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ENANTIOSELECTIVE ALKOXYLATION OF β-SUBSTITUTED AROMATIC NITROALKENES WITH ALLYL ALCOHOL

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Enantioselective alkoxylation of β-substituted aromatic nitroalkenes with propargyl alcohol in the presence of a chiral ligand – N-ethyl-N-{[(2S)-pyrrolidin-2-yl]methyl}ethanamine – leads to enantioselective synthesis of nitro-containing ethers in high yields and enantioselectivity.

Keywords: enantioselectivity; nitro-containing ethers; propargyl alcohol; chiral catalyst

1. Introduction

Chiral nitro-containing ethers are widely distributed in biologically active natural and pharmaceutical preparations [1],[2].

One of the most effective methods for the synthesis of optically active chiral compounds is the catalytic enantioselective addition of nucleophiles to α,β-unsaturated compounds leading to a variety of diverse organic compounds [3]-[8].

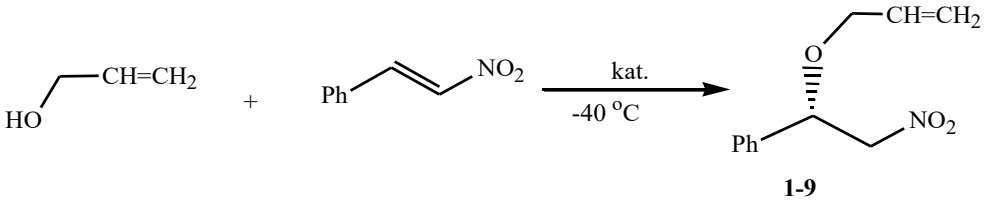
One of the methods for the synthesis of chiral unsaturated nitro-containing ethers is the catalytic enantioselective alkoxylation of unsaturated nitro compounds with propargyl alcohol (*Figure 1*).

The goal of synthesizing chiral unsaturated nitro-containing ethers with excellent yields and enantioselectivity can be achieved using a organocatalyzed reaction.

2. Experimental

The structures and compositions of the obtained target compounds No. 1-9 were confirmed by İR, ^{1}H and ^{13}C NMR spectroscopy as well as elemental analysis data. Some of the spectra are shown as examples.

Methylene protons, when magnetically equivalent, associated with the nitro groups in compounds No. 1-9 are diastereotopic (δ 0.4 ppm) in the form of two separate singlets at 1.03–1.05 ppm and appear in ^{1}H NMR spectra in the form of two doublets with a geminal coupling constant ^{2}J = 11.8 Hz. This shape of the signals in the NMR spectra of these groups of protons is associated with their diastereotopy. Diastereotopicity is due to the appearance of asymmetric centers in the structure as a result of alkoxylation with non-unionized C_3 alcohols to



1-9

Ph= C_6H_5 (**1**), 1-MeC_6H_4 (**2**), 4-MeC_6H_4 (**3**), 2-ClC_6H_4 (**4**), 4-ClC_6H_4 (**5**), 2-BrC_6H_4 (**6**), 4-BrC_6H_4 (**7**), 2-MeOC_6H_4 (**8**), 4-MeOC_6H_4 (**9**)

kat.=N-ethyl-N-{[(2S)-pyrrolidin-2-yl]methyl}ethanamine

Figure 1: Reaction scheme

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the multiple bond of β-substituted nitroalkenes of the aromatic series.

Commercially available reagents from Sigma–Aldrich were used. The melting points were measured with an Electrothermal 9100 melting point apparatus (UK).

3. Results and analysis

As a result of our syntheses, the following compounds were obtained:

Compound No. 1:
{(1S)-2-Nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Phenylnitrostyrene (0.1 mmol, 1.0 eq.) and catalysts (1 mol%) were dissolved in 0.5 ml THF at 40°C before being stirred for 5 mins. Propargyl alcohol (0.12 mmol, 1.2 eq.) was added at 40°C and stirred for 4 hours under TLC control until the nitrostyrenes were completely consumed. The mixture was then purified directly with flash cryogenic column chromatography over silica gel (0.5–2% EtOAc/PE) to obtain the products with a yield of 75%. Compound No.1 is an oily yellow liquid, $[\alpha]_D20$+82.1 (with 0.3, $CHCl_3$), R_f 0.48 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$, *Figure 2*):
δ ppm: 7.29-7.34 (m, 3H), 7.17 (d, J= 7.2 Hz, 2H), 5.85 (d.d.d, J=17.22, 9.15 , 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.22, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.17 (d.d.d, J=9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H), 4.76 (d.d.d, J= 22.1, 10.9, 7.7 Hz, 2H), 4.63 (d.d, J=12.7, 5.9 Hz, 1H), 4.61 (d.d, J=12.13, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.17 (d.d.d, J=12.13, 1.61, 1.23 Hz, OC$\underline{H}_2$,1H)

^{13}C NMR (100 MHz, $CDCl_3$, *Figure 3*):
δ ppm: 136.3, 134.63 (-HC=), 133.7, 131.9, 127.6, 117.67 (H_2C=), 78.5, 72.32 (=C-CH_2O), 49.9

Enantiomeric excess (*ee):* 92%, which was determined by a chiral phase Chiralpak IE column (98/2 hexane/ i-PrOH, flow rate 0.5 mL/min, λ = 238 nm, t_{major} = 22.0 min, t_{minor} = 20.2 min).

Compound No. 2:
1-Methyl-2-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 63%. Oily yellow liquid, $[\alpha]_D20$+80.1 (with 0.3, $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.08-7.14 (m, 2H), 7.06 (t, J= 7.0 Hz, 1H), 6.99 (d, J= 7.7 Hz, 1H), 5.85 (d.d.d, J= 17.23, 9.15, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.23, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H,), 5.16 (d.d.d, J= 9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H), 4.99 (d.d.d, J= 9.8, 6.0 Hz, 1H), 4.87 (d.d, J= 13.2, 9.9 Hz, 1H), 4.64 (d.d, J= 13.2, 6.0 Hz, 1H), 4.61 (d.d, J = 12.15, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.16 (d.d.d, J= 12.15, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 152.4, 136.5, 134.63 (-HC=), 128.3, 126.41, 126.40, 125.8, 117.67 (H_2C=), 77.8, 72.32 (=C-CH_2O), 45.6, 34.7, 31.2, 19.2

ee: 91% - chiral phase Chiralpak IC column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 241 nm, t_{major} = 25.0 min, t_{minor} = 29.3 min)

Compound No. 3:
1-Methyl-4-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 0.44 g (89%). Oily yellow liquid, m.p. 87–90°C. $[\alpha]_D20$+12.0 (c 0.51, $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.08 (d, J= 7.9 Hz, 2H), 7.04 (d, J= 7.8 Hz, 2H), 5.83 (d.d.d, J= 17.20, 9.15, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.20, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.17 (d.d.d, J= 9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H), 4.69-4.77 (m, 2H), 4.60 (d.d, J= 12.14, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.54-4.64 (m, 1H), 4.16 (d.d.d, J=12.14, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H), 2.25 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 152.2, 134.63 (-HC=), 128.7, 127.5, 126.4, 117.67 (H_2C=), 78.8, 72.32 (=C-CH2O), 49.7, 34.7, 31.2, 21.1

ee: 90% - chiral phase Chiralpak IB column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 238 nm, t_{major} = 33.3 min, t_{minor} = 23.0 min).

Compound No. 4:
1-Chloro-3-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 50%. Oily yellow liquid, $[\alpha]_D20$+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$, *Figure 4*):
δ ppm: 7.18 (d, J= 7.4 Hz, 2H), 7.10 (s, 1H), 7.05 (d, J= 7.0 Hz, 1H), 5.84 (d.d.d, J= 17.23, 9.14, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.23, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.17 (d.d.d, J= 9.14, 1.57, 1.23 Hz, H_2C=, 1H), 4.68-4.75 (m, 2H), 4.64- 4.67 (m, 1H), 4.61 (d.d, J= 12.16, 5.34 Hz, OCH_2, 1H), 4.17 (d.d, J= 12.16, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H)

^{13}C NMR (100 MHz, $CDCl_3$, *Figure 5*):
δ ppm: 152.7, 134.63 (-HC=), 128.7, 127.9, 127.6, 126.5, 125.8, 117.67 (H_2C=), 78.2, 72.32 (=C-CH_2O), 49.4, 34.7, 31.2

ee: 93% - chiral phase Chiralpak IE column (98/2 hexane/i-PrOH, flow rate 0.5 mL/min, λ = 238 nm, t_{major} = 18.3 min, t_{minor} = 22.2 min).

Compound No. 5:
1-Chloro-4-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 53%. Oily yellow liquid, $[\alpha]_D20$+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.26 (d, J= 8.4 Hz, 2H), 7.12 (d, J= 8.3 Hz, 2H), 5.85 (d.d.d, J= 17.22, 9.15, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.22, 1.57, 1.61 Hz, H_2C=, 1H), 5.17 (d.d.d, J= 9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H), 4.67-4.75 (m, 2H), 4.63 (d.d, J=12.13, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.59 (k, J= 11.1 Hz, 1H), 4.16 (d.d.d, J=12.13, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H)

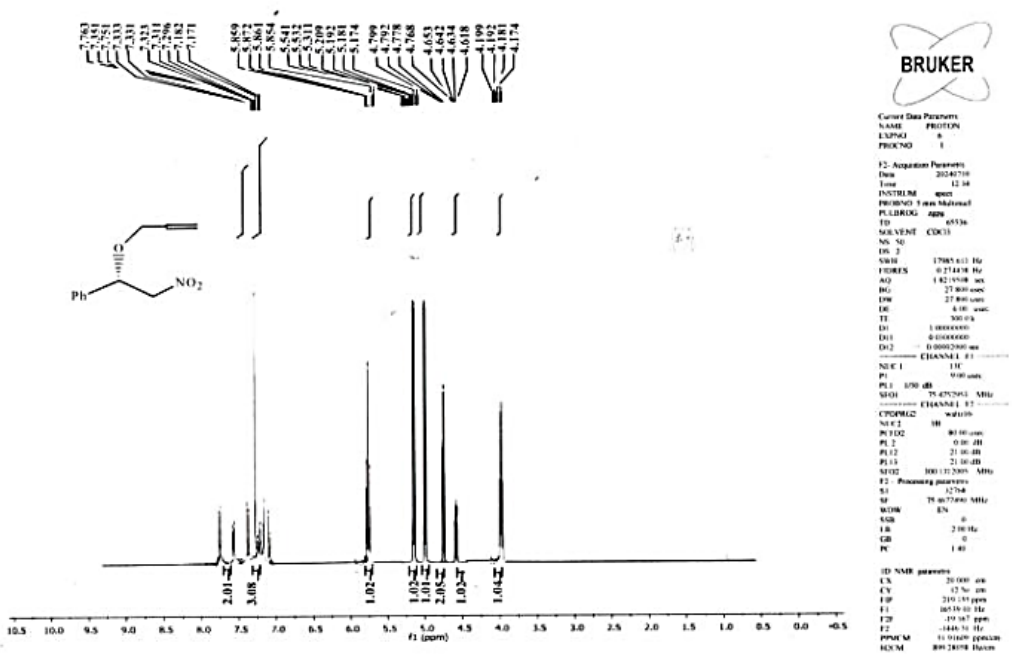

Figure 2: ^{1}H NMR (300 MHz) spectrum of Compound 1

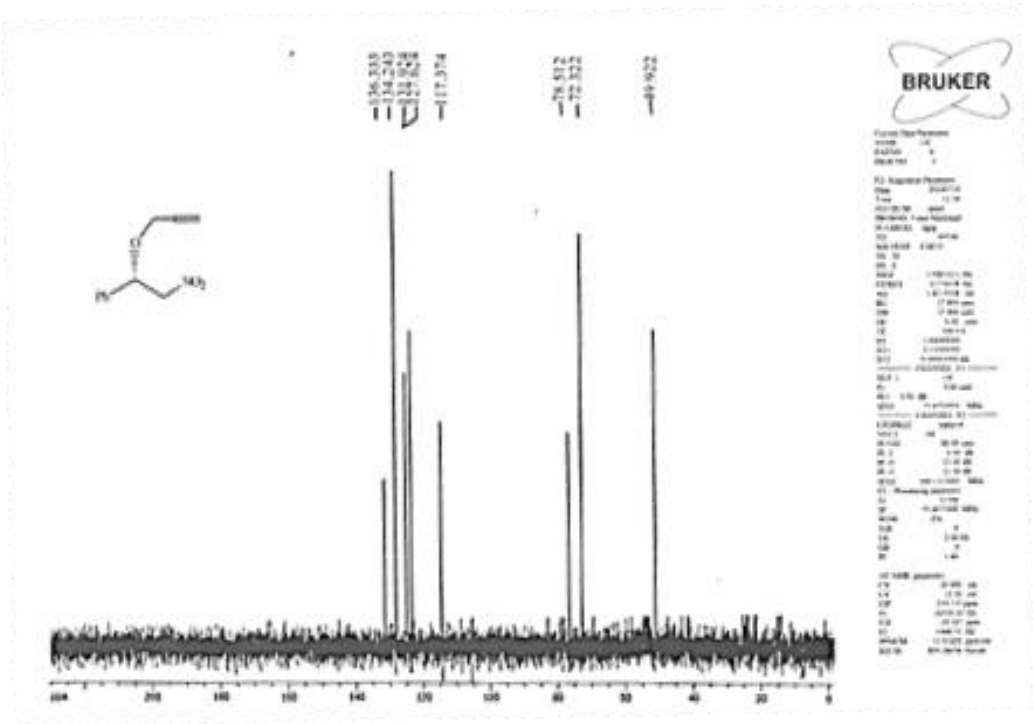

Figure 3: ^{13}C NMR (100 MHz) spectrum of Compound 1

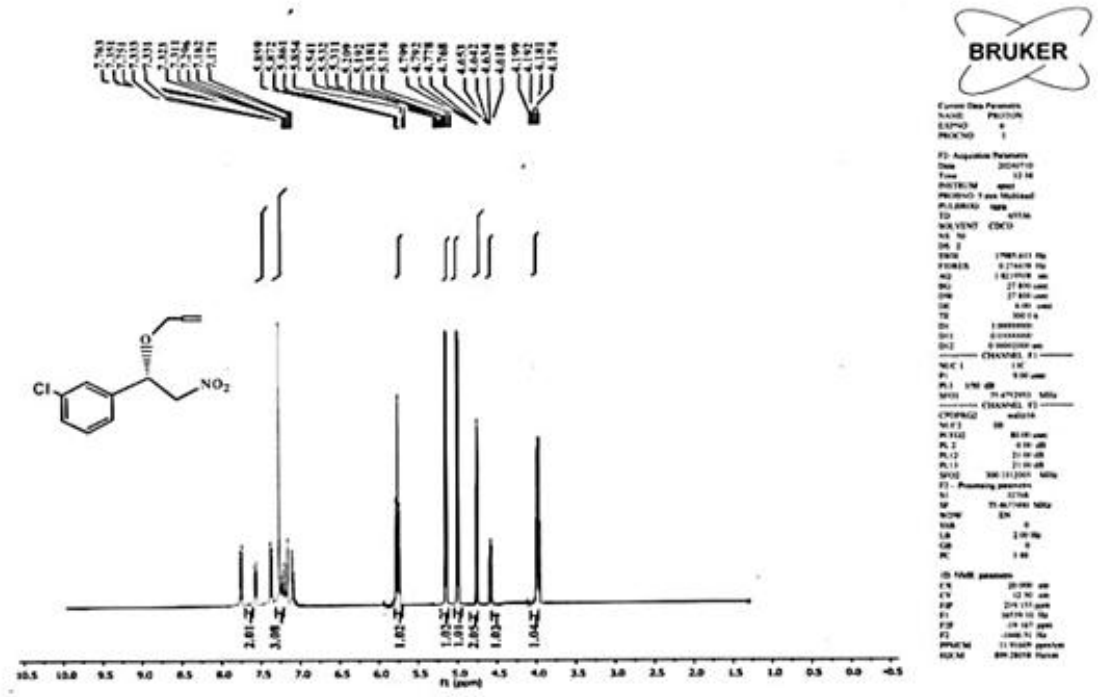

Figure 4: ^{1}H NMR (300 MHz) spectrum of Compound 4 (Acetone-*d6*)

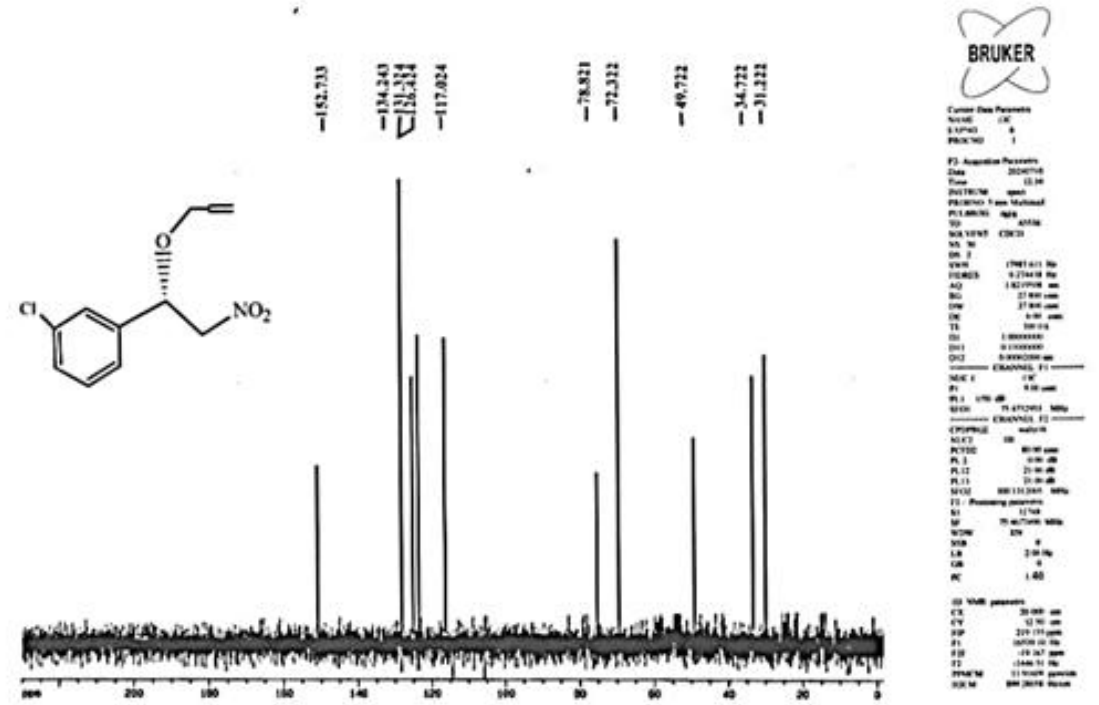

Figure 5: ^{13}C NMR (100 MHz) spectrum of Compound 4 (Acetone-*d6*)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 152.6, 134.63 (-HC=), 129.0, 127.9, 126.5, 117.67 (H_2C=), 78.4, 72.32 (=C-CH_2O), 49.3, 34.7, 31.2

ee: 96.3% - chiral phase Chiralpak IE column (98/2 hexane/i-PrOH, flow rate 0.5 mL/min, λ = 239 nm, t_{major} = 24.0 min, t_{minor} = 21.2 min).

Compound No. 6:
1-Bromine-3-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 50%. Oily yellow liquid, $[\alpha]_D$20+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.33 (d.d, J= 6.1, 2.6 Hz, 1H), 7.22 (t, J=6.3 Hz, 3H), 5.85 (d.d.d, J=17.21, 9.15, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.21, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.16 (d.d.d, J= 9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H), 4.69 (t.t, J= 15.3, 7.7 Hz, 2H), 4.63 (d.d, J= 11.0, 4.1 Hz, 1H), 4.61 (d.d, J= 12.14, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.16 (d.d, J= 12.14 , 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 152.8, 134.63 (-HC=), 130.4, 126.6, 126.5, 126.3, 122.8, 116.67 (H_2C=), 78.11, 72.31 (=C-CH_2O), 49.4, 34.7, 31.2

ee: 98.1% - chiral phase Chiralpak IC column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 238 nm, t_{major} = 16.9 min, t_{minor} = 19.7 min).

Compound No. 7:
1-Bromine-4-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 50%. Oily yellow liquid, $[\alpha]_D$20+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.37 (d, J= 8.3 Hz, 2H), 7.06 (d, J= 8.3 Hz, 2H), 5.85 (d.d.d, J= 17.23, 9.15, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.23, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.17 (d.d.d, J= 9.15, 1.57, 1.23 Hz, H_2C=, 1H), 4.67-4.74 (m, 2H), 4.61 (d.d, J=12.14, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.58-4.63 (m, 1H), 4.17 (d.d.d, J= 12.14, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 152.6, 134.62 (-HC=), 127.8, 126.5, 122.6, 117.66 (H_2C=), 72.31 (=C-CH_2O)

ee: 96.8% - chiral phase Chiralpak IE column (98/2 hexane/i-PrOH, flow rate 0.5 mL/min, λ = 238 nm, t_{major} = 11.8 min, t_{minor} = 12.8 min).

Compound No. 8:
1-Methoxy-3-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 50%. Oily yellow liquid, $[\alpha]_D$20+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz, $CDCl_3$):
δ ppm: 7.14-7.18 (m, 1H), 6.72-6.81 (m, 2H), 6.69 (s, 1H), 5.85 (d.d.d, J= 17.22, 9.15, 5.34 Hz, OCH=, 1H), 5.30 (d.d.d, J= 17.22, 1.57, 1.61 Hz, H_2C=, 1H), 5.16 (d.d.d, J= 9.15, 1.57, 1.23 Hz, $\underline{H}_2C$=, 1H,), 4.70-4.77 (m, 2H), 4.65 (d.d, J= 12.15, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.57-4.63 (m,1H), 4.17 (d.d.d, J= 12.15, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H), 3.66 (s, CH_3O, 3H)

^{13}C NMR (100 MHz, $CDCl_3$):
δ ppm: 159.8, 134.63 (-HC=), 128.3, 126.4, 119.8, 117.66 (H_2C=), 114.1, 113.4, 78.6, 72.32 (=C-CH_2O), 55.2, 50.0, 34.7, 31.2

ee: 95.7% - chiral phase Chiralpak IE column (98/2 hexane/i-PrOH, flow rate 0.5 mL/min, λ = 241 nm, t_{major} = 24.0 min, t_{minor} = 21.2 min).

Compound No. 9:
1-Methoxy-3-{(1S)-2-nitro-1-[(prop-2-en-1-yl)oxy]ethyl}benzene

Yield: 50%. Oily yellow liquid, $[\alpha]_D$20+200.7 (with 0.1 $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2).

^{1}H NMR (300 MHz ???, $CDCl_3$):
δ, ppm: 7.13 (d, J= 8.5 Hz, 2H), 6.78 (d, J= 8.6 Hz, 2H), 5.85 (d.d.d, J= 17.22, 9.13, 5.34 Hz, OCH=, 1H), 5.31 (d.d.d, J= 17.22, 1.57, 1.61 Hz, $\underline{H}_2C$=, 1H), 5.17 (d.d.d, J= 9.13, 1.57, 1.23 Hz, H_2C=, 1H), 4.78–4.69 (m, 2H), 4.63–4.55 (m,1H), 4.61 (d.d, 1H, J= 12.14, 5.34 Hz, OC$\underline{H}_2$, 1H), 4.17 (d.d.d, J= 12.14, 1.61, 1.23 Hz, OC$\underline{H}_2$, 1H), 3.71 (s, CH_3O, 3H)

^{13}C NMR (100 MHz ???, $CDCl_3$):
δ_C, ppm: 159.7, 134.63 (-HC=),128.3, 126.4, 117.66 (H_2C=),114.4, 78.9, 72.31 (=C-CH_2O), 55.3, 49.4, 34.7, 31.2

ee: 98.1% - chiral phase Chiralpak IC column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 241 nm, t_{major} = 18.6 min, t_{minor} = 20.4 min).

4. Discussion

Enantioselective alkoxylation of β-substituted aromatic nitroalkenes with allyl alcohol facilitates the synthesis of individual stereorearrangers of unsaturated nitroesters. The synthesized compounds are of interest as intermediate products in organic synthesis.

5. Conclusions

Enantioselective alkoxylation of β-substituted aromatic nitroalkenes with propargyl alcohol in the presence of a chiral ligand N-ethyl-N-{[(2S)-pyrrolidin-2-yl]methyl}ethanamine leads to enantioselective synthesis of nitro-containing ethers with high yields (up to 98%) and enantioselectivity (up to 99% e.h.). The enantioselective three-component reaction of a carbonyl compound, amine and alkyne was studied as a simple method for the synthesis of chiral propargylamides.

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