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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.

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]. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded in $CDCl_3$ 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, $[\alpha]^{20}_D$ = +37.4 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{16}NO_2$ $[M+H]^+$ 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, $[\alpha]^{20}_D$ = + 40.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{18}NO_2$ $[M+H]^+$ 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, $[\alpha]^{20}_D$ = +38.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{24}NO_2$ $[M+H]^+$ 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, $[\alpha]^{20}_D$ = +39.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{15}ClNO_2$ $[M+H]^+$ 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, $[\alpha]^{20}_D$ = +62.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 159.8 (d, $^1J_{C\text{-}F}$ = 240.6 Hz), 157.3, 139.7 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 138.5 (d, $^3J_{C\text{-}F}$ = 10.9 Hz), 132.4, 129.5, 128.1, 124.7, 122.6 (d, $^3J_{C\text{-}F}$ = 10.2 Hz), 121.1, 104.8 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 104.6 (d, $^2J_{C\text{-}F}$ = 26.4 Hz), 53.6, 49.1, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –119.0; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}FNO_2$ $[M+H]^+$ 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, $[\alpha]^{20}_D$ = +0.5 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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),