Investigation of cis- and trans-4-fluoroprolines as enantioselective catalysts in a variety of organic transformations

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SUPPLEMENTARY MATERIAL

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Synthetic procedures

**Cis-4-fluoroproline hydrochloride (2)**

![Chemical structure](image)

A solution of ester 27 (0.101 g, 0.410 mmol) in 2M aq. HCl (2.0 mL) was refluxed overnight. The solution was cooled, diluted with ethanol, decolourised with activated charcoal, and filtered through Celite®. The filtrate was concentrated *in vacuo* to give the title compound as a white solid (59.9 mg, 86%); m.p. 154–156 ºC; $^1$H NMR (300 MHz, D$_2$O) $\delta$ 5.51 (ddd, $J$ = 2.8, 5.6, 51.8 Hz, 1H, FCH), 4.67–4.62 (m, 1H, C(O)CH), 3.90–3.79 (ddd, $J$ = 2.1, 13.9, 19.0 Hz, 1H, NCHH), 3.67–3.49 (ddd, $J$ = 3.4, 13.9, 37.1 Hz, 1H, NCHH), 2.76–2.55 (m, 2H, CF–CH$_2$–CH); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ –175.0 (m, 1F); $^1$H NMR data in accordance with literature values.$^{[1]}$

**Trans-4-fluoroproline hydrochloride (3)**

![Chemical structure](image)

A solution of ester 29 (0.198 g, 0.802 mmol) in 2M HCl (3.5 mL) was refluxed overnight, then cooled, diluted with ethanol, decolourised with activated charcoal, and filtered through Celite®. The filtrate was then concentrated *in vacuo* to give the title compound as a white solid (0.152 g, $>$99%); m.p. 104–106 ºC; $^1$H NMR (300 MHz, MeOD) $\delta$ 5.42 (d, $J$ = 51.6 Hz, 1H, FCH), 4.63 (m, 1H, C(O)CH), 3.84–3.49 (m, 2H, NCH$_2$), 2.79–2.60 (m, 2H, CF–CH$_2$–CH); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ –175.8 (m, 1F); $^1$H NMR data in accordance with literature values.$^{[1]}$
2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (14)

![Reaction Scheme]

Acetic acid (0.10 mL), hydroquinone (45.5 mg) and freshly distilled methyl vinyl ketone (1.3 mL, 16 mmol) were added to a well-stirred suspension of 2-methyl-1,3-cyclohexanedione (1.01 g, 7.99 mmol) and distilled water (12 mL). The mixture was stirred at 75 ºC for 1 h, then cooled to room temperature. NaCl (4.00 g) was added, followed by ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were washed with brine (2 × 10 mL), dried (MgSO₄) and concentrated in vacuo to give crude ketone 14 as a yellow oil (0.950 g, 61%). In some cases the crude product was further purified by flash chromatography (95:1 hexane / ethyl acetate). Data for 14: ¹H NMR (300 MHz, CDCl₃) δ 2.77–2.57 (m, 4H), 2.33 (t, J = 7.2 Hz, 2H), 2.13 (s, 3H), 2.10 (t, J = 7.2Hz, 2H), 1.89–1.87 (m, 2H), 1.23 (s, 3H); ¹H NMR data in accordance with literature values.[⁶]

Benzoylacetonitrile (24)

![Structure 24]

A mixture of ethyl benzoate (10 mL, 70 mmol), freshly prepared sodium methoxide (12.7 g, 234 mmol) and acetonitrile (90 mL) was refluxed for 3 h. After cooling to room temperature, the formed white precipitate was filtered, redissolved in 3 M HCl (200 mL) and the mixture was extracted with DCM (2 × 300 mL). The combined organic layer was then washed with brine (100 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (3:1 n-hexane/ethyl acetate) provided nitrile 28 as a white solid (5.78 g, 57%); ¹H NMR (400 MHz, CDCl₃) δ 7.91–7.90 (m, 2H, ArH), 7.65 (m, 1H, ArH), 7.53–7.49 (m, 2H, ArH), 4.11 (s, 2H, CH₂); ¹H NMR data in accordance with literature values.[⁷]
**N-Boc-trans-4-hydroxyproline (26)**

\[ \text{HO} \ldots \text{NH} \xrightarrow{\text{Boc}_2\text{O}} \text{HO} \ldots \text{N}\text{Boc} \]

92%

Trans-4-hydroxyproline (5.02 g, 38.3 mmol) was dissolved in 2:1 THF/H₂O (50 mL), after which 2M NaOH solution (21 mL) and Boc₂O (10.0 g, 46.0 mmol) were added. The resulting solution was stirred overnight, then concentrated in vacuo. The residue was dissolved in ethyl acetate, and sat. aq. KHSO₄ was added to adjust to pH = 2. The solution was extracted with ethyl acetate (3 × 70 mL), and the combined organic extracts were washed with water (50 mL) and brine (50 mL) then dried (MgSO₄). The solvent was removed in vacuo to give the title compound as a pale yellow syrup (8.11 g, 92%); ¹H NMR (300 MHz, CDCl₃) δ 4.49–4.32 (m, 2H, CHOH and C(O)CH), 3.63–3.45 (m, 2H, NCH₂), 2.39–2.06 (m, 2H, COH–CH₂–CH), 1.43 (s, 9H, C(CH₃)₃), rotamers; ¹H NMR data in accordance with literature values.[²]

**N-Boc-cis-4-fluoroproline methyl ester (27)**

\[ \text{HO} \ldots \text{N}\text{Boc} \xrightarrow{\text{a) CH₃I}, \text{b) DeoxoFluor™}} \text{CO}_₂\text{Me} \]

53%

Iodomethane (2.5 mL, 40 mmol) was added to a mixture of acid 26 (7.56 g, 32.7 mmol), DMF (120 mL) and K₂CO₃ (22.4 g) at 0 °C, and the mixture was stirred overnight. The solution was then quenched with water (120 mL), extracted with ethyl acetate (5 × 50 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried (MgSO₄), and concentrated in vacuo to give N-Boc-trans-4-hydroxyproline methyl ester as a yellow syrup (5.73 g, 71%); ¹H NMR (300 MHz, CDCl₃) δ 4.48–4.36 (m, 2H, CHOH and C(O)CH), 3.73 (s, 3H, OCH₃), 3.66–3.42 (m, 2H, NCH₂), 2.34–2.02 (m, 2H, COH–CH₂–CH), 1.43 (s, 9H, C(CH₃)₃), rotamers; ¹H NMR data in accordance with literature values.[³]
A solution of N-Boc-trans-4-hydroxyproline methyl ester (3.18 g, 13.0 mmol) in dry DCM (200 mL) was cooled to –78 ºC. DeoxoFluor™ (3.7 mL, 20.1 mmol) was added, and the mixture was stirred overnight while gradually warming to room temperature. The solution was then quenched with sat. NaHCO₃, and the organic portion was then washed with water (150 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (3:1 n-hexane/ethyl acetate) provided the title compound as a yellow syrup (2.36 g, 74%); ¹H NMR (300 MHz, CDCl₃) δ 5.18 (d, J = 53.2 Hz, 1H, FCH), 4.47 (dd, J = 9.5, 35.2 Hz, 1H, OC–CH), 3.89–3.48 (m, 5H, OCH₃ and NCH₂), 2.53–2.20 (m, 2H, CF–CH₂–CH), 1.44 (s, 9H, C(CH₃)₃); ¹⁹F NMR (282 MHz, CDCl₃) δ –173.1 (m, 1F), rotamers; ¹H NMR data in accordance with literature values.[⁴]

**N-Boc-cis-4-hydroxyproline (28)**

Pyridine (0.23 mL, 2.8 mmol) was added to a solution of acid 26 (0.328 g, 1.42 mmol) in anhydrous DCM (10 mL) at 0 ºC. Mesyl chloride (0.22 mL, 2.8 mmol) was added, and the mixture was stirred overnight at 0 ºC. The reaction was then quenched with water (10 mL) and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried (MgSO₄) and concentrated in vacuo without heating to give an intermediate mesylate compound as an orange-brown syrup (0.342 g, 78%). This compound was used directly in the subsequent step without purification or characterisation.

Diisopropylethylamine (7.9 mL, 45 mmol) was added to a solution of the intermediate mesylate compound (14.0 g, 45.1 mmol) in dioxane (200 mL). The mixture was heated at 95 ºC for 2 h, then cooled and concentrated in vacuo. The residue was dissolved in DCM (150 mL) and washed
with water (50 mL) and brine (50 mL), then dried (MgSO₄) and concentrated in vacuo to yield an intermediate lactone compound as a dark brown syrup (7.50 g, 78%); ¹H NMR (300 MHz, CDCl₃) δ 5.26 (br, 1H, OCH), 4.41–4.22 (m, 1H, NCH), 3.89–3.34 (m, 2H, NCH₂), 2.66–1.89 (m, 2H, CH–CH₂–CH), 1.41–1.13 (s, 9H, C(CH₃)₃), rotamers; ¹H NMR data in accordance with literature values.[⁵]

LiOH (5.35 g, 223 mmol) was added to a solution of the intermediate lactone compound (15.9 g, 74.4 mmol) in MeOH:THF:water (2:2:3, 400 mL), and the mixture was stirred overnight. The solvent was removed in vacuo, and ethyl acetate (200 mL) was added. The pH was adjusted to 2 by addition of sat. aq. KHSO₄. The solution was then saturated by addition of NaCl, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), then dried (MgSO₄) and concentrated in vacuo to give the title compound as a dark brown syrup (16.3 g, 95%); ¹H NMR (300 MHz, CDCl₃) δ 4.50–4.33 (m, 2H, CHOH and C(O)CH), 3.88–3.50 (m, 2H, NCH₂), 2.74–2.21 (m, 2H, COH–CH₂–CH), 1.45 (s, 9H, C(CH₃)₃), rotamers; ¹H NMR data in accordance with literature values.[²]

*N-Boc-trans-4-fluoroproline methyl ester (29)*

Iodomethane (40 µL, 0.64 mmol) was added to a mixture of acid (96.2 mg, 0.416 mmol), DMF (10 mL) and K₂CO₃ (1.00 g) at 0 ºC. The mixture was stirred overnight at 0 ºC. The mixture was then quenched with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried (MgSO₄) and concentrated in vacuo to give *N*-Boc-*cis*-4-hydroxyproline methyl ester as a yellow syrup (75.7 mg, 74%); ¹H NMR (300 MHz, CDCl₃) δ 4.49–4.31 (m, 2H, CHOH and C(O)CH), 3.73 (s, 3H, OCH₃), 3.68–3.42 (m, 2H, NCH₂), 2.34–2.02 (m, 2H, COH–CH₂–CH), 1.43 (s, 9H, C(CH₃)₃), rotamers; ¹H NMR data in accordance with literature values.[³]
A solution of N-Boc-cis-4-hydroxyproline methyl ester (0.737 g, 3.00 mmol) in dry DCM (60 mL) was cooled to –78 °C. DeoxoFluor™ (0.83 mL, 4.5 mmol) was added, and the mixture was stirred overnight while gradually warming to room temperature. The solution was then quenched with sat. NaHCO₃, and the layers were separated. The organic phase was washed with water (20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (4:1 n-hexane/ethyl acetate) provided the title compound as a pale yellow syrup (0.252 g, 34%); ¹H NMR (300 MHz, CDCl₃) δ 5.18 (d, J = 53.2 Hz, 1H, FCH), 4.46 (dd, J = 9.4, 34.8 Hz, 1H, C(O)CH), 3.88–3.47 (m, 5H, OCH₃ and NCH₂), 2.52–2.19 (m, 2H, CF–CH₂–CH), 1.43 (s, 9H, C(CH₃)₃); ¹⁹F NMR (282 MHz, CDCl₃) δ –173.0 (m, 1F), rotamers; ¹H NMR data in accordance with literature values.⁴

Determining the optical purity of ketone 21: formation of diastereoisomeric acetals (30)

A mixture of ketone 21 (7.8 mg, 0.055 mmol), (2R,3R)-2,3-butanediol (10 µl, 0.11 mmol) and p-toluenesulfonic acid (5 mol%) in dry benzene (3.0 mL) was refluxed for 1 h, then cooled to room temperature, extracted with ethyl acetate (20 mL) and washed with sat. aq. NaHCO₃ (3 × 15 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to provide the crude acetal as a yellow oil (11.6 mg). The diastereoisomeric ratio was determined by ¹³C{¹H} NMR analysis (100 MHz, CDCl₃), observing signals at δ 43.0 / 42.6, 38.4 / 38.1, 37.0 / 36.7 and 28.8 / 28.4.
HPLC Traces

β-Hydroxyketone 11 (obtained using L-proline 1 as catalyst)

![HPLC trace of β-Hydroxyketone 11 obtained using L-proline as catalyst]

β-Hydroxyketone 11 (obtained using DL-proline as catalyst)

![HPLC trace of β-Hydroxyketone 11 obtained using DL-proline as catalyst]
β-Hydroxyketone 11 (obtained using cis-4-fluoroproline 2 as catalyst)

![Graph for cis-4-fluoroproline]

β-Hydroxyketone 11 (obtained using trans-4-fluoroproline 3 as catalyst)

![Graph for trans-4-fluoroproline]
Robinson product 15 (obtained using L-proline 1 as catalyst)

Robinson product 15 (obtained using DL-proline as catalyst)
Robinson product 15 (obtained using cis-4-fluoroproline 2 as catalyst)

![Graph showing the major enantiomer of Robinson product 15 obtained using cis-4-fluoroproline as catalyst.]

Robinson product 15 (obtained using trans-4-fluoroproline 3 as catalyst)

![Graph showing the major enantiomer of Robinson product 15 obtained using trans-4-fluoroproline as catalyst.]

S-11
Mannich product 18 (obtained using L-proline 1 as catalyst)

Mannich product 18 (obtained using DL-proline as catalyst)
Mannich product 18 (obtained using *cis*-4-fluoroproline 2 as catalyst)

Mannich product 18 (obtained using *trans*-4-fluoroproline 3 as catalyst)
Pyran 25 (obtained using L-proline 1 as catalyst)

Pyran 25 (obtained using DL-proline as catalyst)
Pyran 25 (obtained using cis-4-fluoroproline 2 as catalyst)

![Graph with peaks and molecular structure]

Pyran 25 (obtained using trans-4-fluoroproline 3 as catalyst)

![Graph with peaks and molecular structure]
NMR Spectra

$^1$H NMR (300 MHz, D$_2$O) of acid 2

![NMR Spectra](image-url)
$^{19}$F NMR (282 MHz, D$_2$O) of acid 2

\[ \text{Structure of acid 2} \]
$^{1}$H NMR (300 MHz, MeOD) of acid 3
$^{19}$F NMR (282 MHz, MeOD) of acid 3
$^1$H NMR (400 MHz, CDCl$_3$) of β-hydroxyketone 11
^1H NMR (300 MHz, CDCl\textsubscript{3}) of Robinson triketone intermediate 14
$^1$H NMR (400 MHz, CDCl$_3$) of Robinson product 14
$^1$H NMR (400 MHz, CDCl$_3$) of Michael product 21
$^{13}$C $\{^1$H$\}$ NMR (101 MHz, CDCl$_3$) of acetals 30 (obtained using L-proline 1 as catalyst)
$^{13}$C {$^{1}$H} NMR (76 MHz, CDCl$_3$) of acetals 30 (obtained using DL-proline as catalyst)

![NMR Spectrum]

NO$_2$ (major) + NO$_2$ (minor)
$^{13}$C $^1$H NMR (101 MHz, CDCl$_3$) of acetals 30 (obtained using cis-4-fluoroproline 2 as catalyst)
$^{13}$C $^1$H NMR (101 MHz, CDCl$_3$) of acetals 30 (obtained using trans-4-fluoroproline 3 as catalyst)
$^1$H NMR (400 MHz, DMSO) of pyran 25
References


