UDC 547.466.2+541.128

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ENANTIOSELECTIVE ALKOXYLATION OF β-SUBSTITUTED AROMATIC NITROALKENES WITH PROPARGYL ALCOHOL

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The 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, results in the enantioselective synthesis of nitro-containing ethers with high yields and excellent enantioselectivity. This method accommodates a wide variety of arylthiols and nitroalkene substrates, producing the target compounds in moderate yields (up to 73%) and enantiomeric excess (up to 99% ee). The resulting compounds are valuable intermediates in organic synthesis, as they contain multiple reactive centers, such as terminal triple bond and nitro groups. Moreover, they serve as direct precursors for the synthesis of optically active propargylamines, which are crucial intermediates in the production of many biologically active molecules. Chiral unsaturated nitro compounds are important building blocks for the construction of complex synthetic materials. The addition of propargyl alcohol to unsaturated nitro compounds proceeds both regioselectively and enantioselectively. Experimental data demonstrate that good results can be achieved even with low catalyst loadings.

Keywords: enantioselectivity, nitro-containing ethers, propargyl alcohol, chiral catalyst, asymmetric synthesis.

DOI: 10.32434/0321-4095-2025-160-3-171-175

Introduction

Chiral nitro-containing ethers are widely found in biologically active natural products and pharmaceutical compounds [1]. The presence of both a nitro group and an oxygen atom significantly broadens their potential for practical applications.

One of the most effective methods for synthesizing optically active chiral compounds is the catalytic enantioselective addition of nucleophilic reagents to α,β-unsaturated compounds, which provides access to a wide variety of structurally diverse organic molecules [2–5].

Results and discussion

One of the approaches to synthesizing chiral unsaturated nitro-containing ethers is the catalytic enantioselective alkoxylation of unsaturated nitro compounds with propargyl alcohol.

The goal of obtaining chiral unsaturated nitro-containing ethers with high yields and excellent enantioselectivity can be achieved using an organocatalyst (Scheme).

In compounds 1–9, the methylene protons adjacent to the nitro groups are diastereotopic, appearing as two distinct doublets at 1.03–1.05 ppm ($\Delta\delta = 0.4$ ppm) in the ^{1}H NMR spectrum with a geminal coupling constant of $^2J = 11.8$ Hz. This splitting pattern reflects their diastereotopicity, which arises from the creation of asymmetric centers upon alkoxylation of β substituted nitroalkene **3** with non ionized C_3 alcohols across the multiple bond.

Enantioselective alkoxylation of aromatic β-substituted nitroalkenes with propargyl alcohol,

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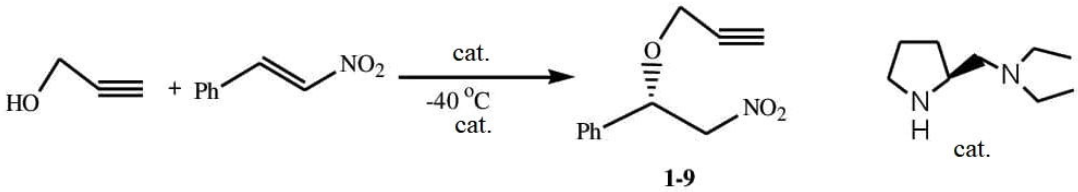

1-9

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**)

Scheme

mediated by the chiral ligand, N-ethyl-N-{[(2S)-pyrrolidin-2-yl]methyl}ethanamide, affords the corresponding nitro-containing ethers in high yields and excellent enantioselectivities (Table).

The yields and enantioselectivities of products **2**, **3**, and **9**, bearing electron-donating substituents (CH_3, CH_3O) on the aromatic ring, are higher than those of products **4**–**8**, which bear electron-withdrawing substituents (Cl, Br).

Halogen substituents on the aromatic ring differentially affect both yield and enantioselectivity: bromo-substituted substrates delivered higher yields and better enantioselectivities than their chloro-substituted analogues (Table).

Methoxy-substituted aromatic substrates exhibited enhanced enantioselectivity (Table).

Our ongoing interest lies in developing an efficient approach to the construction of chiral, oxygen containing molecules via sulfur-nucleophile activation. Here, we demonstrate that the enantioselective addition of propargyl alcohol to β-substituted nitroalkenes can be achieved in excellent yield and enantioselectivity using an organocatalyst. After establishing the optimized reaction conditions, we explored the scope of this transformation across a variety of substrates.

Thus, the aromatic β-unsaturated nitroalkenes and propargyl alcohol reacted smoothly to afford the corresponding nitro-containing ethers in excellent yields and enantioselectivities. The structures and compositions of products **7**–**18** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, and elemental analysis.

Table

Enantioselective alkoxylation of aromatic β-substituted nitroalkenes with propargyl alcohol

Entry	Time, h	Yield, %	ee, %
1	1	73	98
2	1	71	98
3	1	70	98
4	1	61	97
5	1	63	97
6	1	66	95
7	1	70	96
8	1	67	96
9	1	68	99

Experimental

NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13 MHz for ^1H and 75.47 MHz for ^{13}C in $CDCl_3$. In the ^{13}C NMR spectrum, the $CDCl_3$ signal (at ≡C 77.00 ppm) was used as the internal standard; in the ^1H NMR spectrum, the residual $CDCl_3$ proton signal (at δ_H 7.27 ppm) served as the reference. Optical rotations were measured on a Perkin Elmer 341 M polarimeter. Reaction progress was monitored by TLC on Sorbfil plates, visualized with a 10% anisaldehyde solution in ethanol containing sulfuric acid.

{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (1)

Phenylnitrostyrene (0.1 mmol, 1.0 eq.) and catalysts (1 mol.%) were dissolved in 0.5 ml THF at 40°C and stirred for 5 min. Propargyl alcohol (0.12 mmol, 1.2 eq.) was added at 40°C and stirred for 4 hours under TLC control until the nitrostyrenes became 2 were completely consumed. The mixture was then purified directly by flash cryogenic column chromatography over silica gel (0.5–2% EtOAc/PE) to obtain the products. Yield 73%. Oily yellow liquid, $[\alpha]_D$20+83.2 (with 0.2, $CHCl_3$), R_f 0.55 (petroleum ether–EtOAc, 3:2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.27–7.36 (m, Ph, 5H), 4.77 (dd, J=22.1, 10.9, 7.7 Hz, 2H), 4.64 (d.d, J=12.7, 5.9 Hz, 1H), 4.05 (dd, ≡CCH_2O, ^2J=16.2 Hz, ^4J=2.4 Hz, 1H), 3.83 (d.d, ≡CCH_2O, ^2J=16.2 Hz, ^4J=2.4 Hz, 1H), 2.52 (t, ^4J=2.4 Hz, ≡CH, 1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 136.7, 133.7, 131.9, 127.6, 78.51 (≡C–CH_2O), 68.35 (≡CH), 56.11 (≡C–CH_2O), 49.91.

The *ee* was determined (98%) by achiral phase Chiralpak IE column (98/2 hexane/iPrOH, flow rate 0.5 mL/min, t_{major}=11.72 min, t_{minor}=10.69 min).

1-Methyl-2-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (2)

Yield 71%. Yellowish oily substance, $[\alpha]_D$20+83.2 (with 0.2, $CHCl_3$), R_f 0.55 (petroleum ether–EtOAc, 3:2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.29–7.06 (t, J=7.0 Hz, CH, 1H), 7.05–6.95 (m, Ar, 2H), 6.93 (d, J=7.7 Hz, CH, 1H), 4.99 (d.d, J=9.8, 6.0 Hz, 1H) , 4.87 (d.d, J=13.3, 9.9 Hz, 1H), 4.64 (d.d, J=13.3, 6.0 Hz, 1H,), 4.05 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 3.83 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 2.51 (t, ≡CH, ^{4}J=2.4 Hz, 1H), 2.40 (s, CH_3, 3H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 152.4, 136.5, 128.3, 126.43, 126.40, 125.8, 79.46 (≡C–CH_2O), 77.8, 68.35 (≡CH), 56.11 (≡C–CH_2O), 45.6, 34.7, 31.2, 19.2.

The *ee* was determined (98%) by achiral phase Chiralpak IE column (98/2 hexane/iPrOH, flow rate 0.5 mL/min, t_{major}=15.20 min, t_{minor}=10.83 min).

1-Methyl-4-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (3)

Yield 70%. 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 spectrum ($CDCl_3$), δ, ppm: 7.29–7.24 (m, 2H), 7.03–6.93 (m, 2H), 4.99–4.97 (m, 2H), 4.54–4.64 (m, 1H), 4.06 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 3.82 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 2.50 (t, ^{4}J=2.4 Hz, ≡CH, 1H), 2.40 (s, CH_3, 3H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 152.2, 136.5, 128.7, 127.5, 126.4, 79.46 (≡C–CH_2O), 78.8, 68.35 (≡CH), 56.11 (≡C–CH_2O), 49.7, 45.6, 34.7, 31.2, 19.2.

The *ee* was determined (98%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=46.70 min, t_{minor}=40.81 min.

1-Chloro-3-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (4)

Yield 61%. Yellowish oily substance $[\alpha]_D$20+55.4 (with 0.1, $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.36–7.27–7 (m, 5H), 4.79–4.77 (m, 2H), 4.67–4.60 (m, 1H), 4.05 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 3.86 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 2.50 (t, ≡CH, ^{4}J=2.4 Hz, 1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 136.5, 125.8, 79.46 (≡C–CH_2O), 78.2, 68.35 (≡CH), 56.11 (≡C–CH_2O), 49.9.

The *ee* was determined (97%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=16.34 min, t_{minor}=11.59 min).

1-Chloro-4-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (5)

Yield 63%. 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 spectrum ($CDCl_3$), δ, ppm: 7.36–7.27–7 (m, 5H), 4.79–4.77 (m, 2H), 4.63 (k, J=11.1 Hz, 1H,), 4.05 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 3.82 (d.d, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, 1H), 2.51 (t, ≡CH, ^{4}J=2.4 Hz, 1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 152.6, 129.0, 127.9, 126.5, 79.46 (≡C–CH_2O), 78.4, 56.11 (≡C–CH_2O), 68.35 (≡CH), 49.3, 34.7, 31.2.

The *ee* was determined (97%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=8.57 min, t_{minor}=5.57 min).

1-Bromo-3-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (6)

Yield 66%. 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 spectrum ($CDCl_3$), δ, ppm: 7.36–7.27–7 (m, 5H), 4.70 (t.t, 2H, J=15.3, 7.7 Hz, CH_2), 4.63 d.d (1H, J=11.0, 4.1 Hz, CH), 4.04 d.d (1H, ≡CCH_2O, 2J=16.2 Hz, 4J=2.4 Hz, CH_2), 3.83 d.d (1H, ≡CCH_2O, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz), 2.51 (t, 1H, ^{4}J=2.4 Hz, ≡CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 136.3, 127.6, 79.46 (≡C–CH_2O), 78.1, 56.11 (≡C–CH_2O), 68.35 (≡CH), 49.4.

The *ee* was determined (95%) by achiral phase Chiralpak IE column (98/2 hexane/iPrOH, flow rate 0.5 mL/min, t_{major}=16.92 min, t_{minor}=13.31 min).

1-Bromo-4-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (7)

Yield 70%. 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 spectrum ($CDCl_3$), δ, ppm: 7.36–7.27–7 (m, 5H), 4.74–4.66 (m, 2H), 4.58–4.63 (m, 1H), 4.05 (d.d, 1H, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, ≡CCH_2O,), 3.83 d.d (1H, ^{2}J=16.2 Hz, 4J=2.4 Hz, ≡CCH_2O), 2.51 (t, 1H, ^{4}J=2.4 Hz, ≡CH,). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 136.5, 122.6, 79.44 (≡C–CH_2O), 78.3, 68.33 (≡CH), 56.11 (≡C–CH_2O), 49.4.

The *ee* determined (96%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=5.36 min, t_{minor}=4.92 min).

1-Methoxy-3-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (8)

Yield 67%. Oily yellow liquid, $[\alpha]_D$20+200.7 (with 0.1, $CHCl_3$), R_f 0.50 (petroleum ether–EtOAc, 3:2). 1H NMR spectrum ($CDCl_3$), δ, ppm: 7.36–7.27–7 (m, 5H), 4.99 (m, 2H, CH_2), 4.66–4.56 (m, 1H, CH), 4.06 (d.d, 1H, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, ≡CCH_2O,), 3.81 (d.d, 1H, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, ≡CCH_2O,), 3.50 (s, 3H, CH_3O), 2.51 (t, 1H, ≡CH, ^{4}J=2.4 Hz, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 152.9, 136.4, 119.8, 114.1, 113.4, 79.46 (≡C–CH_2O), 78.6, 68.35 (≡CH),

56.11 (≡C−CH_2O), 55.2, 50.0, 34.7, 31.2.

The *ee* was determined (96%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=5.26 min, t_{minor}=7.85 min).

1-Methoxy-4-{(1S)-2-nitro-1-[(prop-2-yn-1-yl)oxy]ethyl}benzene (9)

Yield 68%. 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 spectrum ($CDCl_3$), δ, ppm: 7.36−6.93 (m, 5H), 4.69−4.78 (m, 2H), 4.55−4.63 (m, 1H), 4.05 (d.d, 1H, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, ≡CCH_2O), 3.83 (d.d, 1H, ^{2}J=16.2 Hz, ^{4}J=2.4 Hz, ≡CCH_2O), 3.50 (s, 3H, CH_3O), 2.51 (t, 1H, 4J=2.4 Hz, ≡CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 159.7, 128.3, 126.4, 114.4, 79.45 (≡C−CH_2O), 78.9, 68.34 (≡CH), 56.11 (≡C−CH_2O), 55.3, 49.4, 34.7, 31.2.

The *ee* was determined (99%) by achiral phase Chiralpak IE column (98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, t_{major}=11.99 min, t_{minor}=10.22 min).

Conclusions

Enantioselective alkoxylation of β-substituted aromatic nitroalkenes with propargyl alcohol, mediated by the chiral ligand, N-ethyl-N-{[(2S)-pyrrolidin-2-yl]methyl}ethanamine, affords the corresponding nitro-containing ethers in high yields (up to 98%) and enantioselectivities (up to 99% ee). Additionally, an enantioselective three-component reaction involving a carbonyl compound, an amine, and an alkyne was explored as a straightforward method for the synthesis of chiral propargylamides.

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Received 17.12.2024

ЕНАНТІОСЕЛЕКТИВНЕ АЛКОКСИЛЮВАННЯ β-ЗАМІЩЕНИХ АРОМАТИЧНИХ НІТРОАЛКЕНІВ ПРОПАРГІЛОВИМ СПИРТОМ

Г.М. Талибов

Енантіоселективне алкоксилювання β-заміщених ароматичних нітроалкенів пропаргіловим спиртом у присутності хірального ліганда N-етил-N-{[(2S)-піролідин-2-іл]метил}етанаміну приводить до енантіоселективного синтезу нітровмісних етерів з високими виходами та відмінною енантіоселективністю. Цей метод сумісний із широким спектром арилтіолів і субстратів нітроалкенів, забезпечуючи утворення цільових сполук з помірними виходами (до 73%) і високим енантіомерним надлишком (до 99% ее). Одержані сполуки є цінними проміжними продуктами органічного синтезу, оскільки містять кілька реакційноздатних центрів, зокрема термінальний потрійний зв'язок і нітрогрупу. Крім того, вони виступають безпосередніми попередниками для синтезу оптично активних пропаргіламінів − важливих проміжних речовин у виробництві багатьох біологічно активних молекул. Хіральні ненасичені нітросполуки є важливими будівельними блоками для створення складних синтетичних матеріалів. Додавання пропаргілового спирту до ненасичених нітросполук відбувається як регіоселективно, так і енантіоселективно. Експериментальні дані свідчать, що добрі результати можна отримати навіть при низькому вмісті каталізатора.

Ключові слова: енантіоселективність; нітровмісні етери; пропаргіловий спирт; хіральний каталізатор; асиметричний синтез.

ENANTIOSELECTIVE ALKOXYLATION OF β-SUBSTITUTED AROMATIC NITROALKENES WITH PROPARGYL ALCOHOL

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The 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, results in the enantioselective synthesis of nitro-containing ethers with high yields and excellent enantioselectivity. This method accommodates a wide variety of arylthiols and nitroalkene substrates, producing the target compounds in moderate yields (up to 73%) and enantiomeric excess (up to 99% ee). The resulting compounds are valuable intermediates in organic synthesis, as they contain multiple reactive centers, such as terminal triple bond and nitro groups. Moreover, they serve as direct precursors for the synthesis of optically active propargylamines, which are crucial intermediates in the production of many biologically active molecules. Chiral unsaturated nitro compounds are important building blocks for the construction of complex synthetic materials. The addition of propargyl alcohol to unsaturated nitro compounds proceeds both regioselectively and enantioselectively. Experimental data demonstrate that good results can be achieved even with low catalyst loadings.

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

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