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REGULAR ARTICLE

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Highly enantioselective Michael addition of pyrazolin-5-ones to nitroolefins catalyzed by cinchona alkaloid derived 4-methylbenzoylthioureas

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Abstract

Cinchona alkaloid-derived 4-methyl/nitro benzoylthioureas were synthesized, which smoothly catalyzed the asymmetric Michael addition of pyrazolin-5-ones to nitroolefins. The results showed that electronic effects of substituents in the benzene ring of benzoylthioureas have subtle influences on their catalytic abilities and electron donating methyl group is favored than electron withdrawing nitro group. Preliminary Hartree-Fock calculations revealed that in the catalytic cycle, hydrogen bond energies of the complex formed with 4-methylbenzoylthioureas are about 0.19 to 1.56 kcal/mol higher than with the corresponding 4-nitrobenzoylthioureas. 4-Methylbenzoylthioureas were identified as the most effective catalysts that promoted asymmetric Michael addition of pyrazolin-5-ones to nitroolefins to give the *S*- or *R*-products with high enantioselectivities.

KEYWORDS

4-methylbenzoylthioureas, asymmetric Michael addition, Hartree-Fock calculations, nitroolefins, pyrazolin-5-ones

1 | INTRODUCTION

Pyrazolone, an important five-membered ring heterocyclic motif, is found in many natural and synthetic products with a wide range of pharmacological activities. For example, the novel pyrazolone derivatives were developed as small molecule inhibitors of sirtuins for potential use as chemotherapeutics as well as tools to modulate sirtuin activity.[1] Norman and his co-workers described a potent class of pyrazolone c-Met inhibitors with good

in vivo activity.[2] A series of 1,3,4-trisubstituted-pyrazolone derivatives were demonstrated as potent and nonsteroidal farnesoid X receptor selective antagonists by Huang et al.[3] Hadi et al have exploited SAR studies of pyrazolone scaffold for HIV-1 integrase and discovered a potent compound that exhibited single-digit micromolar activity against IN strand transfer process.[4] Amata et al reported the synthesis and assessment of a series of pyrazolone derivatives of human phosphodiesterase 4 (hPDE4) inhibitors for the assessment of their activity against the trypanosomal phosphodiesterase TbrPDEB1.[5] Further, pyrazolone is a constituent structural feature of many nonsteroidal anti-inflammatory drugs clinically useful in the treatment of arthritis and other musculo skeletal and joint disorders.[6] Therefore, the broad spectrum of biological activities of pyrazolone derivatives have resulted in considerable interest in investigation on the chemistry of pyrazolones especially the development of asymmetric methods for building of pyrazolone-based chiral compounds.[7-14]

Pyrazolin-5-ones are widely used pyrazolone derivatives and have active property, especially at the C-4 location, where nucleophilic reactions can easily occur.[7] It has been used as Michael donors in the asymmetric additions to react with 1,4-dicarbonyl but-2-enes,[8] azodicarboxylates,[9] alkynones,[10] α,β-unsaturated aldehydes,[11] nitroolefins,[7,12-14] etc.

Recent efforts toward the development of chiral dual hydrogen bonding catalysts have produced outstanding efficiency in a wide variety of asymmetric transformations.[15-20] The two donor hydrogens in these scaffolds serve to organize and activate the reaction substrates. And the acidity of the N–H bonds is sensitive and critical for these bifunctional organocatalysts (Figure 1).[20]

In our previous work, we have designed and synthesized cinchona-based benzoylthioureas that can catalyze Michael addition of pyrazolin-5-ones to nitroolefins with high enantio- and diastereoselectivities.[21] In the context of the above chemistry, we designed and synthesized cinchona alkaloid-derived 4-methyl/nitro benzoylthioureas **I-VIII** (Scheme 1) to find more competent catalysts and study the electronic effects of substituents in the benzene ring of benzoylthioureas on their catalytic performances using both experimental and theoretical (Hartree-Fock calculation) methods.

2 | MATERIALS AND METHODS

2.1 | General

9-Amino-9-deoxyepicinchona alkaloids were synthesized according to literature methods.[22,23] Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200-300 mesh). Melting points were measured on an XT-4 melting point apparatus without correction. The ^{1}H-NMR spectra were recorded on BRUKER AVANCE II 400 MHz and 600 MHz spectrometer, while the ^{13}CNMR spectra were recorded at 100 and 150 MHz. Infrared spectra were obtained on Thermo Scientific Nicolet iS5. The high resolution electrospray ionization mass spectrometry (ESI-HRMS) spectra were obtained on Bruker APEX IV mass spectrometer. Optical rotations were measured on Rudolph Research Analytical Autopol III. The enatiomeric excesses of the products were determined by chiral high-performance liquid chromatography (HPLC) analysis using a Lumtech instrument on chiralpak AS-H, IC (n-hexane/2-propanol as eluent). The absolute configuration of the products were determined by comparing HPLC data and specific rotation ratio with data in literatures.[7,24] All calculations were performed with Gaussian 03. Molecular geometries were fully optimized with the HF/sto-3g method.

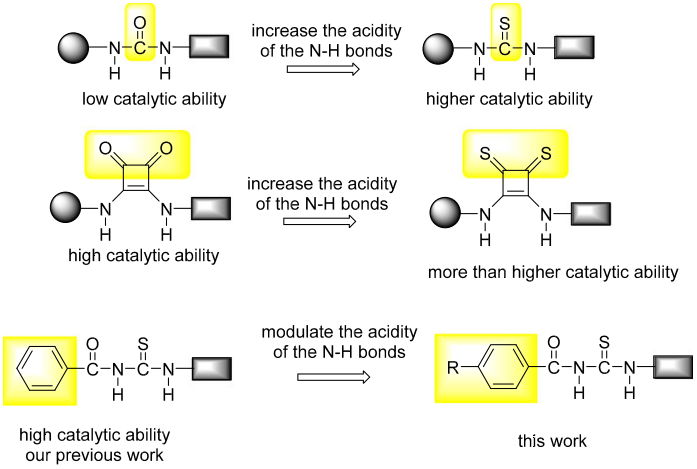
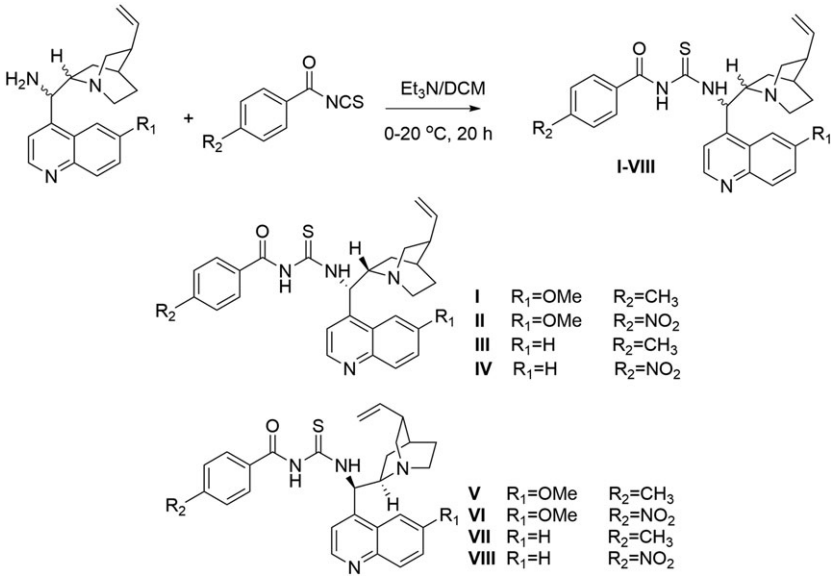


FIGURE 1 Development of relevant chiral organocatalysts bearing two NH-donor hydrogen atoms



SCHEME 1 Synthesis of 4-methyl/nitro benzoylthioureas **I-VIII**

2.2 | Synthesis of organocatalysts I-VIII

9-Amino-9-deoxyepicinchona alkaloid (1 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C, then followed by addition of Et_3N and the solution of isothiocyanate (1.5 mmol) in CH_2Cl_2. After stirred at room temperature for 20 hours (monitored by TLC), the reaction mixture was concentrated and purified by silica gel column chromatography (ethyl acetate–petroleum as the eluent) to give the organocatalysts **I-VIII.**

2.2.1 | N-(((*S*)-(6-methoxyquinolin-4-yl) ((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl)-4-methylbenzamide (I):

white solid; 72.6% yield; m.p. 87.5-90.4°C; $[\alpha]_D^{30} = -302.40$ (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (s, 1H), 8.91 (s, 1H), 8.77 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.77 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.38–7.42 (m, 2H), 7.29 (s, 1H), 6.01 (br. s, 1H), 5.70-5.79 (m, 1H), 4.98-5.04 (m, 2H), 4.02 (s, 3H), 3.35-3.41 (m, 2H), 2.85-2.87 (m, 2H), 2.41 (s, 3H), 2.31-2.37 (m, 1H), 1.68-1.72 (m, 3H), 1.43-1.49 (m, 2H), 0.86-1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.45, 166.77, 158.01, 147.68, 144.94, 144.64, 141.45, 131.90, 129.88, 128.98, 127.64, 122.16, 114.73, 102.16, 56.05, 55.89, 41.61, 39.57, 28.04, 27.48, 26.14, 21.76; IR (ATR): ν 3221.52, 2922.56, 2858.24, 1668.30, 1620.67, 1505.10, 1473.64, 1342.65, 1258.06, 1156.43, 1028.32, 829.11, 747.41, 668.15, 609.41 cm^{-1}; HRMS m/z calcd for $C_{29}H_{33}N_4O_2S$ $[M + H]^+$ 501.2319, found 501.2329.

2.2.2 | N-(((*S*)-(6-methoxyquinolin-4-yl) ((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl)-4-nitrobenzamide (II):

yellow solid; 61.2% yield; m.p. 131.7-134.4°C; $[\alpha]_D^{30} = -309.60$ (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 9.03 (s, 1H), 8.77 (d, J = 4.6 Hz, 1H), 8.26-8.42 (m, 2H), 8.08-7.95 (m, 3H), 7.71 (br. s, 1H), 7.40 (d, J = 5.9 Hz, 2H), 5.70-5.79 (m, 1H), 4.96-5.03 (m, 2H), 4.00 (s, 3H), 3.27-3.37 (m, 3H), 2.80-2.87 (m, 2H), 2.31-2.36 (m, 1H), 1.77-1.90 (m, 2H), 1.64-1.71 (m, 3H), 1.41-1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.76, 164.96, 158.03, 150.62, 147.66, 144.88, 141.34, 137.47, 131.95, 128.98, 124.26, 122.09, 114.83, 102.10, 56.04, 55.84, 41.58, 39.55, 28.03, 27.41, 26.09; IR (ATR): ν 2928.98, 2862.47, 1675.43, 1620.46, 1522.71, 1506.15, 1473.73, 1344.19, 1298.87, 1257.99, 1226.89, 1154.74, 1027.83, 849.97, 790.69, 716.08, 701.76, 606.15 cm^{-1}; HRMS m/z calcd for $C_{28}H_{30}N_5O_4S$ $[M + H]^+$532.2013, found 532.2017.

2.2.3 | 4-Methyl-N-(((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl) benzamide (III):

white solid; 84.5% yield; m.p. 103.2-105°C; $[\alpha]_D^{30} = -219.68$ (c = 0.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.84 (d, J = 5.8 Hz, 2H), 8.40 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.73-7.61 (m, 3H), 7.58 (s, 1H), 7.39 (s, 1H), 7.19 (d, J = 5.5 Hz, 2H), 5.89 (s, 1H), 5.70-5.58 (m, 1H), 4.89 (dd, J = 21.5, 13.8 Hz, 2H), 3.43-3.04 (m, 3H), 2.77 (s, 2H), 2.33 (s, 3H), 2.23 (s, 1H),

1.61 (s, 2H), 1.22 (d, J = 49.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.54, 166.70, 150.26, 148.63, 144.59, 141.36, 130.57, 129.85, 129.34, 129.02, 127.67, 126.92, 123.91, 114.75, 55.93, 41.46, 39.52, 29.80, 27.91, 27.48, 25.83, 21.74; IR (ATR): ν 3225.31, 2922.11, 2859.25, 1667.72, 1610.08, 1589.67, 1495.11, 1342.02, 1256.43, 1184.26, 1155.36, 1116.91, 1074.95, 1018.65, 912.29, 833.45, 818.85, 747.79, 694.99, 668.37, 606.16 cm^{-1}; HRMS m/z calcd for $C_{28}H_{31}N_4OS$ $[M + H]^+$471.2213, found 471.2212.

2.2.4 | 4-Nitro-N-(((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl) benzamide (IV):

yellow solid; 79.4% yield; m.p. 108.3-111°C; $[\alpha]_D^{30}$ = −219.60 (c = 0.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ11.40 (s, 1H), 9.08 (s, 1H), 8.91 (d, J = 4.3 Hz, 1H), 8.43 (s, 1H), 8.32 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.46 (s, 1H), 5.68-5.74 (m, 1H), 4.94-5.00 (m, 2H), 2.84-3.36 (m, 3H), 2.84-2.86 (m, 2H), 2.17-2.32 (m, 2H), 1.64-1.84 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.82, 164.91, 150.66, 150.24, 148.64, 141.30, 137.54, 130.66, 129.45, 129.01, 126.99, 124.26, 123.72, 114.86, 55.98, 41.44, 39.56, 29.83, 27.95, 27.43; IR (ATR): ν 3170.69, 3073.63, 2922.62, 2854.28, 1675.86, 1636.25, 1602.97, 1589.62, 1520.36, 1343.00, 1255.87, 1155.35, 1109.35, 1074.64, 1012.78, 851.45, 794.79, 754.76, 718.74, 701.59, 668.30 cm^{-1}; HRMS m/z calcd for $C_{27}H_{28}N_5O_3S$ $[M + H]^+$502.1907, found 502.1914.

2.2.5 | N-(((1*R*)-(6-methoxyquinolin-4-yl) ((1*S*,2*R*,4*S*)-5-vinylquinuclidin-2-yl)methyl) carbamothioyl)-4-methylbenzamide (V):

white solid; 75.3% yield; m.p. 175-176.8°C; $[\alpha]_D^{30}$ = +352.95 (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ11.50 (s, 1H), 8.90 (s, 1H), 8.75 (s, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 8.3 Hz, 3H), 7.37-7.41 (m, 2H), 7.27-7.29 (m, 2H), 5.90-5.98 (m, 1H), 5.12-5.19 (m, 2H), 4.01 (s, 3H), 3.25 (s, 1H), 2.98-3.08 (m, 4H), 2.41 (s, 3H), 2.31-2.35 (m, 1H), 1.83 (s, 1H), 1.51-1.59 (m, 2H), 1.251.34 (m, 2H), 0.96-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.49, 166.79, 157.99, 147.63, 144.87, 144.61, 140.64, 132.25, 132.15, 131.79, 129.87, 129.03, 128.67, 128.55, 127.64, 122.47, 114.88, 101.81, 77.48, 77.16, 76.84, 55.78, 49.44, 47.64, 39.29, 27.47, 26.75, 25.52, 21.75; IR (ATR): ν 3347.97, 3179.08, 3079.36, 3025.97, 2922.57, 2850.87, 1676.90, 1611.77, 1587.86, 1512.27, 1464.04, 1307.55, 1342.95, 1269.10, 1218.43, 1176.85, 1155.75, 1037.35, 921.05, 844.62, 825.93, 747.34, 611.17 cm^{-1}; HRMS m/z calcd for $C_{29}H_{33}N_4O_2S$ $[M + H]^+$501.2319, found 501.2339.

2.2.6 | N-(((1*R*)-(6-methoxyquinolin-4-yl) ((1*S*,2*R*,4*S*)-5-vinylquinuclidin-2-yl)methyl) carbamothioyl)-4-nitrobenzamide (VI):

yellow solid; 64.4% yield; m.p. 72.9-73.5 °C; $[\alpha]_D^{30}$ = +281.00 (c = 0.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ11.30 (s, 1H), 9.05 (s, 1H), 8.76 (d, J = 4.5 Hz, 1H), 8.33 (d, J = 8.8 Hz, 2H), 7.99-8.03 (m, 3H), 7.69 (br. s, 1H), 7.39–7.42 (m, 2H), 5.90-5.97 (m, 1H), 5.15-5.20 (m, 2H), 4.01 (s, 3H), 3.33 (s, 1H), 3.03-3.13 (m, 4H), 2.33-2.38 (m, 1H), 2.20-2.23 (m, 1H), 2.00-2.04 (m, 2H), 1.56-1.71 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.98, 175.79, 164.99, 158.12, 150.63, 147.60, 144.85, 140.38, 137.51, 130.01, 129.02, 128.70, 124.23, 123.97, 122.53, 115.10, 101.76, 55.78, 49.40, 47.59, 39.10, 36.04, 27.38, 27.34, 26.59; IR (ATR): ν 3353.73, 3180.09, 2919.96, 2849.86, 1719.66, 1660.08, 1631.45, 1603.71, 1522.44, 1469.83, 1429.58, 1344.11, 1260.18, 1174.03, 1028.33, 850.14, 826.01, 717.17, 701.62 cm^{-1}; HRMS m/z calcd for $C_{28}H_{30}N_5O_4S$ $[M + H]^+$532.2013, found 532.1998.

2.2.7 | 4-Methyl-N-(((1*R*)-quinolin-4-yl((1*S*,2*R*,4*S*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl) benzamide (VII):

white solid; 73.2% yield; m.p. 61-62.1°C; $[\alpha]_D^{30}$ = +174.00 (c = 0.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ11.52 (s, 1H), 8.83-8.94 (m, 2H), 8.44 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.66 (dd, J = 16.2, 8.2 Hz, 1H), 7.46 (d, J = 4.5 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 5.90-6.00 (m, 2H), 5.09-5.30 (m, 2H), 3.01-3.10 (m, 3H), 2.42 (s, 3H), 2.32 (d, J = 6.9 Hz, 1H), 2.22 (t, J = 7.7 Hz, 1H), 2.01 (s, 2H), 1.45-1.66 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.64, 166.76, 150.18, 148.55, 144.61, 140.34, 132.26, 129.89, 129.42, 129.09, 127.68, 127.52, 126.89, 123.95, 123.78, 115.10, 49.33, 47.55, 39.37, 32.06, 29.83, 27.53, 27.34, 26.63, 21.76; IR (ATR): ν 3357.22, 3180.63, 2919.84, 2850.42, 1660.50, 1632.21, 1610.28, 1589.80, 1504.14, 1468.80, 1424.64, 1338.63, 1257.95, 1168.09, 1117.84, 1018.93, 912.60, 844.78, 748.38, 720.30, 697.26, 600.09 cm^{-1}; HRMS m/z calcd for $C_{28}H_{31}N_4OS$ $[M + H]^+$471.2213, found 471.2234.

2.2.8 | 4-Nitro-N-(((1*R*)-quinolin-4-yl((1*S*,2*R*,4*S*)-5-vinylquinuclidin-2-yl) methyl)carbamothioyl) benzamide (VIII):

yellow solid; 51.2% yield; m.p. 76.5-80.2°C; $[\alpha]_D^{20}$ = +360.73 (c = 0.275,CH_2Cl_2); IR (ATR): ν

3353.98, 3176.08, 3072.35, 2920.14, 2849.91, 1732.70, 1675.34, 1603.31, 1522.19, 1424.77, 1344.87, 1254.34, 1167.98, 1109.24, 1081.01, 1013.12, 914.53, 849.79, 754.95, 718.42, 701.71, 604.40 cm^{-1}; ^1H NMR (600 MHz, CDCl3) δ 11.36 (s, 1H), 9.19 (s, 1H), 8.89 (d, J = 3.9 Hz, 1H), 8.38 (s, 1H), 8.29 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.67-7.61 (m, 1H), 7.43 (d, J = 3.4 Hz, 1H), 5.93 (ddd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.17 (dd, J = 22.6, 13.9 Hz, 2H), 3.20 (s, 1H), 3.11-3.01 (m, 3H), 2.95 (s, 1H), 2.33 (d, J = 6.2 Hz, 1H), 2.08-1.87 (m, 2H), 1.56 (ddd, J = 32.2, 28.3, 21.7 Hz, 4H); 13C NMR (150 MHz, CDCl3) δ 178.75, 164.86, 150.53, 150.06, 148.48, 140.22, 137.47, 130.48, 129.34, 128.89, 126.78, 124.13, 123.60, 114.99, 60.41, 49.30, 47.48, 39.26, 29.33, 27.37, 26.58; HRMS m/z calcd for $C_{27}H_{28}N_5O_3S$ $[M + H]^+$502.1907, found 502.1913.

2.3 | General procedure of asymmetric Michael addition

To a stirred solution of catalyst (**III** or **V**, 0.02 mmol) and nitroolefin (0.15 mmol) in $CHCl_3$ (1.0 ml) was added pyrazolone **1** (0.1 mmol). The reaction mixture was stirred at −30°C (monitored by TLC). After the reaction is completed, the mixture was concentrated and purified by silica gel column chromatography (ethyl acetate-petroleum as the eluent) to give the products **3**.[7,24] The ee values were determined by chiral HPLC analysis.

2.4 | HF calculations

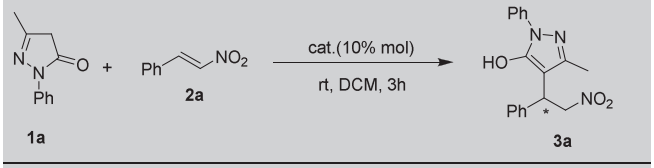
All calculations were performed with Gaussian 03. Molecular geometries were fully optimized with the HF/sto-3g method.

Energy of nitrostyrene **2a**: −504.5446 Hartree.
Energy of **I**: −1859.1948 Hartree.
Energy of **II**: −2021.3227 Hartree.
Energy of complex of **I** + nitrostyrene **2a**: −2363.7672 Hartree.
Energy of complex of **II** + nitrostyrene **2a**: −2525.8926 Hartree.
Hydrogen bond energy of complex of **I** + **2a**: −17.44 kcal/mol.
Hydrogen bond energy of complex of **II** + **2a**: −15.88 kcal/mol.
Energy of **III**: −1746.7766 Hartree.
Energy of **IV**: −1908.9036 Hartree.
Energy of complex of **III** + nitrostyrene **2a**: −2251.3487 Hartree.
Energy of complex of **IV** + nitrostyrene **2a**: −2413.4739 Hartree.
Hydrogen bond energy of complex of **III** + **2a**: −17.25 kcal/mol.
Hydrogen bond energy of complex of **IV** + **2a**: −16.13 kcal/mol.
Energy of **V**: −1859.2058 Hartree.
Energy of **VI**: −2021.3316 Hartree.
Energy of complex of **V** + nitrostyrene **2a**: −2363.7656 Hartree.
Energy of complex of **VI** + nitrostyrene **2a**: −2525.8911 Hartree.
Hydrogen bond energy of complex of **V** + **2a**: −9.54 kcal/mol.
Hydrogen bond energy of complex of **VI** + **2a**: −9.35 kcal/mol.
Energy of **VII**: −1746.7867 Hartree.
Energy of **VIII**: −1908.9072 Hartree.
Energy of complex of **VII** + nitrostyrene **2a**: −2251.3469 Hartree.
Energy of complex of **VIII** + nitrostyrene **2a**: −2413.4716 Hartree.
Hydrogen bond energy of complex of **VII** + **2a**: −9.85 kcal/mol.
Hydrogen bond energy of complex of **VIII** + **2a**: −12.42 kcal/mol.

3 | RESULTS AND DISCUSSION

To study the catalytic activities of **I-VIII**, the Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one (**1a**) with β-nitrostyrene (**2a**) was used as a model reaction. The direct product of this reaction would be a 4-substituted pyrazolinone bearing 2 stereocenters, but prompt aromatization occurs to give the observed aromatized products.[7] The reactions were performed in CH_2Cl_2 with 10 mol% catalysts at the room temperature for 3 hours, and isolated yields and enantioselectivities of **3a** were showed in the Table 1. To our delight, all of catalysts **I-VIII** could promote the reaction smoothly and gave the desired product **3a** with good to and moderate enantioselectivities (Table 1). Importantly, both enantiomers of **3a** can be accessed by using either of the pseudoenantiomeric cinchona alkaloids derivatives. The catalysts **I**, **II**, **III**, and **IV** gave the *S*-enantiomers preferentially, whereas the catalysts **V**, **VI**, **VII**, and **VIII** afforded the *R*-enantiomers predominantly. Moreover, the results showed that electronic effects of substituents in the benzene ring of benzoylthioureas have the subtle influences on their catalytic abilities and electron donating methyl group is favored than withdrawing groups nitro group (except for **VII** and **VIII**, entries 7 and 8, Table 1). 4-Methyl benzoylthioureas **I**, **III**, and **V** could

TABLE 1 Screening of organocatalysts for the enantioselective Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one to β-nitrostyrene[a]



Entry	Cat.	Yield, %[b]	ee, %[c]
1	**I**	92	77(*S*)
2	**II**	78	71(*S*)
3	**III**	95	79(*S*)
4	**IV**	91	73(*S*)
5	**V**	94	79(*R*)
6	**VI**	90	65(*R*)
7	**VII**	91	67(*R*)
8	**VIII**	92	70(*R*)

[a]All reactions were carried out with 3-methyl-1-phenyl-2-pyrazolin-5-one **1a** (0.1 mmol,17.4 mg), β-nitrostyrene **2a** (22 mg, 0.15 mmol) and the catalyst (10 mol%) in 1.0-mL DCM at room temperature for 3 h.

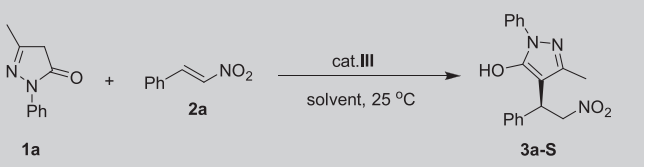
[b]Isolated yield after column chromatography on silica gel.

[c]Determined by chiral HPLC on Chiralpak AS-H column with n-hexane and 2-propanol.

all gave the excellent yields and better ee values (entries 1, 3, and 5, Table 1). In the postulated dual H-bonding enhanced catalytic cycle, the first step is the formation of the complex of nitrostyrene and dual H-donor through hydrogen bonding.[12,14] Then the hydrogen bond energies of complexes the formed with catalysts and nitrostyrene were preliminarily calculated and analyzed by Hartree-Fock method. The results of theoretical calculations demonstrated that the above complexes could be formed through hydrogen bonding between N–H of catalysts and nitro group of nitrostyrene. And the hydrogen bond energies of the complexes are ranged from 9.35 to 17.44 kcal/mol. Moreover, the hydrogen bond energies of the complexes with 4-methyl benzoylthioureas are about 0.19 to 1.56 kcal/mol higher than with the corresponding 4-nitro benzoylthioureas (**I** > **II**, **III** > **IV**, **V** > **VI**). However, an inverse relationship was observed for **VII** and **VIII** both in theoretical calculation and experimental research. The reason need to be further studied. To discuss about the electronic effects of these substituents on the benzene ring, we synthesized quinin-benzoylthioureas with other substituents such as methoxy, CF_3, and H groups. Their catalytical abilities were examined under conditions in Table 1, and hydrogen bond energies were also calculated using Hartree-Fock method. The results (see Supporting Information) indicate that benzoylthioureas with H and electron-donating group (OCH_3, CH_3) have better catalytical abilities (excellent yields and better ee values) and higher hydrogen bond energies. However, there is no completely consistent relationship between hydrogen bond energy and catalytical ability. The above theoretical calculations method could be of interest for predicting the behavior of the catalysts, but the results are too limited to provide a general method.

Based on the above results, the **III** was used to further screen the optimal reaction conditions including solvent, catalyst loading, and temperature (Table 2). Almost each tested solvent gave excellent yields and good enantioselectivities except methanol and DMSO (entries 1-7, Table 2). The best solvent was $CHCl_3$ (94.9% yield and 85% ee, entry 5, Table 2). Then the reaction temperature was investigated, and the results proved that lowering the temperature to −30°C in $CHCl_3$ led to an excellent yield (94.6%) and grateful enantioselectivity

TABLE 2 Screening of the optimum reaction conditions for the enantioselective Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one to β-nitrostyrene[a]



Entry	Solvent	Cat. Loading, mol%	Time, h	Yield, %[b]	ee, %[c]
1	DCM	10	3	95	79
2	MeOH	10	3	83	25
3	THF	10	3	92	69
4	EtOAc	10	3	87	69
5	$CHCl_3$	10	3	95	85
6	Toluene	10	3	90	81
7	DMSO	10	3	62	1
8[d]	$CHCl_3$	10	8	92	91
9[e]	$CHCl_3$	10	3	91	63
10[f]	$CHCl_3$	10	12	95	94
11	$CHCl_3$	5	12	93	91
12	$CHCl_3$	20	12	97	97
13	$CHCl_3$	30	12	93	96

[a]All reactions were carried out at 25°C with 3-methyl-1-phenyl-2-pyrazolin-5-one **1a** (0.1 mmol, 17.4 mg), β-nitrostyrene **2a** (22 mg, 0.15 mmol) and the catalyst **III** in 1.0-mL solvent.

[b]Isolated yield after column chromatography on silica gel.

[c]Determined by chiral HPLC on Chiralpak AS-H column with n-hexane and 2-propanol.

[d]The reaction was carried out at 0°C.

[e]The reaction was carried out at 60°C.

[f]The reactions were carried out at −30°C.

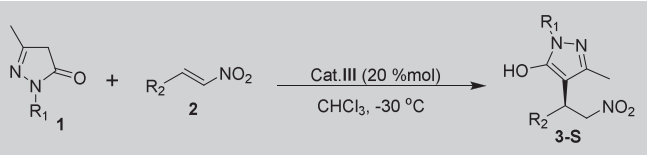
(94% ee) within 12 hours (entry 10, Table 2). Further investigation showed that the catalyst loading had an influence on the enantioselectivity of the product. When increased from 5 to 20 mol%, the ee value of the product improved from 91% to 97% (entries 10-12, Table 2). However, there is a slight decrease in enantioselectivity when using 30 mol% catalyst **III** (entry 13, Table 2). At last, 20 mol% catalyst **III** in $CHCl_3$ at −30°C was identified as the optimized reaction conditions.

Under the optimized experimental conditions, the scope of the Michael addition was further studied using a variety of substituents nitroolefins and pyrazolin-5-ones, and the results were summarized in Table 3. To our delight, the most reactions were occurred smoothly with excellent yields and good to excellent enantioselectivities (77 to >99% ee). The overall performances of **III** were better than our previous benzoylthiourea organocatalyst (In previous work, benzoylthiourea organocatalyst gave the ee value ranged from 52-91%).[21] The **III**-promoted processes were successful with all kinds of nitroalkenes which possessing electron-withdrawing, electron-donating and heterocyclic functionalities (entries 1-14, Table 3). In addition, when 3-Methyl-1-(4-chlorophenyl)-2-pyrazolin-5-one (**1c**) was used as Michael donor the yield and ee values were also satisfied (entry 16, Table 3), whereas 3-Methyl-1-(2-chlorophenyl)-2-pyrazolin-5-one (**1b**) gave the corresponding product with 77% ee (entry 15, Table 3).

To prepare target products with the *R* and *S* enantiomers is very important for asymmetric synthesis. Data from Table 1 have shown that using **V** as the catalyst the model reaction occurred to give the *R*-configuration product with excellent yield and good enantioselctivity.

Then the organocatalyst **V** was examined in the Michael reaction of pyrazolin-5-ones to nitroalkenes, and the results are summarized in Table 4. To our

TABLE 3 Organocatalytic asymmetric Michael reaction of pyrazolin-5-ones to nitroalkenes with catalyst **III**[a]



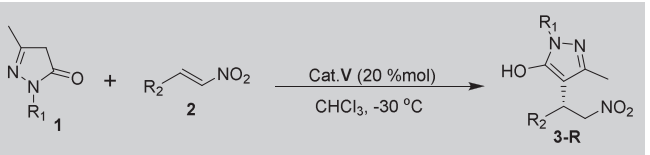
Entry	R_1	R_2	Time, h	Yield, %[b]	ee, %[c]
1	C_6H_5	C_6H_5	12	97	97
2	C_6H_5	4-$CH_3C_6H_4$	12	93	93
3	C_6H_5	2-ClC_6H_4	12	91	>99
4	C_6H_5	4-ClC_6H_4	12	89	95
5	C_6H_5	2,4-$(Cl)_2C_6H_3$	12	91	96
6	C_6H_5	4-FC_6H_4	12	93	95
7	C_6H_5	4-BrC_6H_4	12	90	95
8	C_6H_5	2-$NO_2C_6H_4$	12	89	91
9	C_6H_5	3-$NO_2C_6H_4$	18	87	95
10	C_6H_5	3,4-$(OCH_3)_2C_6H_3$	15	87	91
11	C_6H_5	2,4-$(OCH_3)_2C_6H_3$	15	85	79
12	C_6H_5	4-$CF_3C_6H_4$	12	90	98
13	C_6H_5	2-thienyl	12	88	87
14	C_6H_5	2-furyl	12	88	85
15	2-ClC_6H_4	C_6H_5	12	83	77
16	4-ClC_6H_4	C_6H_5	12	84	93

[a]All reactions were carried out with pyrazolin-5-one **1** (0.1 mmol), nitroalkene **2** (0.15 mmol), and the catalyst **III** (10 mg, 20 mol%) in 1.0-mL CHCl3 at −30°C.

[b]Isolated yield after column chromatography on silica gel.

[c]Determined by chiral HPLC on Chiralpak AS-H, or IC column with n-hexane and 2-propanol.

TABLE 4 Organocatalytic asymmetric Michael reaction of pyrazolin-5-ones to nitroalkenes with catalyst **V**[a]



Entry	R_1	R_2	Time, h	Yield, %[b]	ee, %[c]
1	C_6H_5	C_6H_5	12	95.3	>99
2	C_6H_5	4-$CH_3C_6H_4$	12	96.4	>99
3	C_6H_5	2-ClC_6H_4	12	95.2	97
4	C_6H_5	4-ClC_6H_4	12	93.7	>99
5	C_6H_5	2,4-$(cl)_2C_6H_3$	12	94.5	95
6	C_6H_5	4-FC_6H_4	12	95.6	>99
7	C_6H_5	4-BrC_6H_4	12	94.3	>99
8	C_6H_5	2-$NO_2C_6H_4$	12	94.9	97
9	C_6H_5	3-$NO_2C_6H_4$	18	93.2	95
10	C_6H_5	3,4-$(OCH_3)_2C_6H_3$	15	93.1	93
11	C_6H_5	2,4-$(OCH_3)_2C_6H_3$	15	91.7	95
12	C_6H_5	4-$CF_3C_6H_4$	12	94.6	97
13	C_6H_5	2-thienyl	12	92.8	>99
14	C_6H_5	2-furyl	12	96.2	>99
15	2-ClC_6H_4	C_6H_5	12	92.8	65
16	4-ClC_6H_4	C_6H_5	12	93.5	>99

[a]All reactions were carried out with pyrazolin-5-one **1** (0.1 mmol), nitroalkene 2 (0.15 mmol), and the catalyst **V** (10 mg, 20 mol%) in 1.0-mL CHCl3 at −30°C.

[b]Isolated yield after column chromatography on silica gel.

[c]Determined by chiral HPLC on Chiralpak AS-H, or IC column with n-hexane and 2-propanol.

exciting, the reactions gave satisfied yields and enantioselectivities for most of the substrates. Both of the electron-withdrawing and electron-donating substituents on the benzene ring of nitroalkenes react smoothly with pyrazolone to provide the corresponding product 3-R in excellent yields and enantioselectivities (entries 1-14, Table 4). When other Michael donors such as **1b** and **1c** were used to react with nitroalkene (**2a**), the good results were also observed (entries 15 and 16, Table 4).

4 | CONCLUSION

In conclusion, we have developed highly efficient cinchona alkaloid-derived 4-methylbenzoylthiourea organocatalysts that were successfully used to catalyze the asymmetric Michael addition of pyrazolones to nitroolefins. Not only the high reaction activities and stereoselectivities were obtained, but also both *R*- and *S*-enantiomers were got, respectively. The hydrogen bond energies of the complexes formed with **I-VIII** and β-nitrostyrene were preliminarily calculated and analyzed by Hartree-Fock method. Applications of these organocatalysts in other asymmetric reactions are underway in our laboratory.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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