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Chiral Bis(Oxazolinyl)thiophenes for Enantioselective Cu(II)-Catalyzed Friedel–Crafts Alkylation of Indole Derivatives with Nitroalkenes

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Abstract A series of chiral bis(oxazoline)thiophenes were used as chiral ligands in the Cu(II)-catalyzed asymmetric Friedel–Crafts alkylation of indole derivatives with nitroalkenes, and the effects of reaction conditions on the yield and enantioselectivity were investigated. The ligand **1c** was identified as the best ligand of this family in the same reaction.

Keywords Bis(oxazolinyl)thiophene · Asymmetric catalysis · Friedel–Crafts alkylation · Indole derivative · Nitroalkene

1 Introduction

Indole ring is an important moiety that is present in many natural alkaloids and bioactive molecules. Since its discovery in 1869, indole and its derivatives have been widely applied in pharmaceuticals, fragrances, agrochemicals, pigments and material science [1, 2]. Owing to the importance of the indole framework-containing compounds, the development of new strategies to synthesize indole derivatives remain a subject of interest in the present days. During the past several years, Friedel–Crafts alkylation using metal-based chiral catalysts or chiral organocatalyts was the most frequently employed tool for the synthesis of 3-substituted indole derivatives [3–37]. In particular, chiral oxazoline-containing ligands have been applied to prepare the alkylated indole derivatives in asymmetric Friedel–Crafts alkylations and exhibit excellent enantioselectivities in most cases [30–37]. Although chiral bis(oxazoline)thiophenes have been synthesized and found to perform well in cyclopropanation of 1,1-diphenylethene with EDA [38, 39], their development and application are still lacking. As a rational extension of my project, I would like to report my recent results on the enantioselective $Cu(OTf)_2$-catalyzed Friedel–Crafts alkylation of indole derivatives with nitroalkenes using bis(oxazoline)thiophenes as chiral ligands (Fig. 1).

2 Experimental

2.1 General Information

Thiophene-2,5-dicarboxylic acid and Cu(II) trifluoromethanesulfonate were purchased from Alfa Aesar Co. Bis(oxazolinyl)thiophenes (**1a–e**) were prepared according to the literature's method [39]. Other reagents were of all analytical grade. Silica gel (200–300 mesh) was used for flash chromatography purchased from Qingdao Haiyang Chemistry Company. ^1H and ^{13}C NMR were recorded on Bruker DRX-500, DRX-400, DRX-300 or DRX-100 NMR spectrometers, using TMS as internal standard. ESI-MS were measured on a MDS Sciex API 2000 LC/GC/MS instrument. Optical rotation values were tested on a Polartronic HNQW 5 polarimeter. HPLC analysis was measured using a Daicel Chiracel OD-H or Daicel Chiralpak AD-H column.

2.2 General Procedure for Enantioselective Friedel–Crafts Alkylation Reactions

To a three-neck flask were added 0.01 mmol of the ligand **1**, 3.6 mg (0.01 mmol) of $Cu(OTf)_2$ and 5.0 ml ethyl ether

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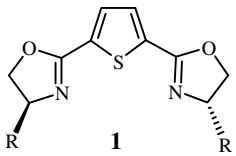


1

1a: R=Et
1b: R=*i*-Pr
1c: R=*t*-Bu
1d: R=Ph
1e: R=Bn

Fig. 1 Structures of bis(oxazoline)thiophene ligands

under the protect of nitrogen atmosphere. The mixture was refluxed for 30 min and cooled to ambient temperature, then nitroalkene (0.25 mmol) was added. The mixture was stirred for another 20 min at the same temperature and cooled to −10 °C. Indole derivative (0.25 mmol) was added at −10 °C. After completion of the addition, the mixture was stirred at the same temperature until indole derivative had disappeared. Ethyl ether was removed and the residue was purified by flash chromatography on silica gel, using petroleum ether–ethyl acetate 5:1–3:1 as eluent to give the desired products. The configurations of the products were determined by optical rotation and the enantiomeric excesses were determined by HPLC analysis using a Diacel Chiracel OD-H or Daicel Chiralpakl AD-H column.

2.2.1 (S)-3-(2-Nitro-1-Phenylethyl)-1H-Indole (**4a**)

Yield: 99 %; white solid; mp 114–116 °C; HPLC analysis [Daicel Chiralcel OD-H, 35 % *i*-PrOH/hexane, 1.0 ml/min; t_{major} 18.7 min, t_{minor} 22.6 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 97 % ee; $[\alpha]_D^{20} = +32.5$ (*c* 1.0, CH_2Cl_2) [Lit [34]. $[\alpha]_D^{20} = +25.3$ (*c* 0.9, CH_2Cl_2), 84 % ee]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (dd, $J_1 = 8.5$ Hz, $J_2 = 12.5$ Hz, 1H), 5.06 (dd, $J_1 = 7.6$ Hz, $J_2 = 12.5$ Hz, 1H), 5.18 (t, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 2.4$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 7.16–7.36 (m, 7H), 7.42 (d, $J = 8.0$ Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 41.6, 79.7, 111.5, 114.7, 119.1, 120.1, 121.7, 122.9, 126.3, 127.7, 127.9, 129.1, 136.7, 139.2; ESI-MS: *m/z* (%) = 267 ($[M+H]^+$, 100).

2.2.2 (S)-5-Methyl-3-(2-Nitro-1-Phenylethyl)-1H-Indole (**4b**)

Yield: 95 %; colorless solid; mp 138–140 °C; HPLC analysis [Daicel Chiralcel OD-H, 20 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 31.7 min, t_{major} 37.1 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 98 % ee; $[\alpha]_D^{20} = -13.3$ (*c* 1.0, CH_2Cl_2) [Lit [12]. $[\alpha]_D^{20} = +9.7$ (*c* 0.9, CH_2Cl_2), 97 % ee, (*R*) configuration]; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 2.38 (s, 3H), 5.12–5.36 (m, 3H), 6.97 (dd, $J_1 = 1.4$ Hz, $J_2 = 8.4$ Hz, 1H), 7.20–7.26 (m, 1H), 7.28–7.40 (m, 5H), 7.45–7.54 (m, 2H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 21.6, 42.3, 80.2, 112.1, 114.3, 119.0, 123.0, 124.3, 127.6, 127.9, 128.8, 129.4, 136.1, 141.4; ESI-MS: *m/z* (%) = 281 ($[M+H]^+$, 100).

2.2.3 (S)-5-Methoxy-3-(2-Nitro-1-Phenylethyl)-1H-Indole (**4c**)

Yield: 94 %; colorless solid; mp 133–135 °C ; HPLC analysis [Daicel Chiralcel OD-H, 15 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 27.8 min, t_{major} 33.5 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 98 % ee; $[\alpha]_D^{20} = -33.3$ (*c* 1.0, CH_2Cl_2) [Lit [17]. $[\alpha]_D^{20} = +25.3$ (*c* 0.4, CH_2Cl_2), 41 % ee, (*R*) configuration]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 4.90–5.02 (m, 2H), 5.59 (dd, $J_1 = 7.0$ Hz, $J_2 = 8.5$ Hz, 1H), 6.80 (t, $J = 7.2$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 7.01–7.25 (m, 6H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 41.6, 56.0, 79.6, 100.9, 112.2, 112.9, 114.2, 122.4, 126.7, 127.7, 127.9, 129.1, 131.7, 139.5, 154.2; ESI-MS: *m/z* (%) = 297 ($[M+H]^+$, 100).

2.2.4 (S)-5-Fluoro-3-(2-Nitro-1-Phenylethyl)-1H-Indole (**4d**)

Yield: 93 %, yellow oil; HPLC analysis (Daicel Chiralpakl AD-H, 10 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 19.4 min, t_{major} 23.0 min, λ = 254 nm) gave the isomeric composition of the product: 94 % ee; $[\alpha]_D^{20} = +20.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.16–5.38 (m, 3H); 6.92 (m, 1H), 7.21–7.24 (m, 2H), 7.30–7.33 (m, 2H), 7.42 (dd, $J_1 = 4.5$ Hz, $J_2 = 8.8$ Hz, 1H), 7.46–7.55 (m, 3H), 10.38 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ = 42.1, 80.1, 104.3 (d, $J_{C\text{-}F} = 23.6$ Hz), 110.8 (d, $J_{C\text{-}F} = 26.5$ Hz), 113.4 (d, $J_{C\text{-}F} = 9.6$ Hz), 115.1 (d, $J_{C\text{-}F} = 4.6$ Hz), 125.0, 127.7 (d, $J_{C\text{-}F} = 9.6$ Hz), 128.1, 128.8, 129.5, 134.3, 141.2, 158.4 (d, $J_{C\text{-}F} = 232.5$ Hz); ESI-MS: *m/z* (%) = 285 ($[M+H]^+$, 100).

2.2.5 (S)-5-Chloro-3-(2-Nitro-1-Phenylethyl)-1H-Indole (**4e**)

Yield: 90 %; colorless solid; mp 133–134 °C; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 13.5 min, t_{major} 15.1 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 89 % ee; $[\alpha]_D^{20} = -31.0$ (*c* 1.0, CH_2Cl_2) [Lit [3]. $[\alpha]_D^{rt} = +18$ (*c* 0.370, $CHCl_3$), 71 % ee, (*R*) configuration]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.90 (dd, $J_1 = 8.0$ Hz, $J_2 = 12.5$ Hz, 1H), 5.01 (dd, $J_1 = 8.0$ Hz, $J_2 = 12.5$ Hz, 1H), 5.11 (t, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H),

7.16–7.35 (m, 7H), 7.53 (d, $J = 1.6$ Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.3, 79.4, 112.9, 113.5, 114.2, 121.6, 122.8, 125.7, 127.7, 127.8, 128.0, 129.2, 135.2, 138.8; ESI-MS: *m/z* (%) = 301 ($[M+H]^+$, 100).

2.2.6 (S)-3-[1-(2-Methoxyphenyl)-2-Nitroethyl]-1H-Indole (**4f**)

Yield: 96 %; colorless solid; mp 92–95 °C; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 13.4 min, t_{major} 15.3 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 88 % ee; $[\alpha]_D^{20} = -57.0$ (*c* 1.0, CH_2Cl_2) [Lit [34]. $[\alpha]_D^{20} = +49.6$ (*c* 0.75, CH_2Cl_2), 61 % ee, (*R*) configuration]; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 3.94 (s, 3H), 5.19 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 2H), 5.64 (t, $J = 8.0$ Hz, 1H), 6.85 (t, $J = 7.5$ Hz, 1H), 6.95–7.06 (m, 2H), 7.08–7.16 (m, 1H), 7.18–7.29 (m, 2H), 7.36–7.45 (m, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 35.9, 56.1, 78.9, 111.9, 112.4, 114.4, 119.5, 119.9, 121.4, 122.6, 123.5, 127.7, 129.0, 129.3, 129.6, 137.8, 158.0; ESI-MS: *m/z* (%) = 297 ($[M+H]^+$, 100).

2.2.7 (S)-3-[1-(2-Chlorophenyl)-2-Nitroethyl]-1H-Indole (**4g**)

Yield: 87 %; colorless oil; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 16.5 min, t_{major} 25.8 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 73 % ee; $[\alpha]_D^{20} = +80.2$ (*c* 1.0, CH_2Cl_2) [Lit [34]. $[\alpha]_D^{20} = +79.4$ (*c* 0.95, CH_2Cl_2), 72 % ee]; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.23 (dd, $J_1 = 7.8$ Hz, $J_2 = 13.2$ Hz, 1H), 5.32 (dd, $J_1 = 8.3$ Hz, $J_2 = 13.2$ Hz, 1H), 5.76 (t, $J = 8.0$ Hz, 1H), 6.98–7.06 (m, 1H), 7.08–7.15 (m, 1H), 7.21–7.31 (m, 2H), 7.43 (m, 2H), 7.44–7.50 (m, 1H), 7.51–7.54 (m, 1H), 7.56 (d, $J = 7.9$ Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.1, 77.8, 111.5, 113.3, 119.0, 120.1, 120.1, 122.1, 122.9, 126.3, 127.4, 129.0, 129.1, 130.2, 133.9, 136.6; ESI-MS: *m/z* (%) = 301 ($[M+H]^+$, 100).

2.2.8 (S)-3-[1-(3-Bromophenyl)-2-Nitroethyl]-1H-Indole (**4h**)

Yield: 95 %; colorless oil; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{major} 21.7 min, t_{minor} 30.8 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 94 % ee; $[\alpha]_D^{20} = +13.5$ (*c* 1.0, CH_2Cl_2) [Lit [12]. $[\alpha]_D^{20} = -15.8$ (*c* 0.64, CH_2Cl_2), 97 % ee, (*R*) configuration]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.88 (dd, $J_1 = 8.4$ Hz, $J_2 = 12.6$ Hz, 1H), 5.01 (dd, $J_1 = 7.5$ Hz, $J_2 = 12.6$ Hz, 1H), 5.13 (d, $J = 8.0$ Hz, 1H), 7.01 (dd, $J_1 = 0.6$ Hz, $J_2 = 2.5$ Hz, 1H), 7.07 (m, 1H), 7.16–7.28 (m, 3H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.38 (m, 1H), 7.41 (dd, $J_1 = 0.7$ Hz, $J_2 = 8.0$ Hz, 1H), 7.44 (t, $J = 1.8$ Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.2, 79.3, 111.7, 113.9, 118.9, 120.4, 121.7, 123.1, 123.3, 126.1, 126.6, 130.6, 131.0, 131.3, 136.7, 141.7; ESI-MS: *m/z* (%) = 346 ($[M+H]^+$, 100).

2.2.9 (S)-3-[1-(3-Nitrophenyl)-2-Nitroethyl]-1H-Indole (**4i**)

Yield: 97 %; yellow oil; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{major} 34.5 min, t_{minor} 48.4 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 92 % ee; $[\alpha]_D^{20} = +12.7$ (*c* 1.0, CH_2Cl_2) [Lit [12]. $[\alpha]_D^{20} = -17.9$ (*c* 0.48, CH_2Cl_2), 95 % ee, (*R*) configuration]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (dd, $J_1 = 9.0$ Hz, $J_2 = 12.6$ Hz, 1H), 5.12 (dd, $J_1 = 6.9$ Hz, 1H), 5.33 (t, $J = 7.8$ Hz, 1H), 7.10–7.13 (m, 2H), 7.24 (t, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.53 (t, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 7.5$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 8.23 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 78.7, 111.7, 112.8, 118.5, 120.1, 121.5, 122.5, 122.7, 123.1, 125.5, 129.8, 134.0, 136.5, 141.6, 148.6; ESI-MS: *m/z* (%) = 312 ($[M+H]^+$, 100).

2.2.10 (S)-3-[1-(4-Methoxyphenyl)-2-Nitroethyl]-1H-Indole (**4j**)

Yield: 90 %; colorless solid; mp 142–144 °C; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{major} 19.1 min, t_{minor} 24.7 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 91 % ee; $[\alpha]_D^{20} = +30.5$ (*c* 1.0, CH_2Cl_2) [Lit [17]. $[\alpha]_D^{20} = -11.8$ (*c* 0.11, CH_2Cl_2), 44 % ee, (*R*) configuration]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 4.89 (dd, $J_1 = 8.4$ Hz, $J_2 = 12.3$ Hz, 1H), 5.03 (dd, $J_1 = 7.5$ Hz, $J_2 = 12.3$ Hz, 1H), 5.14 (t, $J = 8.0$ Hz, 1H), 6.81–6.87 (m, 2H), 7.00 (dd, $J_1 = 0.7$ Hz, $J_2 = 2.5$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.21–7.25 (m, 2H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.44 (dd, $J_1 = 0.7$ Hz, $J_2 = 8.0$ Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 55.4, 80.0, 111.5, 114.5, 115.0, 119.2, 120.2, 121.6, 122.9, 126.3, 129.0, 131.4, 136.8, 159.2; ESI-MS: *m/z* (%) = 297 ($[M+H]^+$, 100).

2.2.11 (S)-3-[1-(4-Chlorophenyl)-2-Nitroethyl]-1H-Indole (**4k**)

Yield: 94 %; colorless solid; mp 133–134 °C; HPLC analysis (Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane,

1.0 ml/min; t_{major} 22.4 min, t_{minor} 29.0 min, λ = 254 nm) gave the isomeric composition of the product: 95 % ee; $[\alpha]_D^{20} = +7.9$ (*c* 1.0, CH_2Cl_2) [Lit [34]. $[\alpha]_D^{20} = +7.5$ (*c* 1.2, CH_2Cl_2), 82 % ee]; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.17–5.34 (m, 3H), 7.01–7.10 (m, 1H), 7.11–7.15 (m, 1H), 7.36–7.31 (m, 2H), 7.42 (m, 2H), 7.45–7.50 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 41.6, 79.9, 112.5, 114.4, 119.4, 120.1, 122.8, 123.0, 127.2, 129.4, 130.6, 133.2, 137.8, 140.5; ESI-MS: *m/z* (%) = 301 ($[M+H]^+$, 100).

2.2.12 (S)-3-[1-(4-Bromophenyl)-2-Nitroethyl]-1H-Indole (**4l**)

Yield: 93 %; colorless solid; mp 148–149 °C; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{major} 26.5 min, t_{minor} 36.6 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 95 % ee; $[\alpha]_D^{20} = -2.7$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.18–5.35 (m, 3H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.41–7.44 (m, 4H), 7.45–7.56 (m, 3H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 41.7, 79.8, 112.5, 114.3, 119.4, 120.1, 121.4, 122.8, 123.0, 127.2, 130.9, 132.4, 137.8, 140.9; ESI-MS: *m/z* (%) = 346 ($[M+H]^+$, 100).

2.2.13 (S)-3-(1-Furan-2-yl-2-Nitroethyl)-1H-Indole (**4m**)

Yield: 86 %; yellow oil; HPLC analysis [Daicel Chiralcel OD-H, 30 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 14.5 min, t_{major} 20.0 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 82 % ee; $[\alpha]_D^{20} = -39.8$ (*c* 1.0, CH_2Cl_2) [Lit [13]. $[\alpha]_D^{20} = +38.2$ (*c* 1.02, CH_2Cl_2), 95 % ee, (*R*) configuration];

^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.17 (dd, J_1 = 7.3 Hz, J_2 = 12.3 Hz, 1H), 5.20–5.31 (m, 2H), 6.29 (d, *J* = 3.2 Hz, 1H), 6.36 (dd, J_1 = 1.9 Hz, J_2 = 3.2 Hz, 1H), 7.01–7.10 (m, 1H), 7.11–7.19 (m, 1H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.48 (dd, J_1 = 0.7 Hz, J_2 = 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 36.4, 78.7, 107.6, 111.2, 112.1, 112.6, 119.4, 120.1, 122.7, 124.2, 127.0, 137.7, 143.1, 154.3; ESI-MS: *m/z* (%) = 257 ($[M+H]^+$, 100).

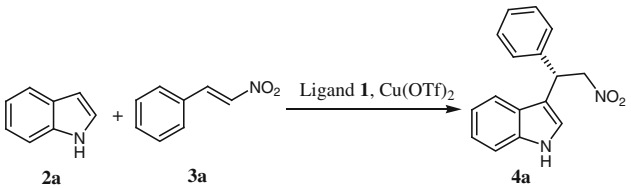
2.2.14 (S)-3-(1-Nitrohexan-2-yl)-1H-Indole (**4n**)

Yield: 92 %; yellow oil; HPLC analysis [Daicel Chiralcel OD-H, 10 % *i*-PrOH/hexane, 1.0 ml/min; t_{minor} 35.7 min, t_{major} 39.6 min, λ = 254 nm (UV)] gave the isomeric composition of the product: 93 % ee; $[\alpha]_D^{20} = -33.3$ (*c* 1.0, CH_2Cl_2) [Lit [6]. $[\alpha]_D^{20} = -30.6$ (*c* 1.0, CH_2Cl_2), 91 % ee]; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 0.82 (t, *J* = 6.5 Hz, 3H), 1.21–1.38 (m, 4H), 1.75–1.96 (m, 2H), 3.78–3.81 (m, 1H), 4.85 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ = 14.2, 23.2, 30.1, 33.3, 37.0, 81.4, 112.5, 114.5, 119.4, 119.8, 122.4, 123.5, 127.5, 137.9; ESI-MS: *m/z* (%) = 247 ($[M+H]^+$, 100).

3 Results and Discussion

The Friedel–Crafts alkylation reaction, one of the oldest organic synthetic methods, is one of the most powerful carbon–carbon bond forming reaction. In the $Cu(OTf)_2$-

Table 1 Enantioselective Cu(II)-catalyzed Friedel–Crafts alkylation of indole with β-nitrostyrene using the ligands **1a–e**



2a **3a** **4a**

Entry	Ligand	Loading (mol %)[a]	Solvent	*t* (h)	T (°C)	Yield (%)[b]	*ee* (%)[c]
1	**1a**	4.0	Et_2O	20	−10	94	84
2	**1b**	4.0	Et_2O	20	−10	98	93
3	**1c**	4.0	Et_2O	20	−10	99	97
4	**1d**	4.0	Et_2O	20	−10	96	89
5	**1e**	4.0	Et_2O	20	−10	95	87
6	**1c**	4.0	Et_2O	10	0	95	86
7	**1c**	4.0	Et_2O	12	−5	93	90
8	**1c**	4.0	Et_2O	36	−20	90	98
9	**1c**	4.0	CH_2Cl_2	20	−10	95	86
10	**1c**	4.0	THF	10	−10	96	82
11	**1c**	4.0	Toluene	20	−10	92	80
12	**1c**	1.0	Et_2O	20	−10	76	80
13	**1c**	2.0	Et_2O	20	−10	87	89
14	**1c**	3.0	Et_2O	20	−10	94	94
15	**1c**	5.0	Et_2O	20	−10	99	98

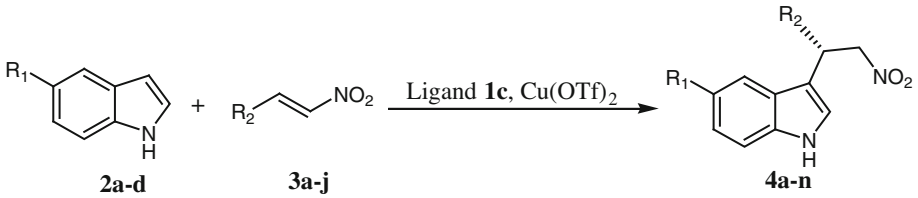
The catalyst was prepared in situ by refluxing ligand **1** and $Cu(OTf)_2$ in 5 ml of solvent

[a] Loading: catalyst/indole (molar ratio)

[b] Conditons: indole (0.25 mmol), β-nitrostyrene (0.25 mmol) and solvent (5.0 ml). The reactions were performed under the protect of a nitrogen atmosphere

[c] Enantiomeric excess was determined by HPLC using a Daicel Chiracel OD-H column. All absolute configurations were determined as *S* by optical roation measurements

Table 2 Enantioselective Cu(II)-catalyzed Friedel–Crafts alkylation of indole derivatives with nitroalkenes using the ligand **1c**



2a-d **3a-j** **4a-n**

Entry	Product	R_1	R_2	Yield (%)[a]	*ee* (%)[b]
1	**4a**	H	Ph	99	97
2	**4b**	Me	Ph	95	98
3	**4c**	MeO	Ph	94	98
4	**4d**	F	Ph	93	94
5	**4e**	Cl	Ph	90	89
6	**4f**	H	2-$MeOC_6H_4$	96	88
7	**4 g**	H	2-ClC_6H_4	87	73
8	**4 h**	H	3-BrC_6H_4	95	94
9	**4i**	H	3-$NO_2C_6H_4$	97	92
10	**4j**	H	4-$MeOC_6H_4$	90	91
11	**4 k**	H	4-ClC_6H_4	94	95
12	**4 l**	H	4-BrC_6H_4	93	95
13	**4 m**	H	2-Furyl	86	82
14	**4n**	H	$CH_3(CH_2)_3$	92	93

[a] Conditions: catalyst/indole derivative = 4.0 mol %, indole derivative (0.25 mmol), nitroalkene (0.25 mmol), ethyl ether (5.0 ml), −10 °C, 20 h

[b] Enantiomeric excesses were determined by HPLC using a Daicel Chiracel OD-H or Daicel Chiralpakl AD-H column. All absolute configurations were determined as *S* by optical rotation measurements

catalyzed asymmetric Friedel–Crafts alkylation of indole **2a** with β-nitrostyrene **3a**, the catalytic activities of bis(oxazoline)thiophenes **1a–e** in hand was first tested. The results are summarized in Table 1. The enantioselectivity of Cu(II)–bis(oxazoline)thiophene complexes is sensitive to the substituents on the oxazoline ring. Good yields and enantiomeric excesses can be obtained for ligands **1b** and **1c** with the bulkier isopropyl and *tert*-butyl substituents (entries 2, 3 vs. entries 1, 4, 5). Of them, the ligand **1c** achieved the best enantioselectivity. Next, the effect of temperature on the catalytic reaction with bis(oxazoline)thiophene **1c** as a chiral ligand was investigated with Et_2O as solvent. The reaction proved to be temperature-dependent. When the reaction temperature was decreased from 0 to −10 °C, the enantiomeric excess value of the product **4a** increased from 86 to 97 % (entries 3, 6 , 7). Although the catalytic reaction proceeded well at −20 °C, the reaction time was prolonged to 36 h and the ee value of **4a** showed no significant improvement (entry 8). As for solvent effect, the reaction exhibited a preference for Et_2O as solvent (entry 3). The use of aprotic solvents such as dichloromethane, tetrahydrofuran and toluene afforded **4a** in good yield with middle enantioselectivity (entries 9–11). Further, catalyst loadings were investigated, and the results indicated that they were generally employed at 4.0 mol %, relative to indole **2a** (entry 3 vs. entries 12–14). The enantioselectivity can be slightly improved to 98 % ee when the catalyst loading increased from 4.0 to 5.0 mol % (entry 3 vs. entry 15).

After the reaction conditions were optimized, the generality of this reaction was further evaluated by examining a variety of structurally different indole derivatives and nitroalkenes (Table 2). High yields and excellent enantioselectivities can be achieved for the indole derivatives with both electron-donating and electron-deficient groups in the five position (entries 1–5). The *ortho*-substitution on the phenyl in nitrostyrenes, either electron-donating or electron-withdrawing groups, decreased the enantiomeric excess of products, perhaps due to the steric effect of *ortho*-substitutes (entries 6 , 7). *Meta* or *para*-substitution on the phenyl in nitrostyrenes and aliphatic-substituted nitroalkenes all reacted well with indole to give the alkylated indoles in good yields and high enantioselectivities (entries 8–12 , 14). The nitroalkene containing furan gave 86 % yield and 82 % ee (entry 13).

The Cu(II)-catalyzed asymmetric Friedel–Crafts alkylation of indole derivatives with nitroalkenes using the

bis(oxazoline)thiophenes **1a–e** can be achieved in the high yields and excellent enantioselectivities in most cases, but its catalytic mechanism is not clear at this stage. All absolute configurations of the alkylated indole derivatives **4a–n** were established as *S* by comparison of their optical properties with those reported in the literatures [3, 6, 12, 17, 26, 34].

4 Conclusion

With chiral bis(oxazoline)thiophenes **1a–e** as templates, the Cu(II)-catalyzed asymmetric Friedel–Crafts alkylation of indole derivatives with nitroalkenes was investigated. In most cases, the catalytic system with the ligand **1c** and Cu(II) trifluoromethanesulfonate gave the best yields (up to 99 %) and enantioselectivities (up to 98 % ee).

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