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Highly enantioselective direct Mannich reaction of seven-membered cyclic imines dibenzo[*b,f*][1,4]oxazepines with acetone via organocatalysis

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ABSTRACT

Various substituted dibenzo[*b,f*][1,4]oxazepines as seven-membered cyclic imines underwent a highly enantioselective direct Mannich reaction with acetone when catalyzed by proline. These reactions gave a range of optically active β -carbonyl seven-membered *N*-heterocycles with excellent enantioselectivity (93%–98% ee). With 2-butanone as a Mannich donor, the single regioselective product was obtained with 96%–97% ee. The absolute configuration of the product was assigned to be *R* by X-ray single crystal analysis of its derivative.

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1. Introduction

Catalytic enantioselective nucleophilic addition to imines provides the most efficient method for the synthesis of *N*-containing compounds with a stereogenic center at the α -position [1]. While a variety of enolized carbonyl compounds can be used as the nucleophile, the enantioselective direct Mannich reaction offers an attractive approach to synthesize optically active β -amino-carbonyl compounds, which are very useful chiral *N*-containing compounds in biologically active natural products, pharmaceuticals, and organic synthesis [2–6]. Since the pioneering work on proline-catalyzed asymmetric Mannich reaction of acyclic aldimines produced in situ from aldehydes and amines by List [7] and Barbas et al. [8] in the 2000s, much progress in the last decade has been made on the organocatalytic asymmetric direct Mannich reaction of acyclic

imine [2–5]. Although cyclic imines are good electrophilic acceptors for the construction of optically active *N*-heterocycles with a β -carbonyl group, only limited six- [9–16] and five-membered [17,18] cyclic imines have been employed as the substrate in catalytic asymmetric direct Mannich reactions. The extension to other novel cyclic imines, such as seven-membered cyclic imines, continues to be a topic of interest because it provides efficient access to the corresponding seven-membered *N*-heterocycles with a stereogenic center at the α -position.

Among the seven-membered cyclic imines, the readily available dibenzo[*b,f*][1,4]oxazepines [19–21] play an important role in many different biologically active compounds [22,23]. Because these structures have an internal C=N bond, they are potential electrophilic acceptors for enantioselective transformations. In 2011, Zhou and coworkers [24] reported

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the Ir-catalyzed asymmetric hydrogenation of ketimines containing the subunits of dibenzo[*b,f*][1,4]oxazepines [24]. Very recently, our group successfully performed the direct Mannich reaction of aldimines dibenzo[*b,f*][1,4]oxazepines and acetophenone derivatives catalyzed by azetidine-2-carboxylic acid [25,26]. As part of our interest in organocatalytic asymmetric addition to cyclic imines [16,27], we report preliminary results on the enantioselective direct Mannich reaction with excellent enantioselectivity of dibenzo[*b,f*][1,4]oxazepines with acetone catalyzed by proline, which afforded 11-substituted-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine derivatives that are biologically important seven-membered *N*-heterocycles [28,29].

2. Experimental

2.1. General methods

All the reactions were carried out in air without special handling unless otherwise noted. Cyclic imines **1** were obtained according to our previous publication [26]. ¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra were recorded in CDCl₃ on a 400 MHz instrument with tetramethylsilane (TMS) as the internal standard. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral column described below. Flash column chromatography was performed on silica gel (200–300 mesh). TLC analysis was performed using glass-backed plates coated with 0.2 mm silica. After elution, the plate was visualized under UV illumination at 254 nm.

2.2. Typical procedure for the catalytic asymmetric Mannich reaction

To the mixture of imine **1** (0.2 mmol) and (*S*)-proline (30 mol%, 0.06 mmol) in DMF (0.4 ml) was added acetone (1.0 mmol) using a micro-syringe. The reaction mixture was stirred at room temperature for some time shown. The direct purification of the reaction mixture by column chromatography on a silica gel (petroleum ether/EtOAc = 40/1–5/1) gave the desired Mannich product. Racemic Mannich products were obtained when the catalyst was racemic proline.

(*R*)-1-(10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2a**): *R*_f = 0.50 (petroleum ether/EtOAc = 5/1); 98% ee, [α]_D²⁰ = +37.4 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.20 (m, 1H), 7.18–7.00 (m, 4H), 6.84 (ddd, *J* = 8.8, 7.7, 1.5 Hz, 1H), 6.68 (td, *J* = 7.9, 1.6 Hz, 1H), 6.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.74 (dd, *J* = 9.8, 3.6 Hz, 1H), 4.44 (s, 1H), 3.56 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.92 (dd, *J* = 18.1, 3.6 Hz, 1H), 2.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.8, 157.0, 143.7, 137.0, 132.3, 129.2, 128.1, 124.6, 124.3, 121.7, 121.2, 119.1, 119.0, 53.9, 48.9, 30.5; HRMS (ESI): *m/z* calculated for C₁₆H₁₆NO₂ [M+H]⁺ 254.1176, found: 254.1172; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): *t*₁ = 10.5 min, *t*₂ = 11.8 min (major, *R*).

(*R*)-1-(8-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2b**): *R*_f = 0.47 (petroleum ether/EtOAc = 5/1); 91% ee, [α]_D²⁰ = +40.7 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.19 (m, 1H), 7.17–7.08 (m, 2H), 7.03 (td, *J*

= 7.4, 1.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.47 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.34 (d, *J* = 1.2 Hz, 1H), 4.72 (dd, *J* = 9.8, 3.5 Hz, 1H), 4.39 (s, 1H), 3.56 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.91 (dd, *J* = 18.1, 3.5 Hz, 1H), 2.16 (s, 3H), 2.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.9, 157.3, 141.8, 136.6, 134.3, 132.5, 129.2, 128.1, 124.3, 121.5, 121.1, 119.8, 119.3, 54.0, 48.9, 30.6, 20.6; HRMS (ESI): *m/z* calculated for C₁₇H₁₈NO₂ [M+H]⁺ 268.1332, found: 268.1336; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): *t*₁ = 11.5 min (major, *R*), *t*₂ = 12.3 min.

(*R*)-1-(8-*tert*-butyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2c**): *R*_f = 0.34 (petroleum ether/EtOAc = 10/1); 97% ee, [α]_D²⁰ = +38.7 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.18 (m, 1H), 7.16–7.08 (m, 2H), 7.06–6.97 (m, 2H), 6.70 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 4.75 (dd, *J* = 9.7, 3.5 Hz, 1H), 4.43 (s, 1H), 3.56 (dd, *J* = 18.1, 9.7 Hz, 1H), 2.93 (dd, *J* = 18.1, 3.5 Hz, 1H), 2.10 (s, 3H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 207.9, 157.3, 147.8, 141.7, 136.2, 132.5, 129.2, 128.1, 124.3, 121.19, 121.16, 116.3, 116.1, 53.9, 49.0, 34.1, 31.4, 30.5; HRMS (ESI): *m/z* calculated for C₂₀H₂₄NO₂ [M+H]⁺ 310.1802, found: 310.1818; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): *t*₁ = 7.0 min (major, *R*), *t*₂ = 7.7 min.

(*R*)-1-(8-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2d**): *R*_f = 0.56 (petroleum ether/EtOAc = 5/1); 98% ee, [α]_D²⁰ = +39.2 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.19 (m, 1H), 7.18–6.93 (m, 4H), 6.59 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.51–6.43 (m, 1H), 4.72 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.56 (s, 1H), 3.59 (dd, *J* = 18.2, 9.8 Hz, 1H), 2.93 (dd, *J* = 18.2, 3.2 Hz, 1H), 2.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.6, 156.9, 142.1, 138.3, 132.2, 129.6, 129.5, 128.1, 124.7, 122.8, 121.1, 118.5, 117.9, 53.7, 49.0, 30.5; HRMS (ESI): *m/z* calculated for C₁₆H₁₅ClNO₂ [M+H]⁺ 288.0786, found: 288.0789; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): *t*₁ = 13.1 min (major, *R*), *t*₂ = 14.5 min.

(*R*)-1-(8-fluoro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2e**): *R*_f = 0.45 (petroleum ether/EtOAc = 5/1); 98% ee, [α]_D²⁰ = +62.6 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.23 (m, 1H), 7.18–7.11 (m, 2H), 7.06 (td, *J* = 7.4, 1.2 Hz, 1H), 7.00 (dd, *J* = 8.8, 5.6 Hz, 1H), 6.31 (ddd, *J* = 8.7, 7.7, 2.9 Hz, 1H), 6.22 (dd, *J* = 10.2, 2.9 Hz, 1H), 4.73 (dd, *J* = 9.8, 3.5 Hz, 1H), 4.56 (s, 1H), 3.61 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.93 (dd, *J* = 18.1, 3.5 Hz, 1H), 2.13 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.7, 159.8 (d, ¹*J*_{C-F} = 240.6 Hz), 157.3, 139.7 (d, ⁴*J*_{C-F} = 2.4 Hz), 138.5 (d, ³*J*_{C-F} = 10.9 Hz), 132.4, 129.5, 128.1, 124.7, 122.6 (d, ³*J*_{C-F} = 10.2 Hz), 121.1, 104.8 (d, ²*J*_{C-F} = 23.3 Hz), 104.6 (d, ²*J*_{C-F} = 26.4 Hz), 53.6, 49.1, 30.5; ¹⁹F NMR (376 MHz, CDCl₃) δ -119.0; HRMS (ESI): *m/z* calculated for C₁₆H₁₅FNO₂ [M+H]⁺ 272.1081, found: 272.1081; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): *t*₁ = 11.5 min, *t*₂ = 12.3 min (major, *R*).

(*R*)-1-(7-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2f**): *R*_f = 0.24 (petroleum ether/EtOAc = 10/1); 96% ee, [α]_D²⁰ = +0.5 (*c* 1.0 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.17–7.09 (m, 2H), 7.03 (td, *J* = 7.4, 1.0 Hz, 1H), 6.91 (d, *J* = 1.1 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 4.72 (dd, *J* = 9.8, 3.5 Hz, 1H),

4.33 (s, 1H), 3.50 (dd, $J = 18.1, 9.8$ Hz, 1H), 2.90 (dd, $J = 18.1, 3.5$ Hz, 1H), 2.22 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.9, 157.0, 144.0, 134.2, 132.3, 129.3, 129.1, 128.2, 125.2, 124.1, 122.0, 121.2, 119.3, 54.2, 48.7, 30.5, 20.2; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{FNO}_2$ $[\text{M}+\text{H}]^+$ 268.1332, found: 268.1325; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 15.4$ min (major, *R*), $t_2 = 16.3$ min.

(*R*)-1-(7-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2g**): $R_f = 0.32$ (petroleum ether/EtOAc = 5/1); 97% ee, $[\alpha]^{20}_{\text{D}} = -13.1$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.22 (m, 1H), 7.18–7.02 (m, 4H), 6.81 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.45 (d, $J = 8.5$ Hz, 1H), 4.72 (dd, $J = 9.9, 3.4$ Hz, 1H), 4.47 (s, 1H), 3.54 (dd, $J = 18.2, 9.9$ Hz, 1H), 2.92 (dd, $J = 18.2, 3.5$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.7, 156.7, 143.8, 135.9, 132.2, 129.4, 128.1, 124.7, 124.6, 123.0, 121.8, 121.2, 119.6, 53.8, 48.7, 30.5; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{15}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$ 288.0786, found: 288.0785; HPLC (Chiralcel IA column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 10.1$ min, $t_2 = 11.9$ min (major, *R*).

(*R*)-1-(7-fluoro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2h**): $R_f = 0.23$ (petroleum ether/EtOAc = 10/1); 97% ee, $[\alpha]^{20}_{\text{D}} = +8.0$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.24 (t, $J = 7.6$ Hz, 1H), 7.18–6.99 (m, 3H), 6.84 (dd, $J = 9.3, 2.7$ Hz, 1H), 6.59 (td, $J = 8.4, 2.7$ Hz, 1H), 6.48 (dd, $J = 8.7, 5.7$ Hz, 1H), 4.73 (dd, $J = 9.9, 3.4$ Hz, 1H), 4.35 (s, 1H), 3.42 (dd, $J = 18.1, 9.9$ Hz, 1H), 2.89 (dd, $J = 18.1, 3.4$ Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.7, 156.37, 156.36 (d, $^1J_{\text{C-F}} = 239.4$ Hz), 144.4 (d, $^3J_{\text{C-F}} = 10.7$ Hz), 133.2 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 132.0, 129.2, 128.2, 124.4, 121.1, 119.7 (d, $^3J_{\text{C-F}} = 8.8$ Hz), 111.2 (d, $^2J_{\text{C-F}} = 22.1$ Hz), 108.8 (d, $^2J_{\text{C-F}} = 24.5$ Hz), 54.1, 48.6, 30.5; ^{19}F NMR (376 MHz, CDCl_3) δ -124.4; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{15}\text{FNO}_2$ $[\text{M}+\text{H}]^+$ 272.1081, found: 272.1088; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 10.8$ min, $t_2 = 12.4$ min (major, *R*).

(*R*)-1-(6-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2i**): $R_f = 0.24$ (petroleum ether/EtOAc = 10/1); 97% ee, $[\alpha]^{20}_{\text{D}} = +28.6$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.28–7.15 (m, 2H), 7.11 (d, $J = 6.7$ Hz, 1H), 7.03 (t, $J = 7.2$ Hz, 1H), 6.73 (t, $J = 7.6$ Hz, 1H), 6.58 (d, $J = 7.2$ Hz, 1H), 6.39 (d, $J = 7.8$ Hz, 1H), 4.75 (dd, $J = 9.8, 3.4$ Hz, 1H), 4.36 (s, 1H), 3.50 (dd, $J = 18.1, 9.8$ Hz, 1H), 2.89 (dd, $J = 18.1, 3.4$ Hz, 1H), 2.42 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.9, 157.0, 143.0, 137.4, 132.6, 130.6, 129.0, 128.2, 124.2, 124.1, 121.5, 121.1, 117.0, 54.0, 49.6, 30.5, 17.2; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 268.1332, found: 268.1341; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 8.6$ min (major, *R*), $t_2 = 10.3$ min.

(*R*)-1-(2-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2j**): $R_f = 0.29$ (petroleum ether/EtOAc = 10/1); 96% ee, $[\alpha]^{20}_{\text{D}} = +39.8$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.10–6.98 (m, 3H), 6.92 (s, 1H), 6.83 (t, $J = 7.4$ Hz, 1H), 6.66 (t, $J = 7.3$ Hz, 1H), 6.51 (d, $J = 7.8$ Hz, 1H), 4.67 (dd, $J = 9.7, 3.4$ Hz, 1H), 4.43 (s, 1H), 3.55 (dd, $J = 18.0, 9.7$ Hz, 1H), 2.92 (dd, $J = 18.0, 3.4$ Hz, 1H), 2.27 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.9, 155.0, 143.9, 137.1, 133.9, 132.0, 129.6, 128.6, 124.6, 121.7, 120.9, 119.1, 119.0, 54.0, 49.0, 30.6,

20.7; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 268.1332, found: 268.1338; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 9.8$ min, $t_2 = 13.6$ min (major, *R*).

(*R*)-1-(2-*tert*-butyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2k**): $R_f = 0.36$ (petroleum ether/EtOAc = 10/1); 96% ee, $[\alpha]^{20}_{\text{D}} = +34.1$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.24 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.13 (d, $J = 2.3$ Hz, 1H), 7.10–7.01 (m, 2H), 6.88–6.74 (m, 1H), 6.71–6.61 (m, 1H), 6.52 (dd, $J = 7.9, 1.1$ Hz, 1H), 4.71 (dd, $J = 9.9, 3.2$ Hz, 1H), 4.47 (s, 1H), 3.61 (dd, $J = 18.1, 9.9$ Hz, 1H), 2.90 (dd, $J = 18.1, 3.3$ Hz, 1H), 2.09 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.0, 154.8, 147.3, 143.9, 137.1, 131.6, 126.0, 125.0, 124.6, 121.7, 120.6, 119.1, 119.0, 54.5, 49.1, 34.4, 31.5, 30.6; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 310.1802, found: 310.1812; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 7.9$ min, $t_2 = 9.0$ min (major, *R*).

(*R*)-1-(2-methoxy-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2l**): $R_f = 0.14$ (petroleum ether/EtOAc = 10/1); 96% ee, $[\alpha]^{20}_{\text{D}} = +18.6$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.15–7.04 (m, 2H), 6.90–6.81 (m, 1H), 6.76 (dd, $J = 8.7, 3.0$ Hz, 1H), 6.72–6.63 (m, 2H), 6.53 (dd, $J = 7.9, 1.2$ Hz, 1H), 4.69 (dd, $J = 9.7, 3.6$ Hz, 1H), 4.45 (s, 1H), 3.76 (s, 3H), 3.61 (dd, $J = 18.0, 9.7$ Hz, 1H), 2.96 (dd, $J = 18.2, 3.3$ Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.8, 156.1, 151.0, 144.0, 137.1, 133.3, 124.6, 121.9, 121.6, 119.0, 118.8, 113.8, 113.4, 55.7, 53.9, 48.9, 30.6; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 284.1281, found: 284.1289; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 13.5$ min, $t_2 = 21.1$ min (major, *R*).

(*R*)-1-(2-chloro-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2m**): $R_f = 0.27$ (petroleum ether/EtOAc = 10/1); 98% ee, $[\alpha]^{20}_{\text{D}} = +38.0$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.20 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.15–7.02 (m, 3H), 6.91–6.82 (m, 1H), 6.71 (dd, $J = 10.9, 4.1$ Hz, 1H), 6.55 (d, $J = 7.9$ Hz, 1H), 4.83–4.58 (m, 1H), 4.44 (s, 1H), 3.52 (dd, $J = 18.2, 9.8$ Hz, 1H), 2.92 (dd, $J = 18.2, 3.5$ Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.3, 155.5, 143.6, 136.7, 133.9, 129.1, 129.0, 128.0, 124.9, 122.7, 121.6, 119.5, 119.2, 53.6, 48.5, 30.5; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{15}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$ 288.0786, found: 288.0792; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 10.5$ min, $t_2 = 20.8$ min (major, *R*).

(*R*)-1-(4-methyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2n**): $R_f = 0.24$ (petroleum ether/EtOAc = 10/1); 98% ee, $[\alpha]^{20}_{\text{D}} = +79.5$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.17–7.09 (m, 2H), 7.03–6.92 (m, 2H), 6.86 (t, $J = 7.1$ Hz, 1H), 6.66 (dd, $J = 10.9, 4.2$ Hz, 1H), 6.54 (dd, $J = 7.9, 0.9$ Hz, 1H), 4.75 (dd, $J = 9.7, 3.5$ Hz, 1H), 4.47 (s, 1H), 3.66 (dd, $J = 18.0, 9.7$ Hz, 1H), 2.97 (dd, $J = 18.0, 3.6$ Hz, 1H), 2.44 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.9, 155.4, 142.9, 137.6, 132.8, 130.8, 130.6, 125.6, 124.7, 124.2, 122.0, 118.7, 118.6, 53.7, 48.9, 30.6, 16.3; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 268.1332, found: 268.1337; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): $t_1 = 8.1$ min, $t_2 = 9.6$ min (major, *R*).

(*R*)-1-(1,3-dimethyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**2o**): R_f = 0.30 (petroleum ether/EtOAc = 10/1); 93% ee, $[\alpha]^{20}_D$ = +22.3 (c 1.0 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.07 (dd, J = 7.9, 1.1 Hz, 1H), 6.90–6.81 (m, 2H), 6.77 (s, 1H), 6.69–6.60 (m, 1H), 6.51 (dd, J = 7.9, 1.2 Hz, 1H), 4.97 (dd, J = 9.3, 3.8 Hz, 1H), 4.48 (s, 1H), 3.74 (dd, J = 18.2, 9.3 Hz, 1H), 2.94 (dd, J = 18.2, 3.8 Hz, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.2, 157.6, 143.2, 138.6, 137.4, 135.1, 128.5, 127.4, 124.8, 121.6, 119.7, 118.4, 118.2, 49.0, 48.6, 30.7, 20.9, 19.6; HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 282.1489, found: 282.1496; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): t_1 = 9.5 min (major, *R*), t_2 = 10.6 min.

(*R*)-1-(10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)butan-2-one (**3a**): R_f = 0.21 (petroleum ether/EtOAc = 10/1); 96% ee, $[\alpha]^{20}_D$ = +36.7 (c 0.95 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.27–7.20 (m, 1H), 7.19–7.00 (m, 4H), 6.84 (t, J = 7.6 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 4.76 (dd, J = 9.8, 3.5 Hz, 1H), 4.46 (s, 1H), 3.52 (dd, J = 17.8, 9.8 Hz, 1H), 2.90 (dd, J = 17.8, 3.5 Hz, 1H), 2.36 (q, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 210.7, 157.0, 143.7, 137.0, 132.4, 129.1, 128.1, 124.6, 124.3, 121.6, 121.1, 119.1, 118.9, 54.1, 47.6, 36.5, 7.6; HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 268.1332, found: 268.1351; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 ml/min, 254 nm): t_1 = 9.6 min, t_2 = 10.8 min (major, *R*).

(*R*)-1-(8-*tert*-butyl-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)butan-2-one (**3c**): R_f = 0.32 (petroleum ether/EtOAc = 10/1); 97% ee, $[\alpha]^{20}_D$ = +27.5 (c 0.99 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.19 (m, 1H), 7.17–7.09 (m, 2H), 7.07–6.97 (m, 2H), 6.70 (dd, J = 8.4, 2.1 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 4.77 (dd, J = 9.7, 3.4 Hz, 1H), 4.44 (s, 1H), 3.52 (dd, J = 17.8, 9.8 Hz, 1H), 2.91 (dd, J = 17.8, 3.6 Hz, 1H), 2.37 (q, J = 7.3 Hz, 2H), 1.22 (s, 9H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 210.8, 157.3, 147.7, 141.7, 136.2, 132.5, 129.1, 128.1, 124.2, 121.1, 116.3, 116.1, 54.1, 47.7, 36.6, 34.1, 31.3, 7.6; HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 324.1958, found: 324.1963; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 0.6 mL/min, 254 nm): t_1 = 14.1 min (major, *R*), t_2 = 15.3 min.

2.3. Procedure for the synthesis of **4** from Mannich product **2a**

(*R*)-1-(10-(4-bromobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-11-yl)propan-2-one (**4**): To a solution of **2a** (26.0 mg, 0.1 mmol) in CH_2Cl_2 (2.0 ml) was added Et_3N (20.2 mg, 0.2 mmol) and 4-bromobenzoyl chloride (32.9 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 12 h, and then water was added. The mixture was extracted with CH_2Cl_2 . The organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent, the crude product was purified by flash chromatography to afford **4** as a white solid: R_f = 0.15 (petroleum ether/EtOAc = 5/1); m.p. = 111–112 °C (from hexane and dichloromethane); 98% ee, $[\alpha]^{20}_D$ = –405.8 (c 0.82 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.11 (m, 9H), 7.10–7.01 (m, 1H), 6.89 (t, J = 6.7 Hz, 1H), 6.76–6.45 (m, 2H), 2.80–2.55 (m, 2H), 2.08 (s, 3H); ^{13}C NMR

(100 MHz, CDCl_3) δ 204.6, 153.5, 152.5, 134.6, 131.1, 130.7, 129.6, 129.2, 128.9, 127.6, 124.4, 124.4, 123.4, 121.5, 121.1, 49.8, 30.0; HRMS (ESI): m/z calculated for $\text{C}_{23}\text{H}_{19}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 436.0543, found: 436.0542; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 60/40, 0.7 ml/min, 254 nm): t_1 = 11.1 min (major, *R*), t_2 = 16.9 min.

A single crystal of compound **4** was grown from its solution in dichloromethane and hexane, which was suitable for X-ray diffraction analysis [30].

3. Results and discussion

The optimization of the Mannich reaction was investigated with the model reaction of seven-membered cyclic imine **1a** with acetone. The results are summarized in Table 1. The reaction was initially conducted in DMSO at room temperature using (*S*)-proline as catalyst. After the full conversion of imine **1a** was observed as monitored by TLC, the desired Mannich product **2a** was isolated in 74% yield with 92% ee (Table 1, entry 1). Encouraged by this good result, the effect of other solvents such as DMF, DMA, MeOH, THF, CH_2Cl_2 , and neat condition (solvent-free) were investigated (Table 1, entries 2–7). The reaction in DMF gave the best result with a quantitative yield

Table 1
Optimization of the Mannich reaction conditions.

Entry	Catalyst	Solvent	t (h)	Yield ^a (%)	ee ^b (%)
1	(<i>S</i>)-Proline	DMSO	2.5	74	92
2	(<i>S</i>)-Proline	DMF	1.5	99	95
3	(<i>S</i>)-Proline	DMA	1	99	94
4	(<i>S</i>)-Proline	MeOH	1.5	26	59
5	(<i>S</i>)-Proline	THF	6	80	91
6	(<i>S</i>)-Proline	CH_2Cl_2	6	73	75
7 ^c	(<i>S</i>)-Proline	Neat	1.5	94	93
8	C-1	DMF	12	65	96
9	C-2	DMF	7	85	96
10	C-3	DMF	1.5	94	83
11	C-4	DMF	12	68	95
12 ^d	(<i>S</i>)-Proline	DMF	1.5	90	98
13 ^e	(<i>S</i>)-Proline	DMF	1.5	99	96
14 ^f	(<i>S</i>)-Proline	DMF	1.5	86	98

Reaction conditions: imine **1a** (0.05 mmol), acetone **2** (0.25 mmol), catalysts (0.15 mmol, 30 mol%), solvent (0.1 ml).

^a Isolated yield based on imine **1a**.

^b Determined by HPLC using a chiral column.

^c 0.1 ml of acetone was used, and no extra solvent was added.

^d 10 mg 3 Å MS was added.

^e 10 mg 4 Å MS was added.

^f 10 mg 5 Å MS was added.

and excellent ee values (Table 1, entry 2). Some chiral cyclic amino acids and their derivatives were also employed as the organocatalyst to test the efficiency of this reaction (Table 1, entries 8–11). Interestingly, in contrast to our former report on the Mannich reaction of acetophenone [26] using four-mem-

Scheme 1. Mannich reaction of different imines **1** with acetone.

bered (*S*)-azetidine-2-carboxylic acid (**C-4**) as catalyst, here the Mannich reaction with acetone afforded the same high enantioselectivity but only moderate yield (Table 1, entry 11 vs 2). Finally, the enantioselectivity was further improved to 98% ee when 3 Å molecular sieve (MS) was used as an additive (Table 1, entry 12). The beneficial effect of the molecular sieve was likely due to the minimization of moisture or reducing the negative effect of the basic nitrogen atom.

Having established the optimal reaction conditions, we then examined various substituted dibenzo[*b,f*][1,4]oxazepines **1** and acetone to explore the generality of this enantioselective direct Mannich reaction. As listed in Scheme 1, a wide range of substituted cyclic imines **1**, such as those with both electron-withdrawing and electron-donating substituents at different positions of the two aryl rings, afforded the desired Mannich products **2a–2o** with excellent enantioselectivity (93%–99% ee) in a short time (within 3 h). For imine **1m** bearing a chloro group at the *para*-position of the oxygen atom, the corresponding Mannich product was obtained only in moderate yield but with the same high ee value. In addition, imine **1o**, which has two methyl groups on the phenyl rings, still served as a good Mannich substrate to yield **2o** in high yield but with a slightly lower enantioselectivity (93% ee) than the other imines.

With the above successful results, we further investigated the Mannich reaction of cyclic imine **1** with 2-butanone, which can form the regioisomers or diastereoisomers (Scheme 2). Under our standard conditions, the Mannich products **3a** and **3c** were isolated as the single regioisomer with excellent enantioselectivity. This indicated a high regioselectivity that favored the product resulting from the less substituted methyl of the 2-butanone.

Next, the Mannich product **2a** can be smoothly converted to its *N*-4-bromobenzoyl amide **4**. The result is illustrated in Scheme 3. Treatment of **2a** (98% ee) with 4-bromobenzoyl chloride led to the isolation of *N*-protected product **4** in 85% yield with the same 98% ee, which was determined by HPLC analysis. Subsequently, the absolute configuration of compound **4** was established by single crystal X-ray analysis, and the stereochemistry of Mannich product **2a** was assigned the *R*-configuration [30]. The absolute configurations of all the other Mannich products were assigned by analogy (Scheme 1). Based on these results, we suggest a transition state for the catalytic asymmetric Mannich reaction. The carbon nucleophile of an active enamine from acetone is much more likely to attack the seven-membered imines **1** from the *re*-face [26], which affords the product as *R* (Scheme 4).

Scheme 2. Mannich reaction of cyclic imines with 2-butanone.

Scheme 3. Synthesis of **4** and its X-ray structure.

4. Conclusions

A highly enantioselective direct Mannich reaction of seven-membered cyclic imines dibenzo[*b,f*][1,4]oxazepines with acetone was catalyzed by proline. This provided optically active 11-substituted-10,11-dihydrodibenzo[*b,f*][1,4]oxazepine derivatives as the β -carbonyl seven-membered *N*-heterocycles with 93%–98% ee. Further studies on the Mannich reactions of dibenzo[*b,f*][1,4]oxazepines with other alkyl acetones will be reported later.

Scheme 4. Transition state.

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Graphical Abstract

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Highly enantioselective direct Mannich reaction of seven-membered cyclic imines dibenzo[*b,f*][1,4]oxazepines with acetone via organocatalysis

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With (*S*)-proline as an organocatalyst, a direct Mannich reaction between dibenzo[*b,f*][1,4]oxazepines and acetone or 2-butanone afforded the optically active β -carbonyl seven-membered *N*-heterocycles with excellent enantioselectivity.

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高对映选择性有机催化的七元环状亚胺二苯并1,4-氧氮杂卓和丙酮的直接Mannich反应

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摘要: 用脯氨酸作为催化剂,研究了各种取代的二苯并1,4-氧氮杂卓衍生物类七元环状亚胺和丙酮的直接Mannich反应,该反应能高对映选择得到一系列旋光活性的含有 β 羰基的七元环状氮杂环化合物(93%–98% ee). 用丁酮作为Mannich给体时,能得到专一的区域选择性和96%–97% ee的产物. 进一步通过X射线单晶衍射分析其中一个产物的衍生物,确定了产物手性中心绝对构型为*R*,其它同类型产物绝对构型随后通过化学类比方法推断确认.

关键词: 丙酮; 不对称催化; 七元环状亚胺; Mannich反应; 有机催化

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