Asian Journal of Chemistry; Vol. 29, No. 3 (2017), 595-600

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20269

Novel Chiral Secondary Amine-Amide Catalysts Friedel-Craft Alkylation Reaction

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Received: 26 August 2016; *Accepted*: 9 November 2016; *Published online*: 30 December 2016; AJC-18208

A highly efficient catalytic asymmetric Friedel-Crafts alkylation of indole with nitroalkenes using novel chiral secondary amine-amide as catalyst has been developed. Various types of nitroalkylated indoles were obtained in excellent yields (81-93 %) and high enantio-selectivities (up to 95 % ee).

Keywords: Nitroalkenes, Indole, Catalyst, Friedel-Craft alkylation.

INTRODUCTION

Enantioselective Friedel-Crafts alkylation reaction represents one of the most significant approaches to the synthesis of chiral aromatic compounds bearing benzylic stereogenic centers [1-5]. Recently, using nitroalkenes as substrates to achieve asymmetric Friedel-Crafts alkylation of indoles has been paid considerable attention [6,7]. It is the result of chemists' effort to develop new types of substrates for the enantioselective version of the Friedel-Crafts reaction [8-11]. In present study, indoles have attracted considerable attention as popular aromatic substrates and many efficient reactions have been developed to synthesize chiral indole derivatives [12,13]. However, the enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes needs to undergo continuous development. In these pioneer reports, relatively high temperature or a long time was used [14,15]. This paper studied hydrogenation reduction of carboxyl group of L-proline. With the protection of amino group of pyrrole by using BOC_2O, it synthesizes BOC-L-proline after a series of reactions as sulfonylation, azidation, hydrolysis, *etc.* [16-20]. Then we synthesized novel chiral secondary amine-amide catalysts (Fig. 1) with reaction of benzoic acid derivatives and naphthalene acid derivatives, which is applied into Friedel-Craft alkylation of nitrobenzenes [21-23] compounds and indole and the study showed excellentresults in chemical yields and enantioselectivity.

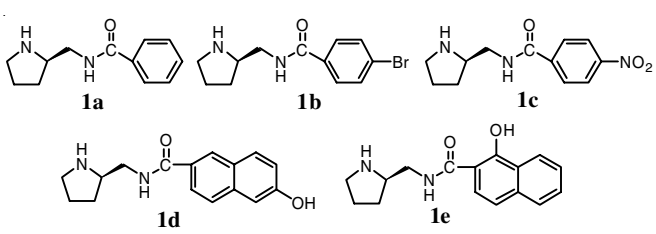


Fig. 1. Secondary amine-amide catalysts

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker DRX (400 MHz) spectrometer in $CDCl_3$ or DMSO using tetramethylsilane (TMS) as an internal standard, X-6 micro digital melting point apparatus, high performance liquid chromatography, chiral daicel (OD-H), Voyager-DE STR mass spectrometer, Vario EL-Cube elemental analyzer, ThermoFisher infrared analyzer.

Synthesis of catalysts: According to previous work [16-20], BOC-L-prolyl is synthesized in compliance with several steps with the feedstock of L-proline. Weigh 0.72 g (3.5 mmol) DCC, 0.47 g (3.5 mmol) HOBt, 0.43 g (3.5 mmol) benzoate, then add another 10 mL dichloromethane into 50 mL boiling flask. Weigh 0.50 g (2.5 mmol) BOC-L-prolyl and put them into the constant pressure funnel with another 2 mL dichloromethane. Tracing the reaction with TLC. We can get intermediates a [2-(benzamidomethyl)pyrrolidin-1-yl pivalate] after column chromatography purification and then the catalyst was obtained by acidification. Similarly, we can get intermediate **1b-1e**.

N-(Pyrrolidin-2-ylmethyl)benzamide (1a): Yield (63 %), ^1H NMR (400 MHz, DMSO), δ: 1.69 (s, 2H), 1.91 (s, 1H), 2.04 (s, 1H), 2.51 (s, 1H), 3.70 (s, 3H), 7.46-7.53 (m, 3H), 7.87 (d, J = 8 Hz 2H), 8.87 (s, 2H), 9.50 (s, 1H). ^{13}C NMR (100 MHz, DMSO), δ: 23.17, 27.68, 40.65, 45.25, 59.83, 127.72, 128.81, 132.05, 134.16, 167.84. FTIR (KBr, ν_{max}, cm^{-1}): 1684.91 (C=O), 1541.43, 725.27 (N-H), 1490.79 (-CH_2-N-C=O), 1437.08 (-CH_2-), 1313.37 (-CH-), 824.56, 801.56

(C-N). MS calcd: 204.27, found: 205.1. Anal. calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.52; H, 7.86; N, 13.61.

4-Bromo-N-(pyrrolidin-2-ylmethyl)benzamide (1b): Yield (59 %), ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.06-2.16 (m, 3H), 3.25 (s, 1H), 3.65-3.87 (m, 2H), 7.28 (s, 2H), 7.55 (d, *J* = 8 Hz 2H), 7.74 (d, *J* = 8 Hz 2H), 8.50 (s, 1H), 9.24 (s, 1H), 10.13 (s, 1H). ^{13}C NMR (100 MHz, DMSO), δ: 23.12, 27.74, 40.62, 45.24, 59.74, 125.73, 129.92, 131.83, 133.47, 166.71. FTIR (KBr, ν_{max}, cm^{-1}): 1677.12 (C=O), 1592.17, 757.2 (N-H), 1430.55 (-CH_2-N-C=O), 1493.40 (-CH_2-), 1319.42 (-CH-), 824.56, 801.06 (C-N), 722.65(C-Br). MS:calcd: 283.16, found: 283.00. Anal. calcd. for $C_{12}H_{15}N_2OBr$: C, 50.90; H, 5.34; N, 9.89. Found: C, 50.82; H, 5.24; N, 9.81.

4-Nitro-N-(pyrrolidin-2-ylmethyl)benzamide (1c): Yield (62 %), ^{1}H NMR (400 MHz, DMSO), δ: 1.23 (s, 1H), 1.69-1.91 (m, 1H), 1.93-1.95 (m, 2H), 2.07 (d, *J* = 8 Hz 1H), 3.59 (s, 3H), 3.69-3.71 (m, 2H), 8.10 (d, *J* = 8 Hz 2H), 8.33 (d, *J* = 8 Hz 2H), 9.17 (s, 1H). ^{13}C NMR (100 MHz, DMSO), δ: 23.10, 27.78, 40.56, 45.20, 59.55, 123.96, 129.32, 140.07, 149.63, 166.00. FTIR (KBr, ν_{max}, cm^{-1}): 1675.77(C=O), 1528.27, 1348.93 (NO_2), 1601.77, 721.95 (N-H), 1430.28 (-CH_2-N-C=O), 1489.56 (-CH_2-), 1301.88 (-CH-), 870.17, 836.83 (C-N). MS:calcd: 249.27, found: 250.1. Anal. calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.77; H, 6.04; N, 16.81.

6-Hydroxy-N-(pyrrolidin-2-ylmethyl)-2-naphthamide (1d): Yield (64 %), ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28 (s, 4H), 1.59 (s, 8H), 4.08 (s, 1H), 7.28 (s, 2H), 7.36 (dd, *J* = 8 Hz 1H), 8.71 (s, 1H), 10.71 (s, 1H). ^{13}C NMR (100 MHz, DMSO), δ: 23.30, 27.77, 40.74, 45.20, 59.81, 109.12, 120.01, 124.78, 126.40, 127.02, 128.14, 128.33, 131.00, 136.67, 157.60, 167.90. FTIR (KBr, ν_{max}, cm^{-1}): 1686.89 (C=O), 1541.53, 722.89 (N-H), 1636.91 (-CH_2-N-C=O), 1437.87 (-CH_2-), 1203.13 (OH), 835.40 (C-N). MS: calcd: 270.33, found: 270.1. Anal. calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.67; N, 10.32.

1-Hydroxy-N-(pyrrolidin-2-ylmethyl)-2-naphthamide (1e): Yield (69 %), ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.78 (s, 3H), 1.97 (d, *J* = 8 Hz 1H), 2.13 (s, 1H), 3.24 (s, 1H), 3.74 (s, 1H), 3.93 (s, 1H), 7.23 (d, *J* = 8 Hz 1H), 7.28 (s, 2H) 7.50-7.59 (m, 3H), 7.71 (d, *J* = 8 Hz 1H), 8.38 (d, *J* = 8 Hz 1H), 9.10 (s, 1H), 9.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO), δ: 23.82, 27.37, 40.52, 45.39, 60.54, 106.21, 118.44, 121.52, 123.66, 125.26, 125.80, 127.32, 129.09, 136.47, 160.55, 172.39. FTIR (KBr, ν_{max}, cm^{-1}): 1683.88 (C=O), 1597.28, 723.85 (N-H), 1545.19 (-CH_2-N-C=O), 1395.76 (-CH_2-), 1206.34 (OH), 801.38 (C-N). MS: calcd: 270.33, found: 270.1. Anal. calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.01; H, 6.68; N, 10.31.

Catalyze the Michael addition reaction: Add indole 5.9 mg (0.05 mmol), dichloromethane 1 mL, catalysis **1e** 1.4 mg (0.005 mmol) into 25 mL round bottomed flask and stir it under the condition of room temperature, tracing the reaction with TCL. Then purify the product after stopping the reaction.

3-(2-Nitro-1-phenylethyl)-1H-indole (4a): White solid, Yield (91 %), m.p.: 96-99 °C (Lit [24] 97 °C -99 °C), 95 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 9.64 min and 14.16 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.97 (m, 1H), 5.10 (dd, *J* = 12 Hz 1H), 5.23 (t, *J* = 8 Hz 1H), 7.03-7.04 (m, 1H), 7.12 (t, *J* = 12 Hz 1H), 7.24 (t, *J* = 16 Hz 1H), 7.28-7.34 (m, 1H), 7.36 (t, *J* = 12 Hz 5H), 7.49 (d, *J* = 8 Hz 1H), 8.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 41.60, 79.59, 111.53, 114.27, 118.94, 119.96, 121.73, 122.69, 123.13, 127.63, 127.83, 128.98, 136.51, 139.27. FTIR (KBr, ν_{max}, cm^{-1}): 1636.30 (C=C), 1548.98 (C-NO_2), 1384.39 (C-N), 688.44.

3-(2-Nitro-1-*p*-tolylethyl)-1H-indole (4b): White solid, Yield (93 %), oil (Lit. [24]), 86 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH=80:20, 1.0 mL/min, 254 nm; t_R = 9.52 min and 13.96 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.35 (s, 1H), 4.92-4.98 (m, 1H), 5.05-5.10 (m, 1H), 5.17-5.21 (m, 1H), 7.03 (s, 1H), 7.10-7.14 (m, 3H), 7.15-7.17 (m, 3H), 7.23-7.25 (d, *J* = 8 Hz 1H), 7.27-7.28 (d, *J* = 4 Hz 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.23, 41.28, 79.72, 111.54, 114.46, 118.99, 119.93, 121.70, 122.66, 126.17, 127.71, 129.68, 136.27, 136.54, 137.29. FTIR (KBr, ν_{max}, cm^{-1}): 1617.38 (C=C), 1559.46 (C-NO_2), 1384.44 (C-N), 619.84.

3-[1-(4-Chlorophenyl)-2-nitroethyl]-1H-indole (4c): White solid, Yield (89 %), m.p.: 104-109 °C (Lit [24] 107-108 °C), 85 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 9.58 min and 14.03 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.92-4.95 (m, 1H), 5.08-5.10 (m, 1H), 5.19-5.21 (m, 1H), 7.15 (s, 1H), 7.02-7.08 (m, 1H), 7.23-7.27 (m, 4H), 7.37-7.39 (d, *J* = 8 Hz 1H), 7.62-7.64 (d, *J* = 4 Hz 2H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 41.00, 79.34, 111.64, 113.79, 118.84, 120.11, 121.66, 122.88, 125.94, 129.15, 129.23, 133.41, 136.54, 137.84. FTIR (KBr, ν_{max}, cm^{-1}): 1617.49 (C=C), 1550.93 (C-NO_2), 1383.99 (C-N), 7445, 688.44.

3-[1-(4-Bromophenyl)-2-nitroethyl]-1H-indole (4d): White solid, Yield (86 %), m.p.: 120.5-123 °C (Lit [24] 121-122 °C), 85 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 9.10 min and 13.88 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.90-4.93 (m, 1H), 4.95-5.07 (m, 1H), 5.16-5.20 (m, 1H), 7.02 (s, 1H), 7.11-7.13 (m, 1H), 7.22-7.24 (m, 3H), 7.27-7.28 (s, 1H), 7.37-7.48 (m, 3H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 41.05, 79.23, 111.59, 113.75, 118.82, 120.12, 121.55, 121.63, 122.89, 125.90, 129.56, 132.09, 136.52, 138.32. FTIR (KBr, ν_{max}, cm^{-1}): 1617.35 (C=C), 1578.47 (C-NO_2), 1384.37 (C-N), 617.12.

3-[1-(4-Fluorophenyl)-2-nitroethyl]-1H-indole (4e): White solid, Yield (81 %), m.p.: 129.6-134 °C; 91 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH=80:20, 1.0 mL/min, 254 nm; t_R = 12.03 min and 21.31 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.93 (dd, *J* = 8 Hz 1H), 5.05-5.10 (m, 1H), 5.17-5.19 (m, 1H), 7.02 (d, *J* = 8 Hz 1H), 7.13 (t, *J* = 16 Hz 1H), 7.32 (dd, *J* = 12 Hz 4H), 7.37 (s, 1H), 7.44 (d, *J* = 8 Hz 2H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 40.89, 79.57, 111.53, 114.19, 115.75, 115.97, 118.87, 120.07, 121.51, 122.84, 125.96, 129.37, 129.45, 134.96, 136.53, 160.88. FTIR (KBr, ν_{max}, cm^{-1}): 1618.18 (C=C), 1551.39 (C-NO_2), 1383.98 (C-N), 744.64.

3-[1-(2-Methoxyphenyl)-2-nitroethyl]-1H-indole (4f): Oil (Lit [14]), Yield (92 %), 88 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH=80:20, 1.0 mL/min, 254 nm; t_R = 13.20 min and 19.86 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.95 (s, 3H), 4.98-5.10 (m, 2H), 5.64-5.66 (d, *J* =

8 Hz 1H), 6.85-6.89 (m, 1H), 7.09-7.10 (m, 3H), 7.12-7.14 (m, 2H), 7.20-7.22 (d, *J* = 8 Hz 1H), 7.26-7.28 (d, *J* = 8 Hz 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 35.54, 55.59, 78.21, 110.87, 111.41, 113.80, 119.11, 119.75, 120.84, 122.11, 122.47, 126.55, 127.26, 128.72, 128.99, 136.44. FTIR (KBr, ν_{max}, cm^{-1}): 1617.40 (C=C), 1559.78 (C-NO_2), 1384.25 (C-N), 620.57.

3-[1-(2-Chlorophenyl)-2-nitroethyl]-1H-indole (4g): Oil (Lit [14]), Yield (86 %), 91 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 13.64 min and 22.16 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.97-5.07 (m, 2H), 5.76-5.80 (m, 1H), 7.09-7.13 (m, 2H), 7.20-7.23 (m, 4H), 7.28-7.37 (m, 1H), 7.39-7.43 (d, *J* = 16 Hz 2H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: FTIR (KBr, ν_{max}, cm^{-1}): 1636.76 (C=C), 1551.30 (C-NO_2), 1383.98 (C-N), 744.67.

3-[2-Nitro-1-(3-nitrophenyl)ethyl]-1H-indole (4h): Oil (Lit [24]), Yield (89 %), 92 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 9.68 min and 14.11 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.00-5.05 (m, 1H), 5.12-5.17 (m, 1H), 5.31-5.35 (t, *J* = 16 Hz 1H), 7.10-7.14 (m, 2H), 7.23-7.28 (m, 2H), 7.41-7.23 (d, *J* = 8 Hz 2H), 7.52-7.56 (t, *J* = 16 Hz 1H), 7.73-7.75 (d, *J* = 8 Hz 1H), 8.13-7.17 (d, *J* = 16 Hz 1H), 8.23-8.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 41.11, 78.89, 111.85, 112.82, 118.51, 120.23, 121.86, 122.74, 122.78, 123.07, 125.73, 130.03, 134.31, 136.55, 141.75, 148.54. FTIR (KBr, ν_{max}, cm^{-1}): 1617.30 (C=C), 1558.98 (C-NO_2), 1384.32 (C-N), 617.50.

1,2-Dimethyl-3-(2-nitro-1-phenyl)-1H-indole (4i): Oil, Yield (83 %), 79 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 94:6, 1.0 mL/min, 254 nm; t_R = 20.32 min and 27.63 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.43 (s, 3H), 3.68 (s, 3H), 5.12-5.18 (m, 1H), 5.23-5.31 (m, 2H), 7.05 (dd, *J* = 8 Hz 1H), 7.18 (t, *J* = 12 Hz 1H), 7.22-7.35 (m, 6H), 7.40 (d, *J* = 8 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 10.52, 29.67, 40.75, 78.80, 108.16, 109.13, 118.66, 119.38, 120.90, 125.95, 127.07, 127.32, 128.78, 134.70, 138.98, 139.82. FTIR (KBr, ν_{max}, cm^{-1}): 1617.72 (C=C), 1547.16 (C-NO_2), 1383.99 (C-N), 743.68, 617.72.

3-(2-Nitro-1-phenylethyl)-2-phenyl-1H-indole (4j): Oil, Yield (89 %), 92 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t_R = 19.95 min and 22.95 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.14-5.25 (m, 2H), 5.33-5.37 (m, 1H), 7.14 (t, *J* = 16 Hz 1H), 7.25-7.28 (m, 3H), 7.31-7.38 (m, 4H), 7.43 (d, *J* = 8 Hz 1H), 7.47-7.50 (m, 4H), 7.55 (d, *J* = 8 Hz 1H), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 40.86, 79.13, 109.51, 111.53, 119.99, 120.32, 122.50, 127.04, 127.24, 127.52, 128.65, 128.82, 128.94, 128.98, 132.19, 136.11, 137.03, 139.92. FTIR (KBr, ν_{max}, cm^{-1}): 1617.57 (C=C), 1549.88 (C-NO_2), 1384.00 (C-N), 609.78.

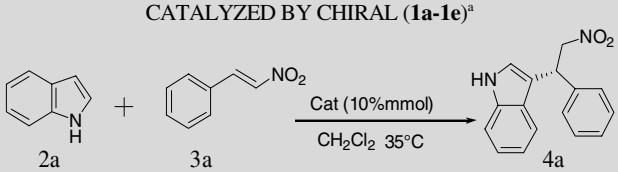
1-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (4k): White solid, Yield (86 %), m.p.: 95-97 °C (Lit [24] 94-95 °C), 85 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm; t_R = 29.60 min and 57.47 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.78 (s, 3H), 4.97 (dd, *J* = 16 Hz 1H), 5.08 (dd, *J* = 16 Hz 1H), 5.21 (t, *J* = 16 Hz 1H), 6.89 (s, 1H), 7.10 (t, *J* = 16 Hz 1H), 7.23-7.38 (m, 7H), 7.48 (d, *J* = 8 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 32.86, 41.57, 79.59, 109.58, 112.80, 119.02, 119.49, 122.26, 126.42, 126.58, 127.55, 127.79, 128.95, 137.31, 139.44. FTIR (KBr, ν_{max}, cm^{-1}): 1617.49 (C=C), 1558.72 (C-NO_2), 1383.54 (C-N), 736.41, 701.28.

2-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (4l): White solid, Yield (81 %), m.p.: 101-103 °C (Lit [24] 101-102 °C), 93 % ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t_R = 28.32 min and 38.65 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.43 (s, 3H), 5.14-5.27 (m, 3H), 7.05 (t, *J* = 12 Hz 1H), 7.14 (t, *J* = 16 Hz 1H), 7.25-7.34 (m, 6H), 7.41 (d, *J* = 8 Hz 1H), 7.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 11.96, 40.52, 78.68, 08.74, 10.82, 118.62, 119.75, 121.33, 126.85, 127.13, 127.36, 128.83, 133.00, 135.44, 139.55. FTIR (KBr, ν_{max}, cm^{-1}): 1618.15 (C=C), 1552.03 (C-NO_2), 1383.51 (C-N), 745.64, 697.76.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions, at first, the catalytic effect was examined by carrying out the Friedel-Crafts alkylation reaction. We compare five novel chiral secondary amine-amide small organic molecules by using solvent CH_2Cl_2 and catalyst dosage (10 % mmol) at 35 °C. The study shows that these five secondary amine-amide performed fairly catalytic activity and higher yields. However, the catalyst **1a-1d** have no find superior enantioselective (entry1-4) and the catalyst **1e** (1-hydroxy-N-(pyrrollidin-2-ylmethyl)-2-naphthamide) obtains superior enantioselective (95 % ee, entry 5). Its possible that the *ortho* hydroxyl group are enhance steric and electronic effects, this can be used to maximize the use of multiple hydrogen bonds in the molecular structure of the catalyst to further activate the reaction system in the corresponding, to enable it achieves better three-dimensional control and obtain better catalytic activity in the asymmetric reaction.

TABLE-1
ASYMMETRIC FRIEDEL-CRAFTS ALKYLATION OF INDOLE (**2a**) WITH NITROSTYRENE (**3a**) CATALYZED BY CHIRAL (**1a-1e**)[a]



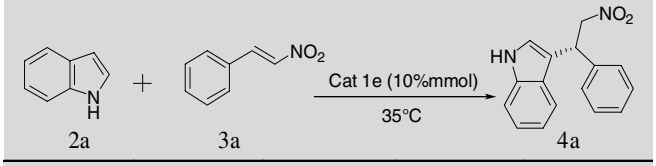
Entry	Catalyst	Time	Yield (%)[b]	ee (%)[c]
1	**1a**	24	84	10
2	**1b**	20	83	7
3	**1c**	26	89	14
4	**1d**	18	83	64
5	**1e**	12	91	95

[a]Reaction conditions: indole **2a** (0.50 mmol) with nitrostyrene **3a** (0.50 mmol) in 2 mL of CH_2Cl_2 under 10 mmol % secondary amineamide; [b]Isolated yield after column chromatography; [c]Determined by HPLC analysis using Chiralpak OD-H column.

We further examined different solvents. Some typical results are presented in Table-2. A number of solvents were successfully applied to the catalytic enantioselective Friedel-Crafts reaction (entries 1-10) with the presence of 10 mmol % **1e**, at 35 °C for 12 h (Table-2), used as system. The reaction was

influenced by the polarity of the solvent and in oxygen-containing solvents, such as Et_2O, THF, EtOAc, petroleum ether and DMF (entries 1, 4, 5, 7 and 8), probably because the oxygen atom coordinated to **1e**, thus reducing its catalytic activity. On the contrary, other solvents such as hexane, toluene, CH_2Cl_2 and $CHCl_3$ were all effective in producing the desired product **4a** in good yields. Using alkyl halides as the solvent gave **4a** in high yield with superior enantioselectivity (entries 3 and 6) and dichloromethane was the best choice (entry 6).

TABLE-2
EFFECT OF SOLVENTS IN FRIEDEL-CRAFTS ALKYLATIN OF INDOLE (**2a**) WITH NITROSTYRENE (**3a**)[a]



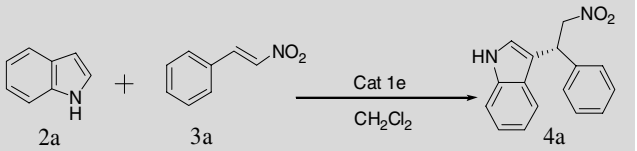
Entry	Cat **1e** (mmol %)	Solvents	Yield (%)[b]	ee (%)[c]
1	10	Et_2O	21	32
2	10	CH_3CH_2OH	49	41
3	10	$CHCl_3$	76	72
4	10	THF	35	28
5	10	EtOAc	47	36
6	10	CH_2Cl_2	91	95
7	10	PE	29	12
8	10	DMF	31	51
9	10	Toluene	64	72
10	10	Hexane	63	74

[a]Reaction conditions: indole **5a** (0.50 mmol) with nitrostyrene **6a** (0.50 mmol) in 2 mL of toluene under 10 mmol % **1e** secondary amine-amide. [b]Isolated yield after column chromatography; [c]Determined by HPLC analysis using Chiralpak OD-H column.

After identifying the optimal solvent, to get the most optimized reaction conditions, we further studied different temperature and catalyst loading. Some typical results are presented in Table-3. The heating and increase catalyst loading the reaction led to improvement in the enantioselectivity and yield (entries 1 and 4). With the decrease of temperature and the constant of catalyst loading led to the increase of reaction time and the decrease of yield (entries 6, 7 and 8). When the reaction was performed at 35 °C, **4a** was obtained in 95 % ee (entry 1). Enhancement of the catalyst loading decreased the enantioselectivity ovious change (entries 2 and 3). Finally, we determined that using 10 mmol % **1e** in CH_2Cl_2 at 35 °C to catalyze the reaction was the most practical.

The generality of the reaction was further demonstrated by variation of the nitroalkene. Aromatic- and aliphatic-substituted nitroalkenes all reacted well with indole to afford alkylated indoles in excellent yields and high enantioselectivities (entries 1-8). An electron withdrawing substituent such as chlorine in the 1 and 2-position of the indole ring in **2b** caused moderate decrease in both yield and enantioselectivity (entry 9). When we introduced a methyl substituent to the indolic nitrogen atom, the reaction proceeded very well, giving the corresponding derivatives **4k** in high yield and enantioselectivity (entry 11). The *ortho* substitution on the phenyl ring present in nitrostyrene, either electrodonating or electron-withdrawing groups, lowered the enantiomeric excess of products, perhaps due to

TABLE-3
FURTHER OPTIMIZATION OF REACTION CONDITIONS FOR FRIEDEL-CRAFTS ALKYLATION OF INDOLE (**2a**) WITH NITROSTYRENE (**3a**)[a]



Entry	Temp. (°C)	Cat **1e** (mmol %)	Time (h)	Yield (%)[b]	ee (%)[c]
1	35	10	12	91	95
2	35	5	18	84	81
3	35	2.5	26	56	76
4	25	10	19	74	85
5	25	5	27	49	77
6	15	10	32	56	74
7	10	10	37	53	69
8	5	10	46	54	72

[a]Reaction conditions: indole **5a** (0.50 mmol) with nitrostyrene **6a** (0.50 mmol) in 2 mL of CH_2Cl_2 using **1e** secondary amine-amide as the catalyst, [b]Isolated yield after column chromatography; [c]Determined by HPLC analysis using Chiralpak OD-H column.

the steric effect of *ortho*-substituents. The catalytic hydrogen bonds may activate receptor, in other words, the donor hydrogen bonds and Friedel-Crafts alkylation receptor function so that it reduces the electron areal density and activate that effectively. Hence enhances the emergence of nucleophile in the solvent and promoted the Friedel-Crafts alkylation. the reaction could be easily extended to aliphatic nitroalkenes.

According to the literature [21-23], we have speculated that NH and OH of secondary amine-amide catalyst similar to the two NH of thiourea type organic catalyst, nitro olefins in the nitro group by its role in hydrogen bonding, reducing the density of their own and the receptor is activated and the affinity of the receptor is increased, through the chiral framework to control the direction of attack. Thus, we obtained the product configuration excessively and even with N-protected indole the enantioselectivity was kept at a high level.

In conclusion, we have developed a more practical catalytic asymmetric Friedel-Crafts alkylation of indoles (**2**) with a variety of nitroalkenes (**3**) using secondary amine-amide complex as catalyst, which can activate nitroalkenes and orient indoles effectively.

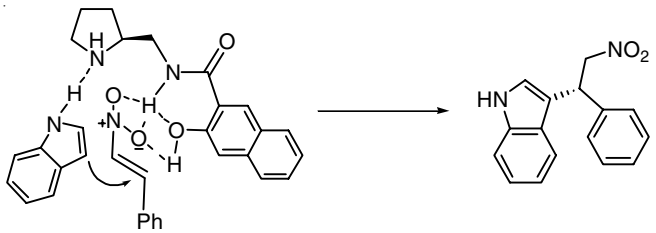
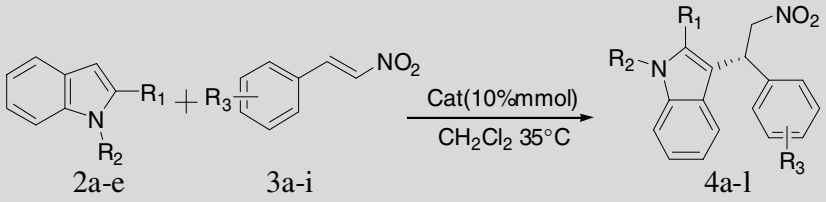


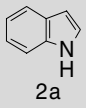
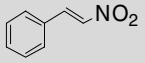
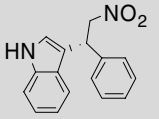
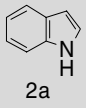
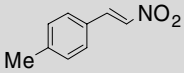
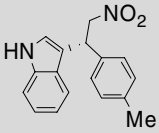
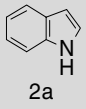
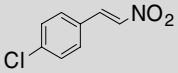
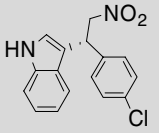
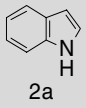
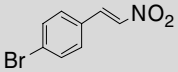
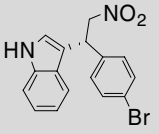
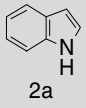
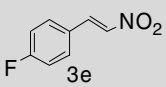
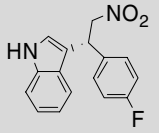
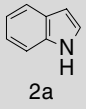
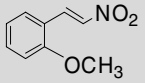
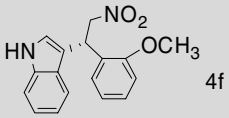
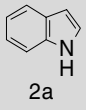
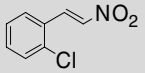
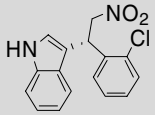
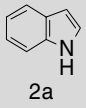
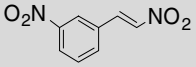
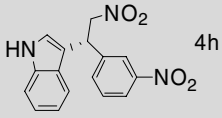
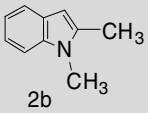
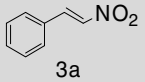
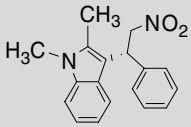
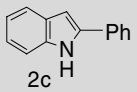
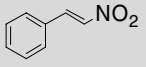
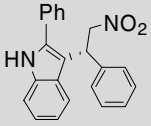
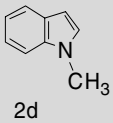
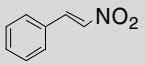
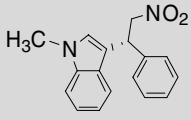
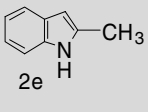
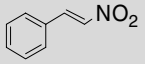
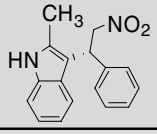
Fig. 2. Possible mechanism of catalyst **1e**

Conclusion

In summary, we have found that new chiral secondary amine-amide **1e** can promote the Friedel-Craft alkylation reaction of indole and nitroalkenes, which can activate indole and nitroalkenes effectively. Various types of the nitroalkylated

TABLE-4
FRIEDEL-CRAFTS ALKYLATION OF INDOLES (**2**) WITH NITROALKENE (**3**) CATALYZED BY **1e**[a]



Entry	Indoles	Nitroolefins	Product	Yield (%)[b]	ee (%)[c]
1	 2a	 3a	 4a	91	95
2	 2a	 3b	 4b	93	86
3	 2a	 3c	 4c	89	85
4	 2a	 3d	 4d	86	85
5	 2a	 3e	 4e	81	91
6	 2a	 3f	 4f	92	88
7	 2a	 3h	 4g	86	91
8	 2a	 3i	 4h	89	92
9	 2b	 3a	 4i	83	79
10	 2c	 3a	 4j	89	92
11	 2d	 3a	 4k	86	85
12	 2e	 3a	 4l	81	93

[a]Reaction conditions: indole **5** (0.50 mmol) with nitroalkene **6** (0.50 mmol) in 2 mL of CH_2Cl_2 using 10 mmol % **1e** secondary amine-amide as catalyst at 35 °C for 12 h. [b]Isolated yield after column chromatography; [c]Determined by HPLC analysis using Chiralpak OD-H column.

indoles were obtained in excellent yields and high enantioselectivities (up to 95 % ee). Further studies are now in progress in our laboratory to expand the reaction scope and to develop novel chiral catalysts.

ACKNOWLEDGEMENTS

The authors thank The National Natural Science Foundation of China, No. 21362006, for financial support of this work.

REFERENCES

1. M. Bandini and A. Umani-Ronchi, Catalytic Asymmetric Friedel-Crafts Alkylations, Wiley-VCH: Weinheim, Germany (2009).
2. For selected reviews, see: M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem. Int. Ed.*, **43**, 550 (2004).
3. T.B. Poulsen and K.A. Jørgensen, *Chem. Rev.*, **108**, 2903 (2008).
4. S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, **38**, 2190 (2009).
5. V. Terrasson, R.M. de Figueiredo and J.M. Campagne, *Eur. J. Org. Chem.*, **2010**, 2635 (2010).
6. R.P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem. Int. Ed.*, **44**, 6576 (2005).
7. W. Zhuang, R.G. Hazell and K.A. Jørgensen, *Org. Biomol. Chem.*, **3**, 2566 (2005).
8. K.B. Jensen, J. Thorhauge, R.G. Hazell and K.A. Jørgensen, *Angew. Chem. Int. Ed.*, **40**, 160 (2001).
9. W. Zhuang, N. Gathergood, R.G. Hazell and K.A. Jørgensen, *J. Org. Chem.*, **66**, 1009 (2001).
10. N.A. Paras and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **124**, 7894 (2002).
11. J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, **124**, 9030 (2002).
12. D.A. Horton, G.T. Bourne and M.L. Smythe, *Chem. Rev.*, **103**, 893 (2003).
13. S. Cacchi and G. Fabrizi, *Chem. Rev.*, **105**, 2873 (2005).
14. S.F. Lu, D.M. Du, J. Xu, *Org. Lett.*, **8**, 2115 (2008).
15. J. Weng, R.-J. Fan, Q.-M. Deng, R.-R. Liu, J.-R. Gao and Y.-X. Jia, *J. Org. Chem.*, **81**, 3023 (2016).
16. D. Enders, P. Fey and H. Kipphardt, *Org. Synth.*, **65**, 173 (1988).
17. A.F. Spatola, M.K. Anwer, A.L. Rockwell and L.M. Gierasch, *J. Am. Chem. Soc.*, **108**, 825 (1986).
18. G.W. Kabalka, M. Varma, R.S. Varma, P.C. Srivastava and F.F. Knapp, *J. Org. Chem.*, **51**, 2386 (1986).
19. N. Dahlin, A. Bøgevig and H. Adolfsson, *Adv. Synth. Catal.*, **346**, 1101 (2004).
20. H. Iwamura, S.P. Mathew and D.G. Blackmond, *J. Am. Chem. Soc.*, **126**, 11770 (2004).
21. S. Lee and D.W.C. MacMillan, *J. Am. Chem. Soc.*, **129**, 15438 (2007).
22. Y.-Z. Liu, R.-L. Cheng and P.-F. Xu, *Org. Chem.*, **76**, 2884 (2011).
23. C.C. Wang, S.L. Xie and Z.F. Xie, *Chinese J. Org. Chem.*, **33**, 1919 (2013).
24. J. Xie, X. Zhu, M. Huang, F. Meng, M. Wang and Y. Wan, *Synth. Commun.*, **40**, 3259 (2010).