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Research Article

A Novel Prolinamide Organo-Catalyst for the Asymmetric Aldol Reaction: Synthesis of β- Hydroxyketones

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ABSTRACT

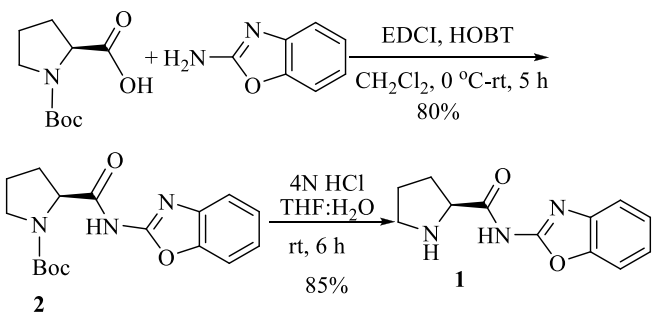
A new L-prolinamide catalyst has been synthesized for the enantioselective aldol reaction of various aldehydes with acetone. This method provides high yields of β-hydroxyketones (up to 90%) with good enantioselectivity (up to 90%) using a low catalyst loading (5 mol%).

Key words: Aldol reaction, benzo[d]oxazol-2-amine, proline, enantioselectivity.

1. Introduction

Chiral β-hydroxy carbonyl compounds, which are the building blocks for antibiotics, pheromones and many biologically active compounds, can be readily converted to 1,3-syn-diols and anti-diols and amino alcohols.,[1] which are subunits of many natural products, the stereoselective aldol reaction is one of the most powerful synthetic methods for the synthesis Chiral β-hydroxy carbonyl compounds. There has been great progress in proline catalysed direct aldol reactions since the first report of L-proline catalysed enantioselective C–C bond formation [2] via an intermolecular aldol reaction by List et al. [3] The asymmetric direct aldol reaction [4] more atom economical does not require a preformed enolate. The major proline derived organocatalysts are mainly 4-substituted L-proline, proline derived N-sulfonyl carboxamide small peptides, different types of prolinamides and other chiral amino acids. [5–7] However, the catalytic systems, which give high enantioselectivity with broad substrate scope at a low catalyst loading are still in demand.

Scheme 1. Facile Synthesis of Prolinamide Catalyst (1)



Many of the reported proline derivatives or other organocatalysts [8] are bifuntional, and contain one or more additional stereogenic centres that are often found to catalyse direct aldol reactions leading to products with high enantioselectivities. Thus, the catalytic potentials of simple prolinamide derivatives remain unfamiliar.

We became interested in extending the application of (S)-prolinamide catalysts to carbon-carbon bond forming reactions. We have reported enantioselective aldol reaction catalyzed by quinoline based prolinamide.[9] Herein, we report a facile enantioselective direct aldol reaction of acetone with various aromatic aldehydes using a novel L-prolinamide-Benzaoxazole catalyst 1 (Scheme 1).

2. Experimental section

2.1. (S)-tert-butyl 2-(benzo[d]oxazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (2):

To a stirred solution of N-*t*-butyloxycarbonyl-*L*-proline (4.1 g, 17.7mmol) in dry dichloromethane (10 mL), was added HOBT (5.24 g, 39.55 mmol). The mixture was allowed to stir for 20 min and then cooled to 0 °C and then EDCI (7.35 g, 39.61 mmol) was added. After 20 min, a solution of benzo[d]oxazol-2-amine (2.6 g, 69 mmol) in dichloromethane (50 mL) was added to the above reaction mixture. The resulting mixture was stirred for 5 h at room temperature. After completion as monitored by TLC, the reaction was quenched with water and extracted with dichloromethane (3x50 mL). The combined organic layers were washed with saturated brine solution (10 mL), followed by drying over Na_2SO_4 and evaporating in *vacuo*. The crude product was purified by column chromatography (EtOAc/hexane, 40:60) to give the pure amide **2** as a pale yellow solid (5.12 g, 80% yield): $[\alpha]^{25}_D$: -88° (*c* 1.0, $CHCl_3$); 3238, 2980,

2877, 1690, 1555, 1500, 1230, 1160, 827, 796, 760, 574, 538 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.54-1.8 (m, 2H), 1.88-1.20 (m, 2H), 3.36-3.56 (m, 2H), 4.42 (m, 1H), 7.46-7.52 (dd, 2H, *J* = 5, 0.9 Hz), 7.6-7.77 (dd, 1H, *J* = 5, 0.7 Hz), 8.98 (br s, 1H) ppm: ^{13}C NMR (50 MHz, $CDCl_3$): 175.1, 165.2, 166.1, 154.2, 151.6, 137.1, 136.2, 126.2, 122.2, 81.6, 70.8, 52.2, 31.2, 29.6, 23.6; ESI-MS: (*m/z*):332.3 $(M+H)^+$.

2.2 (S)-N-(benzo[d]oxazol-2-yl)pyrrolidine-2-carboxamide (1):

At first, Boc-amide **2** (5 g) was dissolved in a mixture of 4 N HCl/THF (1:6) (25 mL) at 0 °C and the stirring was continued for 6 h at room temperature. After completion as monitored by TLC, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3x100 mL). The organic layers were dried over Na_2SO_4. After removal of the solvent, the crude residue was purified through column chromatography on silica gel (ethyl acetate/hexane 1:1 as eluent) to afford *L*-prolinamide **1** as colourless oil (2.96 g, 85%): $[\alpha]^{25}_D$: -120° (*c* 2.0, $CHCl_3$); 3400, 3000, 2900, 1740, 1555, 1500, 1260, 1190, 850, 798, 753, 574, 560 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.60-1.79 (m, 2H), 1.88-1.98 (m, 2H), 2.22 (br. s, 1H), 3.22-3.48 (m, 2H), 4.28-4.34 (m, 1H), 7.48-7.51 (dd, 2H, *J* = 4, 1Hz), 7.60-7.70 (dd, 1H, *J* = 4.5, 0.6Hz), 8.49 (br s, 1H) ppm: ^{13}C NMR (50 MHz, $CDCl_3$): 170.1, 161.2, 160.1, 149.4, 134.2, 133.4, 127, 121.2, 64.3, 49.6, 28.6, 23.2; ESI-MS: (*m/z*):232.1 $(M+H)^+$.

2.3. General Procedure:

The catalyst, L-prolinamide **1** (0.05 mmol) was stirred in 5 mL of acetone/DMF (3:2) for 30 min at -20 °C. To this solution, the corresponding aldehyde (1 mmol) was added and the resulting mixture was stirred for appropriate time. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution and then extracted with ethyl acetate (3x 10 mL). The organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography over silica gel using ethyl acetate/hexane as eluent to afford the pure the aldol product. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD-H.

2.4. (R)-4-hydroxy-4-(2-nitrophenyl)butan-2-one (4):

Enantiomeric excess: 90%, determined by HPLC analysis using chiral pak AD-H 250×4.6mm, 5u, column (isopropanol/hexanes 1:9), UV- 210 nm, flow rate 1.0 ml/min, major isomer t_R 8.28 min, minor isomer t_R 12.39 min. $[\alpha]^{25}_D$: 3416, 2934, 1719, 1512, 1376; 1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.59-2.74 (m, 1H), 2.98-3.12 (m, 1H), 5.58-5.67 (m, 1H), 7.36-7.45 (m, 1H), 7.59-7.68 (m, 1H), 7.85-7.97 (m, 2H) ppm; 13C NMR (50 MHz, $CDCl_3$):δ 30.3, 51.1, 65.5, 125.0, 128.0, 128.2, 133.9, 138.1, 147.2, 207.9 ppm; ESIMS (m/z):210 (M+H)+

2.5. (R)-4-hydroxy-4-(3-nitrophenyl)butan-2-one (5):

Enantiomeric excess: 78%, determined by HPLC analysis using chiral pak AD 250×4.6mm,5u, column (ethanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 21.00 min, minor isomer t_R 31.01 min; $[\alpha]^{25}_D$:+58.2° (c 0.45, $CHCl_3$): IR (KBr): 3414, 2931, 1715, 1519, 1370 cm^{-1};1H NMR (300 MHz, CDCl3): δ 2.21 (s, 3H), 2.82-2.89 (m, 2H), 3.60-3.77 (m, 1H), 5.23 (t, *J* = 6.7 Hz, 1H), 7.46-7.55 (m, 1H), 7.65-7.77 (m, 1H), 8.08-8.22 (m, 2H) ppm;^{13}C NMR (50 MHz, $CDCl_3$):δ 30.2, 51.0, 65.6, 124.2, 128.0, 128.1, 133.6, 138.4, 146.9, 208.6, 207.9 ppm; ESIMS (m/z): 232 $(M+Na)^+$.

2.6. (R)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (6):

Enantiomeric excess: 85%, determined by HPLC analysis using diacel AD-H 250×4.6mm,5u, column (isopropanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 21.03 min, minor isomer t_R 31.31 min;$[\alpha]^{25}_D$:+53.2° (c 0.42, $CHCl_3$):IR (KBr): 3419, 2930, 1716, 1514, 1480, 1370 cm^{-1};^1H NMR (300 MHz, CDCl3): δ 2.23 (s, 3H), 2.84-2.89 (m, 2H), 3.68 (d, *J* = 2.4 Hz, 1H), 5.27-5.29 (m, 1H), 7.62 (d, 2H, *J* = 6.6 Hz), 8.19 (d, 2H, *J* = 6.6 Hz) ppm;^{13C} NMR (50 MHz, CDCl3):δ 30.7, 51.4, 68.8, 123.7, 126.2, 147.1, 149.7, 208.2 ppm;ESIMS (m/z):210 $(M+H)^+$.

2.7 (R)-4-(2,4-dichlorophenyl)-4-hydroxybutan-2-one (7):

Enantiomeric excess: 78%, determined by HPLC analysis using Diacel AD-H, 250×4.6mm,5u, column (ethanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 9.02 min, minor isomer t_R 10.93 min; $[\alpha]^{25}_D$:+39.5° (c 0.44, $CHCl_3$); IR (KBr):3414, 2932, 1718, 1517, 1373, 1167, 689 cm^{-1};^1H NMR (300 MHz, CDCl3):δ 2.20 (s, 3H), 2.49-2.62 (m, 1H), 3.50-3.63 (m, 1H), 5.38 (d, *J* = 9.4 Hz, 1H), 7.23-7.35 (m, 2H), 7.53-7.60 (m, 1H) ppm; 13C NMR (50 MHz, $CDCl_3$): δ 30.4, 50.2, 65.9, 127.3, 127.6, 128.9, 131.3, 133.4, 138.7, 208.9 ppm; ESIMS (m/z): 255 $(M+Na)^+$.

2.8 (R)-4-(4-Chlorophenyl)-4-hydroxybutan-2-one (8):

Enantiomeric excess: 70%, determined by HPLC analysis using chiral pak AD-H, 250×4.6mm,5u, column (isopropanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 8.99 min, minor isomer t_R 9.78 min;$[\alpha]^{25}_D$:+33.2° (c 0.7, $CHCl_3$);IR (KBr):3418, 2934, 1713, 1489, 1369, 1077, 538 cm^{-1};^1H NMR (300 MHz, $CDCl_3$):δ 2.21 (s, 3H), 2.70-2.82 (m, 2H), 3.44 (d, *J* = 3.2 Hz, 1H), 5.11-5.15 (m, 1H), 7.30 (d, 2H, *J* = 5.5 Hz), 7.42 (d, 2H, *J* = 5.5 Hz) ppm;^{13}C NMR (50 MHz, CDCl3): δ 30.6, 51.4, 68.7, 127.0, 128.1, 133.3, 141.1, 207.8 ppm; ESIMS (m/z):221 $(M+Na)^+$.

2.9. (R)-4-Hydroxy-4-(naphthalene-1-yl)butan-2-one (9):

Enantiomeric excess: 65%, determined by HPLC analysis using chiral pak AD-H, 250×4.6mm,5u, column (isopropanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 14.53 min, minor isomer tR 17.69 min; $[\alpha]_{25}^D$: +72.0° (c 0.2, $CHCl_3$): IR (KBr):3421, 3050, 2923, 1687, 1614 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.00-3.20 (m, 1H), 3.46 (d, *J* = 3.3 Hz, 1H), 5.87-5.96 (m, 1H), 7.47-7.54 (m, 3H), 7.71 (d, *J* = 10.3 Hz,1H), 7.81 (d, *J* = 11.4 Hz, 1H), 7.88-8.00 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$):δ 29.7, 50.1, 65.4, 121.4, 121.8, 124.2, 125.0, 126.7, 127.7, 128.7, 129.0, 131.0, 136.7, 207.6 ppm; ESIMS (m/z):237 $(M+Na)^+$.

2.10. (R)-4-Hydroxy-4-(2,4-dinitrophenyl)butan-2-one (10):

Enantiomeric excess: 70%, determined by HPLC analysis using chiral pak AD-H, 250×4.6mm,5u, column (isopropanal/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 22.92 min, minor isomer t_R 27.66 min; $[\alpha]^{25}_D$:-21.8° (*c* 0.4, $CHCl_3$); IR (KBr):3399, 2923, 1697, 1607, 1535, 1344, 1218, 1085 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.62-2.80 (m, 1H), 3.01-3.18 (m, 1H), 4.0 (brs, 1H), 5.71-5.84 (m, 1H), 8.12-8.27 (m, 1H), 8.45-8.57 (m, 1H), 8.77-8.88 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$):δ 30.3, 50.6, 65.3, 119.9, 127.6, 130.2, 145.2, 146.7, 146.9, 207.8 ppm; ESIMS (m/z):277 $(M+Na)^+$.

2.11. 3-((R)-1-Hydroxy-3-oxobutyl)benzonitrile (11):

Enantiomeric excess: 75%, determined by HPLC analysis using chiral pak AD-H, 250×4.6mm,5u, column (isopeopanol/hexanes 1.2:8.8), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 21.89 min, minor isomer t_R 24.89min;$[\alpha]^{25}_D$:+21° (c 0.6, $CHCl_3$):IR (KBr): 3455, 2923, 2230, 1712, 1527, 1460, 1364, 1162cm^{-1}:^{1}H NMR (300 MHz, $CDCl_3$):δ 2.20 (s, 3H), 2.78-2.82 (m, 2H), 5.12-5.18 (m, 1H), 7.41-7.48 (m, 1H), 7.53-7.68 (m, 3H) ppm;^{13}C NMR (50 MHz, CDCl3): δ 30.6, 51.49, 68.55, 112.23, 118.8, 129.1, 130.0, 131.0, 144.3, 208.4 ppm; ESIMS (m/z):212$(M+Na)^+$.

2.12. (R)-Hydroxy-4-phenylbutan-2-one (12):

Enantiomeric excess: 68%, determined by HPLC analysis using chiral pak AD-H 250×4.6 mm, 5u, column (isopropanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 8.9 min, minor isomer t_R 9.1min; $[\alpha]^{25}_D$: +65 (c 0.4, $CHCl_3$): IR (KBr):3413, 2934, 1718, 1452, 890 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.75-2.80 (m, 1H), 2.98-3.11 (m, 1H), 5.04-5.15 (m, 1H), 7.17-7.33 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.6, 147.7, 127.1, 128.9, 127.6, 69.4, 51.9, 30.1 ppm; ESIMS (m/z):164 $(M+H)^+$.

2.13. (4R)-Hydroxy-4(4-methoxyphenyl)-butan-2-one (13):

Enantiomeric excess: 55%, determined by HPLC analysis using chiral pak AD-H 250×4.6 mm, 5u, column (isopropanol/hexanes 1:9), UV, 210 nm, flow rate 1.0 ml/min, major isomer t_R 9.6 min, minor isomer t_R 10.7 min. $[\alpha]^{25}_D$:+42 (c 0.45, $CHCl_3$); IR (KBr): 3422, 2917, 1728, 1455,1108, 1075; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.75-2.86 (m, 2H), 3.82 (s, 3H), 5.15 (dd, *J* =9.0, 3.3 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.28 (d, *J* = 8.9 Hz, 2H) ppm;^{13} C NMR (50 MHz, $CDCl_3$): δ 207.9, 159.5, 136.1, 127.0, 114.5, 69.4, 55.8, 51.9, 30.1 ppm; ESIMS (m/z): 164 (M+H)+.

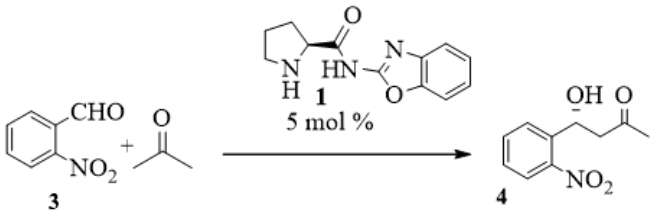
3. Results and Discussion

The catalyst 1 was prepared from benzo[d]oxazol-2-amine and N-Boc-L-proline. According to the synthetic route shown in Scheme 1, deprotection of the Boc group using 4 N HCl in THF/H_2O afforded the prolinamide 1 in good yield.

Table 1. Effect of solvent for the synthesis of 4 using chiral catalyst (1)

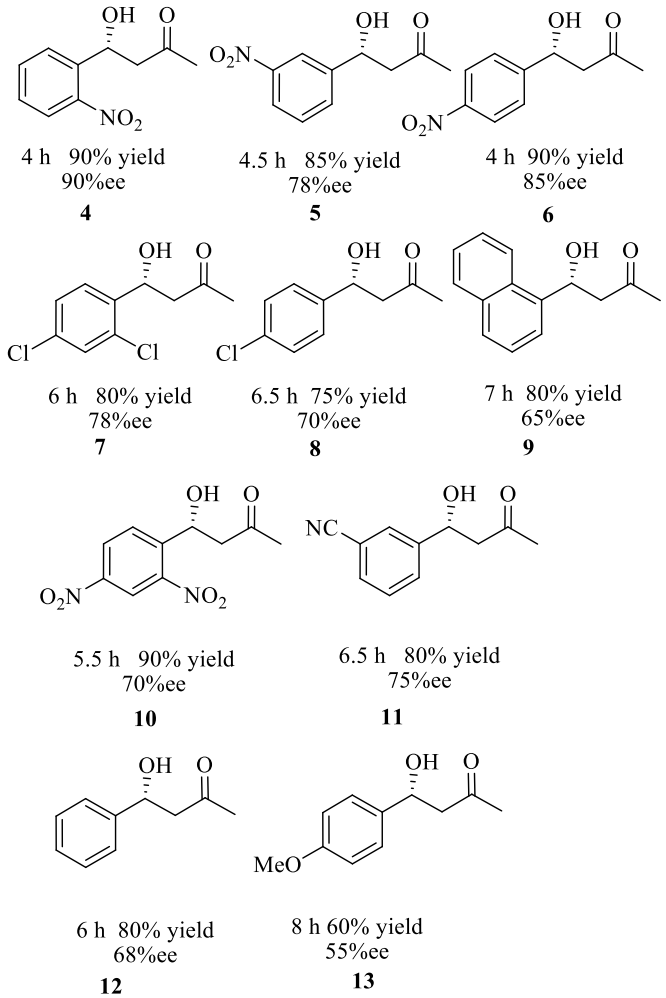
Entry	Solvent	Time (h)	Yield (%) [a]	ee (%) [b]
a	DMF	4	85	90
b	THF	8	60	85
c	MeCN	8.5	75	75
d	Water	24	40	45
e	Acetone	10	70	70
f	Chloroform	8	66	80
g	Toluene	16	45	66
h	Hexane	No reaction even after 48 h	-	-

[a] Yield refers to pure products after chromatography.
[b] ee % was calculated by chiral HPLC



With the novel catalyst in hand, we began to evaluate its catalytic behaviour for the C-C bond formation reaction. The aldol reaction of 2-nitrobenzaldehyde (3) and acetone was selected as a model, and the influence of solvents on the reaction catalyzed by 1 was studied at room temperature with 5 mol % catalyst loading. Encouraging results were obtained and are summarized in Table 1. When the reaction proceeded under neat conditions, the isomer was obtained with moderate enantioselectivity (55%), however, the enantiomeric excess decreased further when water was used as a solvent.

Figure 1. Scope and generality of this process with various aldehydes under optimized conditions



Common organic solvents, such as chloroform, n-hexane, tetrahydrofuran, toluene, and acetonitrile, were studied for catalyst 1 but good yields and high enantioseletivity were observed in DMF. Although a slight difference in enantioselectivity was observed in $CHCl_3$, and THF the reaction required longer reaction times. By further optimizing the reaction conditions, the enantioselectivity was increased to 78% at 0 °C. When decreasing the reaction temperature to -20 °C,

product 4 was obtained with 90% ee. It was found that the enantioselectivity was dependent on the reaction temperature. When the temperature was too low (-40 ^{o}C), the reaction was sluggish (24 h). The best enantio-selectivity was obtained in the direct aldol reaction by 5 mol% L-prolinamide 1 in DMF at -20 ^{o}C. This result is presumably due to the steric bulk of the catalyst, which may play an important role in the stereoselectivity. Moreover, when the loading of the catalyst was decreased from 5 to 2.5 mol%, there was no change in the enantiomeric excess but the reaction took 24 h to afford similar results. Next, we examined the scope and generality of this process with various aldehydes under optimized conditions; the results are presented in Figure 1. The best results were obtained with ortho-nitrobenzaldehyde (Figure 1, entry 4). Similarly other nitro substituted benzaldehydes also produced the corresponding products in good yields with good enantioselectivities (Figure 1, entry 5, 6 and 10). The halo and cyano substituted benzaldehydes were also effective for this conversion (Figure 1, entry 7, 8 and 11).

In the case of naphthaldehyde, benzaldehyde both the yield and enantioselectivity were moderate (Figure 1, entry 9 and 12). In the case of p-methoxybenzaldehyde, the enantioselectivity and yield were very low (Figure 1, entry 13). This may be due to the electron donating ability of the methoxyl group, which may increase the electron density at the carbonyl group. The stereochemistry of the Aldol products was assigned by comparing the spectral data with the data reported in literature.5

In summary, we have synthesized a new prolinamide catalyst for enantioselective direct aldol reaction. The corresponding β-hydroxy ketones were obtained in good yields (up to 90%) with good enantioselectivity (up to 90% ee).

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Competing interests

The authors have declared that no competing interests exist.

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