2O_2^+$. Calculated $[M + H]^+$: 335.2693. Δ = 0.9 ppm.

2.4.3. (1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-(3,7-diazabicyclo[3.3.1]nonan-3-yl)butanoate (**10c**)

Yellow oil. Yield: 95% (0.398 g). $[\alpha]_D^{23} = -22.44$ (C = 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.96 (dd, *J* = 13.7, 3.5 Hz, 1H, CH), 1.17–1.36 (m, 2H, 2CH), 1.58–1.99 (m, 9H, 2CH2 + 5CH), 2.21 (t, *J* = 7.1 Hz, 2H, CH_2), 2.26–2.41 (m, 5H, CH_2, CH_2, CH), 2.93 (d, *J* = 13.7 Hz, 2H, CH_2), 2.98–3.09 (m, 4H, $2CH_2$), 3.36 (br.s, 1H, NH), 4.90 (ddd, *J* = 9.9, 3.5, 2.0 Hz, 1H, CH). ^{13}C NMR (76 MHz, $CDCl_3$) δ 13.6, 18.8, 19.7, 22.4, 27.1, 28.1, 30.0, 32.4, 33.3, 36.9, 44.9, 47.8, 48.8, 52.4, 58.5, 59.6, 59.6, 79.8, 173.9. Found $[M + H]^+$: *m*/*z* = 349.2854. $C_{21}H_{37}N_2O_2^+$. Calculated $[M + H]^+$: 349.2850. Δ = 1.1 ppm.

3. Results and Discussion

The initial study featured symmetric *N*,*N*′-dialkyl bispidines 1 [42] and 2 [57], containing monoterpene and benzyl fragments, respectively, as possible organocatalysts. At the first stage of the work, the following initial conditions for catalytic reactions were chosen according to [52,53]: 1 eq. *β*-nitrostyrene 3, 5 eq. diethyl malonate 4, 0.2 eq. organocatalyst, toluene, 4 h, room temperature (Scheme 4). If the reaction did not progress within this time (no signs of product 5 formation), the time was extended to 3 days. When compound 1, which contains two chiral monoterpene fragments, was used as a catalyst, no addition of product 5 was observed after 3 days. The use of structurally simpler *N*,*N*′-dibenzyl substituted bispidine 2 also did not lead to the formation of product 5 (Scheme 4). Thus, it can be concluded that bispidine-based organocatalysts containing only tertiary nitrogen atoms in their structure did not have any catalytic activity in this reaction.

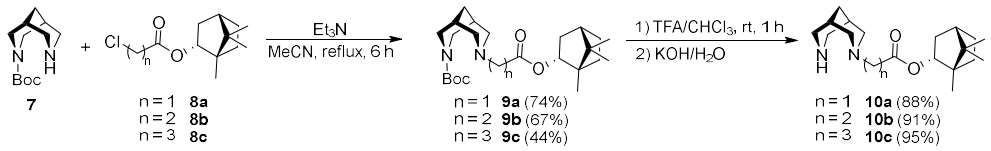


Scheme 4. Reaction of the addition of malonate **4** to nitrostyrene **3** in the presence of organocatalysts **1, 2, 6, 7, and 10 (a-c)**.

Further study focused on asymmetric mono-*N*-substituted bispidines (*N*-benzylbispidine **6** and *N*-Boc-bispidine **7**), which were prepared according to the described methods [54]. It was found that using *N*-benzylbispidine **6** as an organocatalyst under similar conditions

led to the desired product **5**. The reaction proceeded in 4 h with the complete conversion of *β*-nitrostyrene **3** (Scheme 4). In contrast, in the presence of *N*-Boc-bispidine **7** as a catalyst, no formation of product **5** was observed (Scheme 4), even when the reaction time was extended for 3 days.

Mono-*N*-substituted bispidines containing fragments of (-)-borneol **10a-c** were also synthesized and studied as chiral organocatalysts. Derivatives of bispidine **10a-c** were obtained by alkylation of *N*-Boc-bispidine **7** with halogen derivatives of (-)-borneol **8a-c** obtained according to known procedures [55], followed by removal of the Boc-group with yields of 88–95% at the final stage (Scheme 5).



Scheme 5. Preparation of chiral organocatalysts **10a-c** containing a monoterpenoid fragment.

The use of chiral bispidines **10a-c** as catalysts resulted in the complete conversion of *β*-nitrostyrene **3** within 4 h, as in the case of *N*-benzylbispidine **6**, leading to the formation of the desired addition product **5** (Scheme 4). The enantiomeric excess was determined by HPLC on a chiral stationary phase column. It was found that the product was formed in a racemic form in all cases.

The study of the influence of the nature of bispidine-based organocatalysts on their catalytic properties in the diethyl malonate addition reaction to *β*-nitrostyrene shows that the catalyst structure should have at least one secondary nitrogen atom of the bispidine framework, and the second nitrogen atom should be a tertiary amine (compounds **6** and **10a-c**) rather than of the amide type (compound **7**).

To verify the preservation of the catalytic activity of bispidine **6**, a reaction was carried out with 1 eq. of *β*-nitrostyrene and 5 eq. of diethyl malonate in the presence of 0.2 eq. (20 mol %) of bispidine **6**. After complete conversion of the initial **3** and formation of the product **5**, an additional 1 eq. of **3** was added to the mixture. The resulting reaction also took place with the complete conversion of **3** and the formation of the desired product **5**. Thus, it was concluded that the catalytic activity of bispidine **6** was preserved for at least two cycles.

The next step was the study of the optimal solvent for the reaction. A set of nine solvents of different natures (polar/non-polar, protic/aprotic) was tested: toluene, 1,4-dioxane, THF, dichloromethane, chloroform, acetonitrile, ethanol, hexane, and water. *N*-benzylbispidine **6** was used as a catalyst, which showed the catalytic activity of toluene. The study was carried out in the presence of 1 eq. *β*-nitrostyrene, 5 eq. diethyl malonate, and 0.2 eq. bispidine **6** at room temperature for 24 h. The reaction (Scheme 4) was observed to occur in almost all of the solvents that were chosen, leading to a full conversion of the initial *β*-nitrostyrene, except in the cases when hexane and water were utilized (since the reaction components were not soluble in these solvents). The reaction mixtures were allowed to stand at room temperature for one day and then analyzed by TLC and ^{1}H NMR (the results are shown in Table S1; see Supplementary Information). The optimal solvents were found to be toluene and 1,4-dioxane—in these solvents, the reaction proceeded without any side processes, and only the desired product **5** was obtained with yields of 98 and 96%, respectively. The reaction in THF proceeded with the formation of a complex mixture of products, including the desired compound. When dichloromethane and chloroform were used as solvents, the formation of the product was accompanied by precipitation and resinification of the reaction mixture. A similar situation was observed when acetonitrile and ethanol were used as solvents. Photos of reaction mixtures are provided in the Supplementary Information section (Figure S1). Thus, toluene was chosen as the solvent for all subsequent experiments.

It is worth noting that reducing the molar ratio of *β*-nitrostyrene to diethyl malonate to 1:3 and 1:1, respectively, resulted in a significant decrease in the rate of the catalytic reaction, according to TLC analysis. Optimization of other reaction conditions, such as catalyst loading and reaction temperature, was not carried out since the initially selected conditions were found to be successful for this reaction.

For the investigation of observed side processes in the catalytic reaction, ^{1}H NMR spectroscopy was used. To this end, the study featured the paired interactions of reagents, product, and catalyst: diethyl malonate **4**—*N*-benzylbispidine **6**, *β*-nitrostyrene **3**—diethyl malonate **4**, the addition product **5**—*N*-benzylbispidine **6**, *β*-nitrostyrene **3**—*N*-benzylbispidine **6**; all experiments were conducted in deuterotoluene.

The interaction between diethyl malonate and bispidine **6** in a deuterotoluene solution was studied by adding malonate to 1 eq. of bispidine. The concentration was gradually increased up to 5 eq. in 0.2 eq. steps. ^{1}H NMR spectra were recorded for each ratio of the component. No obvious shifts of the component signals were observed in the ^{1}H NMR spectra, which certainly indicates the absence of deprotonation of diethyl malonate. However, a 0.02 ppm downfield shift of the singlet signal belonging to the CH_2 group of malonate **4** was observed (see Supplementary Information, Figure S18), probably due to the formation of a supramolecular complex in which malonate protons interact with bispidine nitrogen atoms (see Supplementary Information, Scheme S1).

The processes occurring between *β*-nitrostyrene and diethyl malonate were also studied by means of ^{1}H NMR spectroscopy in deuterotoluene. Diethyl malonate was added to the *β*-nitrostyrene solution in deuterotoluene in 0.2 eq. increments until the ratio of components was established at 1:5. ^{1}H NMR spectra were recorded for each point. The ^{1}H NMR spectra demonstrated a downfield shift of the signals of the double bond protons of *β*-nitrostyrene (*ca.* 0.09 ppm) along with its aromatic component (*ca.* 0.05 ppm). This implies the possible participation in this pairwise interaction of supramolecular complexes, presumably formed due to the π-π-interaction of the conjugated π-system of nitrostyrene with the C=O-groups of diethyl malonate. (see Supplementary Information, Figure S19).

No spectral changes were detected in the ^{1}H NMR spectra of the binary mixture of bispidine **6** and the addition product **5** in deuterotoluene, in comparison with the signals in the spectra of the individual compounds.

The study of the interaction of *β*-nitrostyrene **3** with bispidine **6** in deuterotoluene was carried out by incrementally adding the latter in 0.2 equivalent steps until a 1:1 ratio of components was achieved. ^{1}H NMR spectra were recorded at each point (Figure 2). Immediately after the addition of the first portion of bispidine **6** to the nitrostyrene solution, a new set of signals was observed in the NMR spectra (highlighted in Figure 2). The intensity of these signals increased with increasing concentrations of bispidine. After establishing a 1:1 ratio of reactants in solution, the mixture was allowed to stand at room temperature for approximately 30 min. Over time, the light-yellow solution of the mixture changed its color to dark brown, and precipitation was observed. At the same time, in the ^{1}H NMR spectrum, a complete disappearance of the signals of the initial *β*-nitrostyrene, bispidine **6,** and of the product formed in the first minutes of the interaction was observed, accompanied by the appearance of a complex set of signals and a decrease in the resolution of the spectrum.

Since the unknown products could not be isolated as individual compounds, we recorded the 2D ^{1}H-^{13}C HSQC spectrum of a freshly prepared 1:1 mixture of *β*-nitrostyrene and bispidine **6** in deuterotoluene to establish and confirm the structure of the new compounds (see Supplementary Information, Figure S20). Based on the results obtained, we propose that the new product formed by the interaction between *β*-nitrostyrene and bispidine **6** is the product of conjugated NH-addition to the C=C bond (**11-1**, Scheme 6; hereafter, number **11-n** refers to the products of the interaction of bispidine and nitrostyrene, where **n** is the number of nitrostyrene units). The reaction scheme and the correlation of signals based on the 2D ^{1}H-^{13}C HSQC spectrum (see Supplementary Information, Figure S20) of the resulting adduct **11-1** are shown in Scheme 6. The formation of prod-

ucts of such structures is documented in this study for the first time and has not been previously reported.

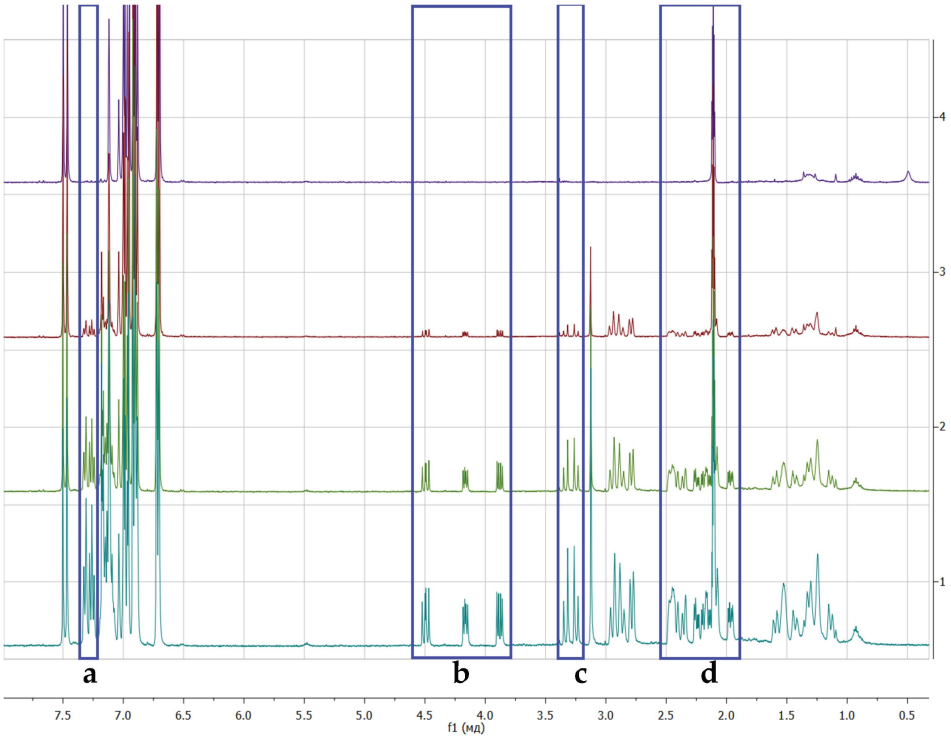
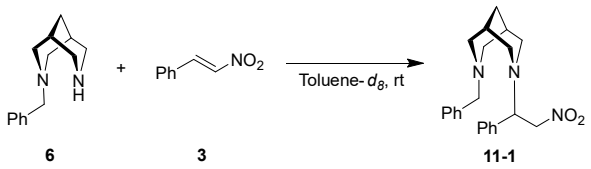
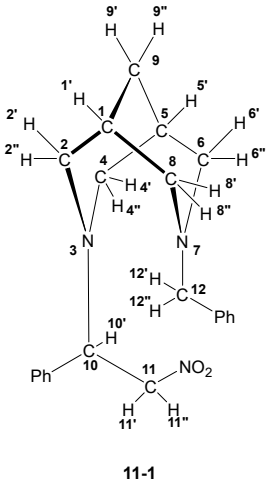


Figure 2. ^{1}H NMR (400 MHz, toluene-d_8) spectra of mixtures of nitrostyrene—bispidine **6** in the ratios 1:0 (purple), 1:0.2 (red), 1:0.6 (light green), and 1:1 (green) (top to bottom): new signals in the aromatic region (**a**); new *ABM*-pattern (**b**); new *AB*-pattern (**c**); new signals of the bispidine framework (**d**).





H-atoms

9'	1.16 (d, *J* = 13.3 Hz, 1H)
9"	1.34 (d, *J* = 13.3 Hz, 1H)
1', 5'	1.55 (br.s, 2H)
8',8"	2.15 - 2.24 (m, 2H)
6', 6"	2.44 - 2.52 (m, 2H)
4', 4"	2.41 - 2.48 (m, 1H), 2.00 (dd, *J* = 10.1, 4.5 Hz, 1H)
2', 2"	2.27 (dd, *J* = 10.3, 4.5 Hz, 1H), 2.38 (d, *J* = 10.1 Hz, 1H)
12', 12"	3.26 (d, *J* = 13.1 Hz, 1H), 3.35 (d, *J* = 13.1 Hz, 1H)
11', 11"	3.92 (dd, *J* = 12.2, 5.7 Hz, 1H), 4.52 (dd, *J* = 12.2, 9.3 Hz, 1H)
10'	4.18 (dd, *J* = 9.3, 5.6 Hz, 1H)

C-atoms

9	29.2
1	29.3
5	29.3
8	57.3
6	57.2
4	52.6
2	53.8
12	63.1
11	75.9
10	66.5

Scheme 6. Proposed scheme of adduct **11-1** formation and correlation of signals obtained by 2D ^{1}H-^{13}C HSQC spectroscopy.

To understand the nature of the occurring processes, the reaction mixture was studied using ultra-high-resolution mass spectrometry with matrix-assisted laser desorption/ionization (MALDI). Molecular ions $[M + H]^+$ with m/z 1260.51002, 1409.55838, and 1558.60662 were detected in the mass spectrum of the reaction mixture registered for the solution, which correspond to the molecular formulas $[C_{70}H_{70}N_9O_{14}]^+$ (**11-7**) (calc. m/z 1260.50367), $[C_{78}H_{77}N_{10}O_{16}]^+$ (**11-8**) (calc. m/z 1409.55135), and $[C_{86}H_{84}N_{11}O_{18}]^+$ (**11-9**) (calc. m/z 1558.59903), respectively (see Supplementary Information, Figures S29–S31). For the ions found, the following structures are proposed (Figure 3).

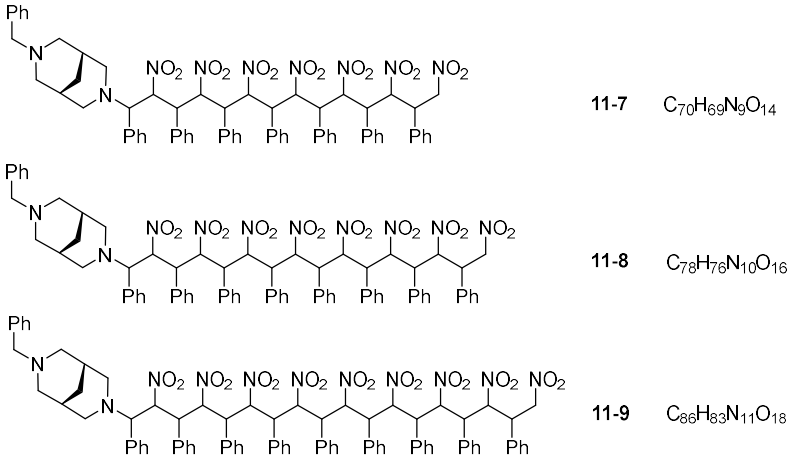


Figure 3. Proposed structures of **11-n** oligomers corresponding to molecular ions found using MALDI-MS.

The precipitate formed in the reaction (Scheme 6) was isolated and analyzed by NMR and IR spectroscopy, ultra-high-resolution mass spectrometry with matrix-assisted laser desorption/ionization (MALDI), elemental analysis, TGA-DSC analysis (see Supplementary Information, Figure S36), and SEM-EDX (see Supplementary Information, Figure S37). The recorded NMR spectra did not allow for the determination of the structure of the precipitate due to the extremely low solubility of the sample in common deuterosolvents and the low resolution of the spectra. Using MALDI-MS also failed to register signals in the mass spectrum, probably due to the low ionization of the sample. In the IR spectrum of the precipitate (see Supplementary Information, Figure S33), the presence of absorption bands at 1562 cm^{-1} and 1367 cm^{-1}, characteristic of the NO_2-group vibrations, was found. The absence of absorption bands at 1514 and 1346 cm^{-1} corresponding to the conjugated NO_2 group in the initial β-nitrostyrene was also confirmed (see Supplementary Information, Figure S32). It should be noted that the IR spectrum of the precipitate obtained by the interaction of β-nitrostyrene and bispidine **6** in toluene is identical to the spectrum of the precipitate formed by the same reaction in chloroform (see Supplementary Information, Figure S34). The elemental analysis data of the precipitate obtained as a result of the interaction of equimolar amounts of **3** and **6** in toluene (C 66.24%, H 4.58%, N 9.86%) cannot be interpreted unambiguously. However, it is possible to assume an approximate structure that fairly corresponds to the results obtained (Figure 4). The average number of monomeric units of β-nitrostyrene in the assumed structure of the oligomer was found to be 10.

According to the TGA-DSC analysis, the sample of precipitate has been losing mass since the beginning of measurement, apparently due to the loss of residual solvent. The change in mass to 101 °C was 3.4%. Furthermore, the rate of mass change increased. Two consecutive exothermic peaks with maxima at 136 and 171 °C and the onset temperature of the first 101 °C correspond to a mass change of ~23%. Upon further heating, a broad exothermic peak was recorded in the temperature range of 190–270 °C, corresponding to a mass change of ~21%. The next temperature range of 270–350 °C was accompanied by a mass change of 21%. It is possible to distinguish an exothermic effect at the onset tempera-

ture of 350 °C and the endset temperature of 416 °C. The mass loss in this range was 12%. A mass loss of 9% corresponded to the exo-effect in the temperature range of 416–550 °C (see Supplementary Information, Figure S36). It appears that a consistent, uniform change in mass corresponded to the sequential separation of three identical polymer fragments. Consequently, a sequential detachment of 8–9 groups corresponding to the monomeric unit of *β*-nitrostyrene can be assumed.

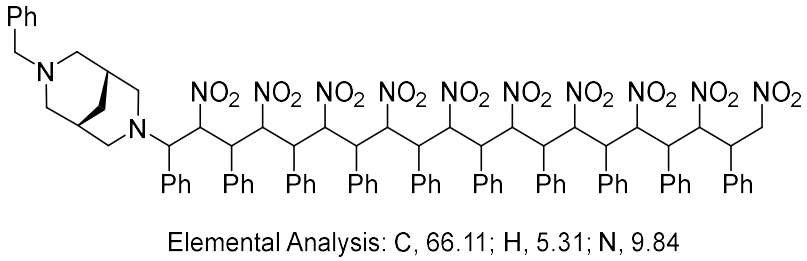


Figure 4. The proposed structure of the main fraction of an insoluble oligomer, based on the results of elemental analysis (**11-10**).

In addition, a reaction between equimolar amounts of *β*-nitrostyrene and the chiral bispidine **10a** was carried out in toluene at room temperature. In the course of time, as in the case of *N*-benzylbispidine **6**, a color change of the reaction mixture solution from light yellow to dark brown was observed, accompanied by precipitation. Analysis of the precipitate and the reaction mixture by means of ^{1}H NMR spectroscopy was not possible due to the complex signal set and low resolution of the spectrum. The IR spectrum of the sample contained an absorption band at 1739 cm^{-1}, corresponding to the presence of the ester C=O group, and bands at 1562 and 1366 cm^{-1}, corresponding to the NO_2 group (see Supplementary Information, Figure S35). On the basis of the data obtained, it can be assumed that the precipitate was a mixture of oligomers containing fragments of the chiral bispidine **10a** and *β*–nitrostyrene in the structure (Figure 5).

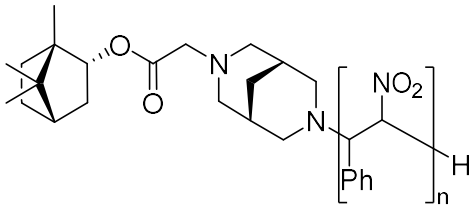
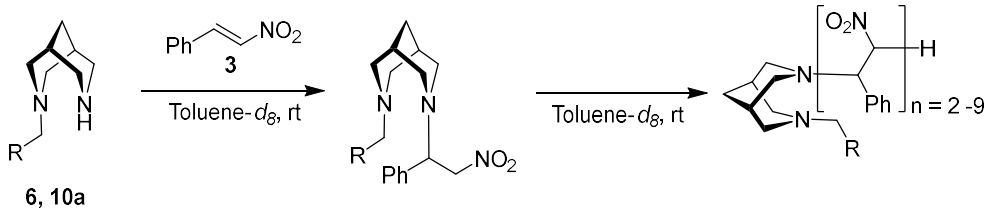


Figure 5. The proposed structure of the oligomers formed by the interaction of styrene **3** and chiral bispidine **10a**.

Thus, the study of binary mixtures of components of the catalytic reaction allowed us to establish the following processes: (1) the absence of deprotonation of diethyl malonate by *N*-benzylbispidine **6** and presumably the formation of a supramolecular complex between them; (2) the probable formation of a supramolecular complex between diethyl malonate and *β*-nitrostyrene; and (3) the formation of products of conjugated addition of bispidines **6** and **10a** to C=C-bonds of nitrostyrene with their subsequent oligomerization (Scheme 7). The anionic polymerization of *β*-nitrostyrene and its derivatives initiated by bases, including amines, has been described [58–64], as well as under the action of high-energy gamma radiation [65,66]. However, the above studies were mainly aimed at studying the kinetics of the polymerization process and determining the molecular weight characteristics of the resulting polymers. A detailed study of the reaction mechanism and the establishment of the structures formed during the reaction of oligomers using modern physicochemical methods of analysis have not been carried out, which is due, among other things, to their low solubility.



Scheme 7. Interaction of *N*-substituted bispidines **6** and **10a** with nitrostyrene **3**.

In order to gain a deeper understanding of the processes directly occurring in the catalytic reaction between diethyl malonate and *β*-nitrostyrene in the presence of *N*-benzylbispidine **6** as a catalyst, changes in the reaction mixture over time were monitored by means of ^{1}H NMR spectroscopy and high-resolution mass spectrometry. ^{1}H NMR monitoring was performed for a solution of 9.1 mg (0.06 mmol) of *β*-nitrostyrene, 3.5 mg (0.3 mmol) of diethyl malonate, and 2.9 mg (0.01 mmol, 20 mol %) of *N*-benzylbispidine **6** in 570 µL of deuterotoluene. The ^{1}H NMR spectra were recorded in 10 min increments. It was found that the reaction proceeded with the complete conversion of *β*-nitrostyrene **3** in 4 h with the formation of the target addition product **5** (some signals of product **5** are shown in Figure 6). In addition, the appearance of signals corresponding to the product of the addition of *N*-benzylbispidine **6** to the double C=C bond (**11-1**) and their disappearance at the end of the reaction were observed. (Figure 7).

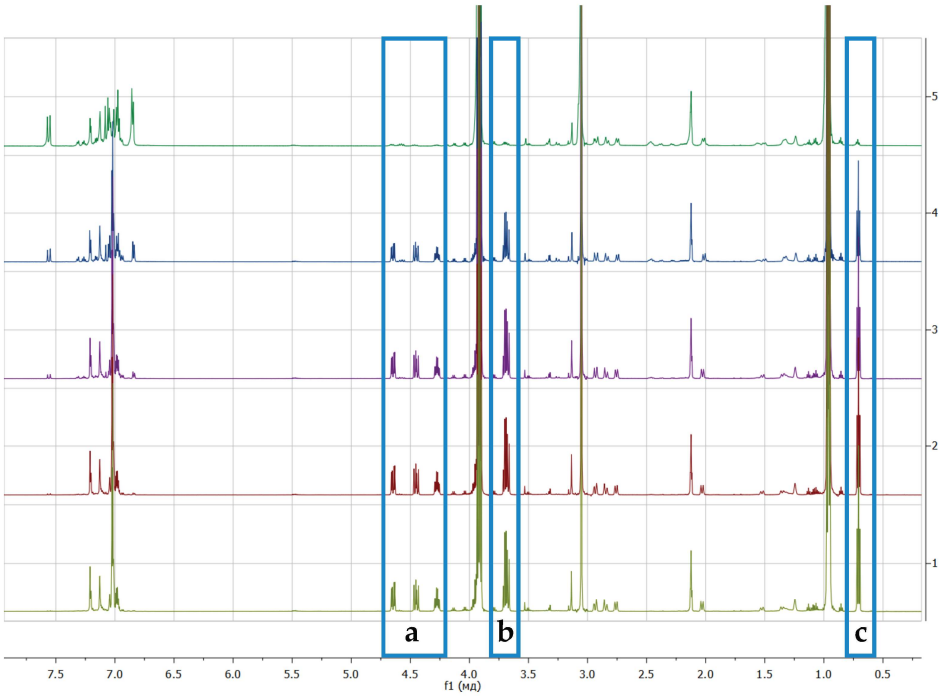


Figure 6. ^{1}H NMR spectra (600 MHz, toluene-d$_8$) of the catalytic reaction, recorded after 0 (green), 60 (blue), 120 (purple), 180 (red), and 240 (light green) min (top to bottom); product **5** signals are highlighted in rectangles: (**a**) *ABM*-pattern; (**b**,**c**) signals corresponding to the ethyl group.

^{1}H NMR monitoring in deuterotoluene was also performed for the reaction using the chiral catalyst **10a**. The reaction was monitored for 4 h, with registration of ^{1}H NMR spectra in 10 min increments (see Supplementary Information: Figures S21 and S22). It was found that the reaction proceeded with the complete conversion of *β*-nitrostyrene and the formation of the desired addition product **5** in exactly 4 h. In addition, it is worth noting that, as well as in the case of the use of bispidine **6** as a catalyst, signals that presumably correspond to the product of the addition of bispidine **10a** to the double C=C bond of

β-nitrostyrene were observed in the spectra, which disappeared by the end of the reaction (see Supplementary Information, Figure S22).

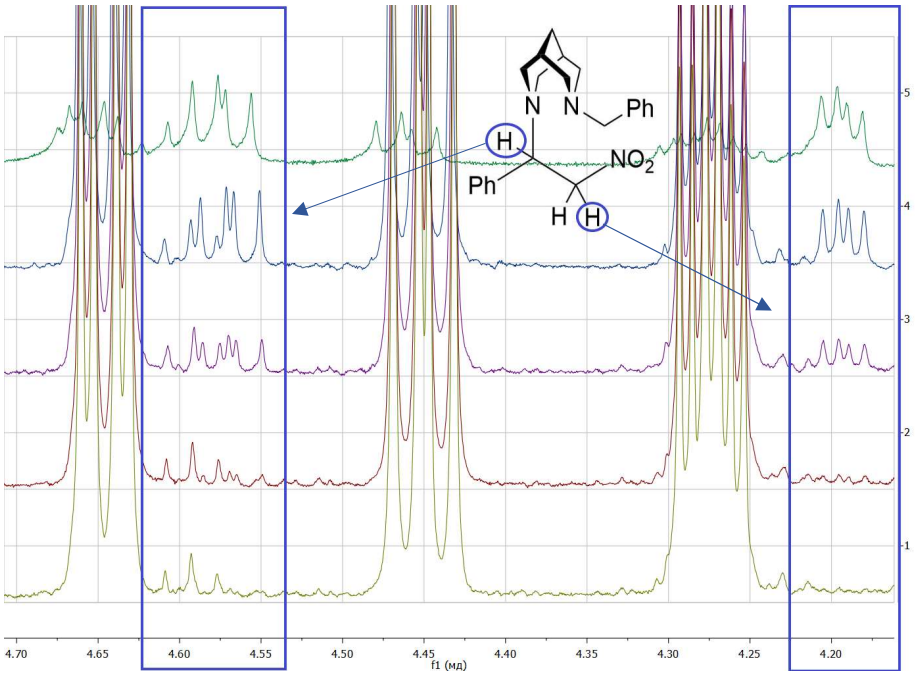


Figure 7. Fragments of the ^{1}H NMR spectra (600 MHz, toluene-d_8) of the catalytic reaction, recorded after 0 (green), 60 (blue), 120 (purple), 180 (red), and 240 (light green) min (**top** to **bottom**). Signals corresponding to adduct **11-1** are highlighted in rectangles.

Offline monitoring of the catalytic reaction in the presence of catalyst **6** using high-resolution mass spectrometry (ESI-HRMS) was carried out within 2 h of mixing the reagents. The presence in the reaction mixture of molecular ions $[M + H]^+$ with m/z 366.2192, 515.2641, 664.3110, 813.3567, and 962.4032 was found, which correspond to the molecular formulas $[C_{22}H_{28}N_3O_2]^+$ (**11-1**) (calc. m/z 366.2176), $[C_{30}H_{35}N_4O_4]^+$ (**11-2**) (calc. m/z 515.2653), $[C_{38}H_{42}N_5O_6]^+$ (**11-3**) (calc. m/z 664.3130), $[C_{46}H_{49}N_6O_8]^+$ (**11-4**) (calc. m/z 813.3606) and $[C_{54}H_{56}N_7O_{10}]^+$ (**11-5**) (calc. m/z 962.4083), respectively (see Supplementary Information, Figures S24–S28). For the ions found, the following possible structures are proposed (Figure 8).

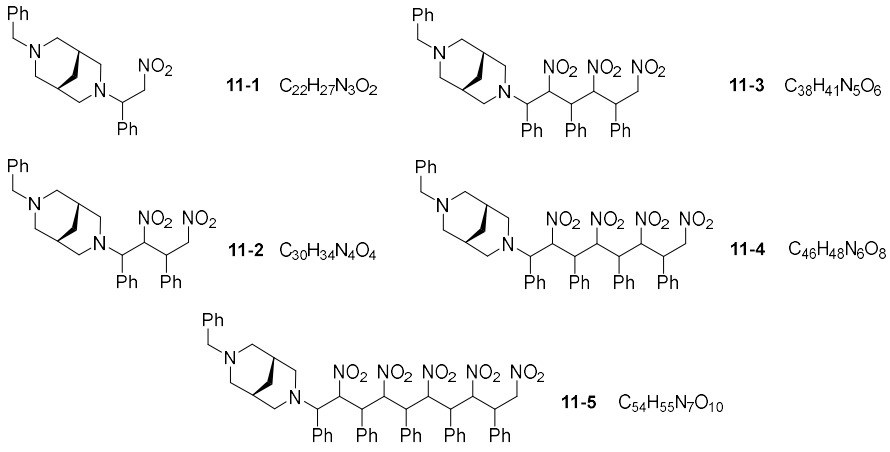


Figure 8. Proposed structures of **11-n** oligomers corresponding to molecular ions found using ESI-HRMS when monitoring the reaction for 2 h.

The traditional consideration of the mechanism of the catalytic reaction of the addition of diethyl malonate to nitrostyrene involves both the activation of the nitro component due to the formation of double hydrogen bonds and the methylene component due to the promotion of the formation of the enol form (see Scheme 3). For catalysis by bispidines in an acidic medium, the formation of bispidinium ions is possible; these also activate the nitro component due to the formation of hydrogen bonds (see Scheme 2).

The data obtained in the course of this study indicate the following: (1) catalysis by *N*,*N*′-dialkylbispidines **1** and **2**, as well as *N*-Boc bispidine **7**, does not occur; (2) the catalysis of the Michael reaction and the formation of oligomers **11-n** are observed only in the case of NH, *N*′-alkyl bispidines **6** and **10**.

In the case of bispidines **1**, **2**, **6,** and **10**, which are more basic than **7** (for the relevant literature on bispidine's basicity, see [67–69]), deprotonation of the malonate and the appearance of bispidinium ions would be expected; however, the corresponding anions and cations were not detected in the reactions by either NMR spectroscopy or mass spectrometry. Moreover, for the most basic compounds in the series studied, namely **1** and **2**, the reaction did not occur at all, i.e., the basicity of bispidine did not play any significant role in promoting the reaction.

Therefore, it can be assumed that the reaction does not proceed through the formation of bispidinium ions, as was assumed at the beginning of the study. How then can the addition of diethyl malonate to nitrostyrene be catalyzed? This is where the bispidine-nitrostyrene **11-1** adduct, unusual for this chemistry, comes into play (in the mechanism shown in Scheme 8, it is designated as **Ad,** because it is the '**ad**dition' product). In fact, the primary product of NH-addition to nitrostyrene is the corresponding betaine (**Ad**$^{-+}$), protonation of which with NH^+ (intra- or intermolecular) leads to the formation of a neutral adduct (**Ad**), which is observed in NMR spectra.

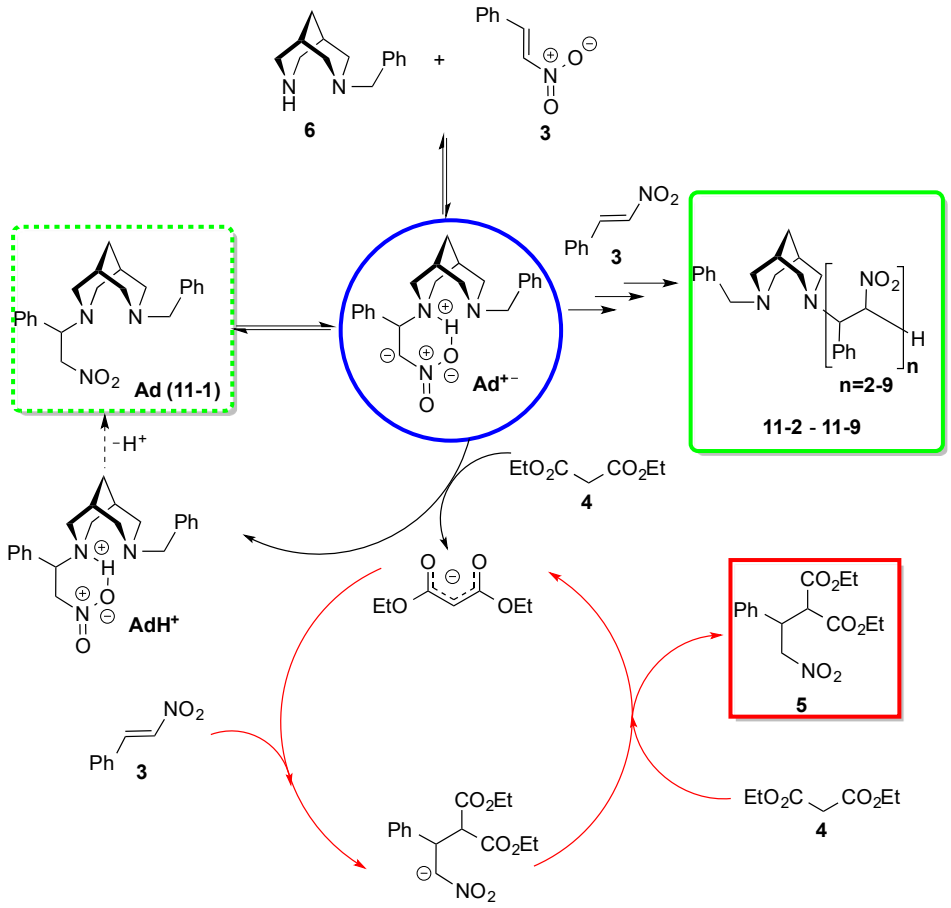
On the other hand, it can be assumed that primary betaine (**Ad**$^{-+}$) cannot rapidly transform into a neutral adduct, since the NH^+ fragment is stabilized by the formation of hydrogen bonds not only with an adjacent nitrogen atom (which is well documented in the chemistry of bispidines [70–73]), but, highly likely, also with an oxygen atom of a closely located nitro group. In this case, betaine (**Ad**$^{-+}$) may exist for a sufficient time to enable its carbanionic part to act as a strong base for the deprotonation of diethyl malonate. The latter, in the form of a carbanion, quickly adds to nitrostyrene to form the corresponding anion, which can be protonated to give the desired product of Michael reaction **5**. In this case, the proton source can be either nitrogen-protonated bispidine **AdH**$^+$ or a new malonate molecule **4**; the latter is more probable since the malonate presents in a very large excess in the reaction mixture. The second direction starts the catalytic cycle (Scheme 8).

Thus, in the proposed mechanism, bispidine is a precursor of the catalyst, and the catalytic activity is due to the more basic adduct **Ad**$^{+-}$. This betaine is also responsible for the side reaction of the oligomerization of nitrostyrene **3** to give **11-n**. The oligomerization mechanism has some similarities to the first two stages of the Morita-Baylis-Hillman reaction: the product of nucleophilic addition subsequently reacts with an electrophile, but unlike in the MBH reaction, the added nucleophile is retained in the product structure rather than being subjected to the elimination process. These suggestions also explain the lack of any stereochemical preferences in product **5**.

Short soluble oligomers of type **11-n** (in the form of the corresponding betaines) may also have catalytic activity. It is possible that the formation of a "cocktail" of organocatalytic particles might be considered analogous to the mechanism of palladium catalysis in cross-coupling reactions. At present, there is no solid evidence of this, which will be the subject of future research.

The proposed mechanism is also supported by the fact that the addition of diethyl malonate to nitrostyrene can be initiated by the formation of catalytic amounts of malonate anion, which was obtained in a separate experiment by the action of 0.3 eq. sodium hydride on a mixture of malonate (5 eq.) and nitrostyrene (1 eq.) in toluene. The reaction proceeded even faster than in the presence of bispidine **6**, which confirms the possibility

of the existence of the catalytic cycle shown in the lower part of Scheme 8 (see SI for a brief description).



Scheme 8. The proposed mechanism of the studied catalytic reaction. Blue circle means the proposed intermediate; rectangles mean the molecules that are seen by NMR and/or mass-spectra in the reaction mixture.

The proposed mechanism also explains the lack of catalytic activity in the case of bispidines **1**, **2,** and **7**, since they should have much lower N-nucleophilicity than **6** and **10**.

4. Conclusions

The combination of structural effects and reactivity studies aimed at the development of NH-containing bispidines as organocatalysts for the addition of diethyl malonate to nitrostyrene. Together with the crucial role of the NH-group in the process, this study helped to establish that the reaction occurs through the formation of the Michael adduct of bispidine and nitrostyrene. The data suggest that this adduct is the true *catalyst* initiating the reaction by deprotonating diethyl malonate, while bispidine is an *activator* of the process. The same adduct also seemed to be responsible for the formation of previously unknown nitrostyrene oligomers identified by ultra-high-resolution mass spectrometry. The unexpected in situ catalyst formation can be of general importance for the understanding of many organocatalytic reaction mechanisms.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry6030023/s1, Figure S1: The reaction mixtures after the indicated time after mixing the reagents: (a) toluene—1 h 15 min, THF—1 h 10 min, 1,4-dioxane—1 h, DCM—50 min, MeCN—45 min, n-hexane—40 min, H_2O—35 min, EtOH—25 min, CHCl3—10 min; (b) after 24 h; Figure S2: ^{1}H NMR spectrum of nitrostyrene **3** (600 MHz, toluene-

d_8); Figure S3: ^{1}H NMR spectrum of diethyl malonate **4** (600 MHz, toluene-d_8); Figure S4: ^{1}H NMR spectrum of N-benzylbispidine **6** (600 MHz, toluene-d_8); Figure S5: ^{1}H NMR spectrum of the addition product **5** (400 MHz, toluene-d_8); Figure S6: ^{1}H NMR spectrum of the compound **9a** (400 MHz, $CDCl_3$); Figure S7: ^{13}C NMR spectrum of the compound **9a** (101 MHz, $CDCl_3$); Figure S8: ^{1}H NMR spectrum of the compound **9b** (400 MHz, $CDCl_3$); Figure S9: ^{13}C NMR spectrum of the compound **9b** (101 MHz, $CDCl_3$); Figure S10: ^{1}H NMR spectrum of the compound 9c (400 MHz, $CDCl_3$); Figure S11: ^{13}C NMR spectrum of the compound 9c (101 MHz, $CDCl_3$); Figure S12: ^{1}H NMR spectrum of the compound 10a (300 MHz, $CDCl_3$); Figure S13: ^{13}C NMR spectrum of the compound **10a** (76 MHz, $CDCl_3$); Figure S14: ^{1}H NMR spectrum of the compound **10b** (300 MHz, $CDCl_3$); Figure S15: ^{13}C NMR spectrum of the compound **10b** (76 MHz, $CDCl_3$); Figure S16: ^{1}H NMR spectrum of the compound **10c** (300 MHz, $CDCl_3$); Figure S17: ^{13}C NMR spectrum of the compound **10c** (76 MHz, $CDCl_3$); Figure S18: ^{1}H NMR spectra (400 MHz, toluene-d_8) of the binary mixtures of bispidine **6** and diethyl malonate in ratios: 1:0; 1:1; 1:3 and 1:5 (top to bottom); Figure S19: ^{1}H NMR spectra (400 MHz, toluene-d_8) of the binary mixtures of β-nitrostyrene and diethyl malonate in ratios: 1:0.2, 1:1, 1:2, 1:5 (top to bottom); Figure S20: 2D NMR ^{1}H-^{13}C HSQC (toluene-d_8) spectrum of the binary mixture of β-nitrostyrene and bispidine **6** (1:1). Only the cross-peaks associated with the new reaction product are marked. The cross-peaks within the aromatic region are related to the phenyl groups of all three of the components in the mixture, although no clear correlation can be made; Figure S21: ^{1}H NMR spectra (600 MHz, toluene-d_8) of the catalytic reaction using bispidine **10a** as a catalyst at 0, 60, 120, 180 and 240 min after the start of the reaction (top to bottom); Figure S22: ^{1}H NMR spectra (600 MHz, toluene-d_8) of the catalytic reaction using bispidine **10a** as a catalyst at 0, 60, 120, 180 and 240 min after the start of the reaction in the region of 4.34–4.92 ppm (top to bottom); Figure S23: Experimentally detected and theoretical ESI-(+)MS spectrum of bispidine 6 from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 217.1704 Da, calculated for $C_{14}H_{21}N_2$ = 217.1699 Da, Δ = 2.3 ppm; Figure S24: Experimentally detected and theoretical ESI-(+)MS spectrum of 11-1 from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 366.2192 Da, calculated for $C_{22}H_{28}N_3O_2$ = 366.2176 Da, Δ = 4.4 ppm; Figure S25: Experimentally detected and theoretical ESI-(+)MS spectrum of **11-2** from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 515.2641 Da, calculated for $C_{30}H_{35}N_4O_4$ = 515.2653 Da, Δ = 2.3 ppm; Figure S26: Experimentally detected and theoretical ESI-(+)MS spectrum of 11-3 from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 664.3110 Da, calculated for $C_{38}H_{42}N_5O_6$ = 664.3130 Da, Δ = 3.0 ppm; Figure S27: Experimentally detected and theoretical ESI-(+)MS spectrum of 11-4 from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 813.3567 Da, calculated for $C_{46}H_{49}N_6O_8$ = 813.3606 Da, Δ = 4.8 ppm; Figure S28: Experimentally detected and theoretical ESI-(+)MS spectrum of **11-5** from the reaction mixture after 2 h; main experimental peak $[M+H]^+$ = 962.4032 Da, calculated for $C_{54}H_{56}N_7O_{10}$ = 962.4083 Da, Δ = 5.3 ppm; Figure S29: Experimentally detected and theoretical MALDI-(+)MS spectrum of **11-7** from the binary reaction mixture (nitrostyrene **3** + bispidine **6**) after 24 h; main experimental peak $[M+H]^+$ = 1260.51002 Da, calculated for $C_{70}H_{70}N_9O_{14}$ = 1260.50367 Da, Δ = 5.0 ppm; Figure S30: Experimentally detected and theoretical MALDI-(+)MS spectrum of **11-8** from the binary reaction mixture (nitrostyrene **3** + bispidine **6**) after 24 h; main experimental peak $[M+H]^+$ = 1409.55838 Da, calculated for $C_{78}H_{77}N_{10}O_{16}$ = 1409.55135 Da, Δ = 4.9 ppm; Figure S31: Experimentally detected and theoretical MALDI-(+)MS spectrum of **11-9** from the binary reaction mixture (nitrostyrene **3** + bispidine **6**) after 24 h; main experimental peak $[M+H]^+$ = 1558.60662 Da, calculated for $C_{86}H_{84}N_{11}O_{18}$ = 1558.59903 Da, Δ = 4.9 ppm; Figure S32: IR spectrum (KBr) of nitrostyrene **3**; Figure S33: IR spectrum (KBr) of precipitate from binary reaction between nitrostyrene **3** and bispidine **6** in toluene; Figure S34: IR spectrum (KBr) of precipitate from binary reaction between nitrostyrene **3** and bispidine **6** in $CHCl_3$; Figure S35: IR spectrum (KBr) of precipitate from binary reaction between nitrostyrene **3** and bispidine **10a** in toluene; Figure S36: TGA-DSC analysis of the precipitate from the reaction between nitrostyrene **3** and bispidine **6** in toluene; Figure S37: Results of SEM-EDX study of precipitate from binary reaction mixture between nitrostyrene **3** and bispidine **6** in toluene. A, B—scanning electron microscopy images with 5000× and 50,000× magnifications; C—element distribution maps obtained by energy dispersive spectroscopy; D—EDX spectrum of precipitate; Figure S38: Figure S38: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the addition reaction of diethyl malonate **4** with nitrostyrene **3** in the presence of NaH. The signals corresponding to the reaction product **5** are marked in the figure; Scheme S1: Proposed formation of a supramolecular complex between *N*-benzylbispidine **6** and diethyl malonate (**4**); Table S1: The results of the catalytic reaction1 in solvents of various nature [74,75].

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