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# DE NOVO ASYMMETRIC APPROACHES TO 2-AMINO-*N*-(BENZYLOXYCARBONYL)-1-(2'-FURYL)ETHANOL AND 2-AMINO-*N*-(*tert*-BUTOXYCARBONYL)-1-(2'-FURYL)ETHANOL[1]

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**Abstract** – Several methods were investigated for the de novo asymmetric synthesis of 2-amino-*N*-(benzyloxycarbonyl)-1-(2'-furyl)ethanol and 2-amino-*N*-(*tert*-butoxycarbonyl)-1-(2'-furyl)ethanol. A five step procedure was developed for the practical preparation of optically pure 2-amino-*N*-(benzyloxycarbonyl)-1-(2'-furyl)ethanol and a shorter 2-step procedure was developed for 2-amino-*N*-(*tert*-butoxycarbonyl)-1-(2'-furyl)ethanol. Both routes used a Noyori reduction to install the asymmetry.

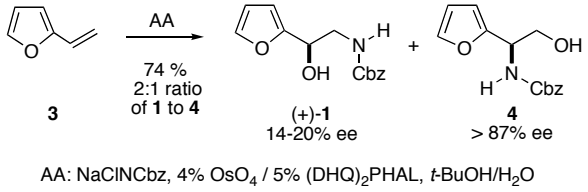
## INTRODUCTION

Traditionally, 6-amino-6-deoxysugars are obtained from an azide displacement of a protected *C*-6-halosugar followed by reduction to the free amine.[2,3] Recently, our group has had success using asymmetric catalysis for the synthesis of D- and L-sugars and iminosugars from achiral starting materials.[4,5] Central to this "de novo approach" to sugars was the recognition that the Achmatowicz reaction of optically pure furan alcohols could be used to install the chirality of the hexose.[6] For example, four of hexose stereoisomers of the 6-deoxyamino sugars **2** were prepared from Cbz-protected aminoalcohol **1** in 4-6 steps (Scheme 1).[7] Similarly, two iminosugars were prepared from the regioisomeric Cbz-protected furfurylamine **4** using an aza-Achmatowicz route.[8]


Scheme 1. Achmatowicz approach to 6-deoxyamino-sugars

While both furan-aminoalcohols **1** and **4** could prepared as a mixture by the Sharpless aminohydroxylation (AA)[9] of vinylfuran, the aminoalcohol product **1** was for formed in near racemic form. Thus we desired a shorter more practical de novo route to **1**. Herein we report the full account of our investigation of several methods for the de novo synthesis of 2-amino-*N*-(benzyloxycarbonyl)-1-(2'-furyl)ethanol **1**, which culminated in the discovery of a two step de novo approach to 2-amino-*N*-(*tert*-butoxycarbonyl)-1-(2'-furyl)ethanol **12** (*vide infra*).

## RESULTS AND DISCUSSION

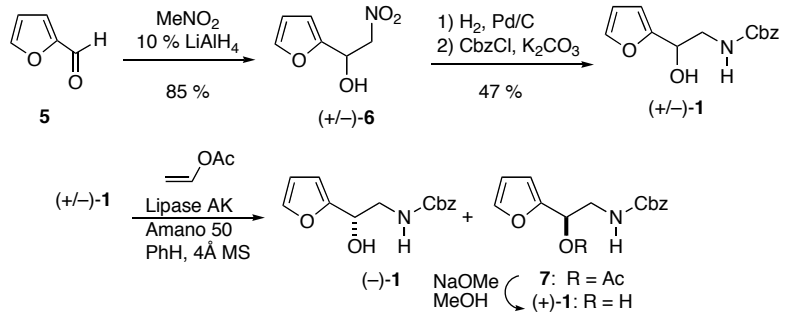



Scheme 2. Sharpless aminohydroxylation of vinylfuran

Previously we have found that *N*-Cbz protected aminoalcohol **1** was produced (42% yield) as the major regioisomer (2:1 ratio) from the asymmetric aminohydroxylation (AA) of vinylfuran **3**, however in low enantioexcess.[10] Using the $(DHQ)_2PHAL$, ligand the minor isomer (+)-**4** was produced in greater than 87% enantiomeric excess,[11] while the major isomer (+)-**1** was formed with 14% enantiopurity (Scheme 3). Similarly, the pseudo-enantiomeric ligand $(DHQD)_2PHAL$ provided the enantiomer (–)-**1** in a slightly higher enantiomeric excess (20%) and (–)-**4** in a similar enantiomeric excess (> 87%). Although the use of $(DHQ)_2AQN$ as a ligand in the AA has been reported to achieve a reversal of regioselectivety,[12] its use in the AA of vinylfuran produced similar results to $(DHQ)_2PHAL$ (1:2 ratio of regioisomers favoring the furfuryl alcohol; furfuryl amine, 74% ee; furfuryl alcohol, 14% ee).[13,14]

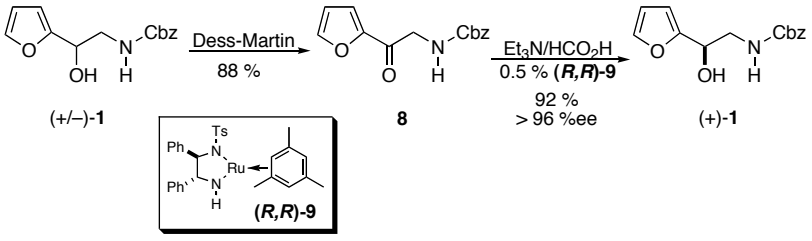
While the aminohydroxylation provided enough material to investigate the Achmatowicz reaction sequence, we still desired a more practical and enantioselective approach to **1**. Racemic aminoalcohol **1** was readily prepared from furfural via a Henry reaction[15]/hydrogenation/Cbz-protection sequence (**5** to (+/–)-**1**, Scheme 3). This procedure routinely provided multigram quantities of racemic **1** in a 40%

overall yield and with the use of only one chromatographic purification. While we initially investigated the use of an asymmetric Henry reaction[16] to provide **1**, the reduction of the nitro-group gave significant amounts of partially reduced by-products. Accordingly, a more reliable higher yielding method was stilled desired. With access to scalemic and racemic materials we investigated resolving the materials.




Scheme 3. Racemic synthesis and resolution of Cbz-protected aminoalcohol **1**

To improve the enantiopurity of the scalemic or racemic samples of **1**, we investigated the use of a lipase enzymatic resolution procedure (Scheme 3). Fortunately, the initial lipase that we screened (Lipase AK Amano 20) gave us excellent results. In practice, shaking a benzene solution of scalemic (–)-**1** (20% ee), vinyl acetate (3 equiv) and the AK-lipase (5% by weight) with 4 Å molecular sieves for 2 days (~ 56% conversion) gave a 39% yield of optically pure (–)-**1** and 42% yield of acetate **7** (78% ee). Running the enzyme reaction to low conversion (e.g., 48% conversion; 4 h, 10 wt% enzymes) gave a 47% yield of acetate **7** in excellent enantiopurity ($[\alpha]_D$ +71.5, > 99% ee), which was hydrolyzed to (+)-**1** with NaOMe in MeOH. Similar results were found for the resolution of racemic **1** (6 days, 56% conversion to achieve material of equal optical purity).

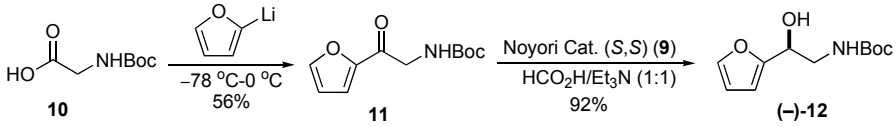



Scheme 4. Asymmetric synthesis of Cbz-protected aminoalcohol **1** by Noyori reduction

Progress to a more practical approach really began with the investigation of the Noyori reduction of ketone **8**. Exposing racemic **1** to Dess-Martin reagent (1.1 equiv in $CH_2Cl_2$) gave an 88% yield of ketone **8**. While we had only modest success with the oxazaborolidine-catalyzed asymmetric borane reduction[17] of ketone **8** (68% yield and 78% ee with 1 equiv of catalyst at rt),[18] we found a Noyori

reduction of **8** furnished excellent results.[19] In practice, treating a neat admixture of $Et_3N/HCO_2H$ (5:2) and ketone **8** to the Noyori reagent system (0.5 mol% of **9** in a neat 5:2 ratio of $Et_3N/HCO_2H$)[20] gave (+)-**1** in excellent yield and enantioexcess (92% yield, > 96% ee).

Switching the nitrogen-protecting group from Cbz to Boc lead to the discovery of a truly practical 2 step approach (52% overall yield, Scheme 5). Thus, treatment of *N*-Boc glycine **10** with 2-lithiofuran gave acylfuran **11** in 56% yields. As with **8**, the Noyori asymmetric hydrogenation of **11** provided furyl alcohol **12** in 92% yields and ideal enantioexcess (>95% ee, by Mosher ester). Because of the acid sensitivity of the *N*-Boc group the ratio of $Et_3N$ to $HCO_2H$ was adjusted to 1:1.[21] Unfortunately the less hindered Cbz protecting group in *N*-Cbz glycine did not survive the basic reaction conditions and failed to give good yields of **8**.




Scheme 5. Alternative asymmetric approach to Boc-protected aminoalcohol **12**

## EXPERIMENTAL

**General Methods and Materials.** $^1H$ and $^{13}C$ NMR spectra were recorded on 200 MHz, 270 MHz, 300 MHz and 500 MHz spectrometers. Chemical shifts are reported relative to internal tetramethylsilane ($\delta$ 0.00) or $CDCl_3$ ($\delta$ 7.26) for $^1H$ NMR and $CDCl_3$ ($\delta$ 77.0) for $^{13}C$ NMR. Infrared (IR) spectra were obtained on FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (60 Å, $F_{254}$) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. $R_f$ values are obtained by elution in the stated solvent ratios (v/v). Ether ($Et_2O$), THF, methylene chloride ($CH_2Cl_2$) and triethylamine ($Et_3N$) were dried by passing through activated alumina columns with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Melting points are uncorrected. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven-dried glassware and standard syringe/septa techniques.

**2-Vinylfuran (3).**

1-(2′-Furyl)-2-trimethylsilylethan-1-ol (10.0 g, 54.2 mmol) and $Et_2O$ (20 mL) were added to a 100 mL

flask followed by addition of aqueous HCl (1M, 20 mL) with vigorous stirring for 1 h, at which time the starting material had completely disappeared as judged by TLC analysis. The phases were separated and the aqueous layer was extracted with $Et_2O$ (2 × 8 mL). The combined organic layers were shaken vigorously with sat. aqueous $NaHCO_3$ (10 mL). Separation of phases with careful swirling produced a 1.5 M solution of vinylfuran **3**.

**(1*R*)-(1-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (4)** and **(1*R*)-(2-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (1).**

A 1 L flask was charged with benzyl carbamate (6.99 g, 46.2 mmol) and *t*-BuOH (160 mL). To this stirred solution was added a freshly prepared aqueous solution of NaOH (1.776 mg, 44.4 mmol in 160 mL water), followed by *tert*-butyl hypochlorite (4.929 g, 45.4 mmol). After 5 min a solution of $(DHQ)_2PHAL$ (1.87 g, 2.4 mmol, 6 mol %) in *t*-BuOH was added; the reaction became homogeneous at this point. Vinylfuran **3** (54.2 mmol, dissolved in 30 mL of $Et_2O$, from the above procedure) was then added, followed by $OsO_4$ (508 mg, 2.0 mmol, 5 mol %). The light green solution was stirred at 25 °C and became yellow after 1 h, indicating completion. The reaction was quenched by the addition of a sat. aqueous $Na_2SO_3$ solution (100 mL) and stirred for 15 min. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with water (50 mL), brine (100 mL), dried over anhyd $Na_2SO_4$, and concentrated to afford the crude mixture of regioisomers (10.80 g crude mass; **1** / **4** = 66 : 34 by $^1$H NMR) and some benzyl carbamate. Flash chromatography ($SiO_2$, 5-40% EtOAc / hexane gradient elution) provided regioisomer **4** (598 mg, 14 %, 86% ee) as a waxy solid (mp 84-86 ºC). Material of higher % ee has been obtained from smaller scale reactions (3 mmol scale, 94 % ee, $[\alpha]^{25}_D$ +32.1 º (*c* 3.82 $CH_2Cl_2$)). For **4**: $R_f$ 0.15 (EtOAc / hexane = 3 : 7), $[\alpha]^{23}_D$ +29.2 º (*c* 1.89, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 6H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1 H), 5.57 (d, *J* = 8.4 Hz, 1 H, NH), 5.11 (s, 2 H), 4.94 (m, 1 H), 3.91 (dd, *J* = 11.2, 5.1 Hz, 1 H), 3.85 (dd, *J* = 11.2, 4.5 Hz, 1 H), 2.46 (br s, 1 H, OH); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.2, 152.0, 136.1, 128.5, 128.2, 128.1, 110.4, 107.1, 67.7, 64.0, 51.1; IR (thin film) 3331, 3033, 2957, 1707, 1540, 1455, 1251, 1143, 1070, 739, 696 cm$^{-1}$; HRMS (CI, $NH_3$) for $C_{14}H_{16}NO_4$ requires $(M+H)^+$ *m/z* 262.1079; found *m/z* 261.1065. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.34; H, 5.79. Found: C, 64.12; H 5.70.

For **(1*R*)-(2-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (1):** a white crystalline solid (1.20 g, 28%, 14% ee by Mosher ester analysis), mp 49.5-50.0 °C; $R_f$ 0.24 (EtOAc / hexane = 3 : 7), $[\alpha]^{23}_D$ +2.9$^{22}$ (*c* 2.85, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 6H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H),

6.28 (d, *J* = 3.3 Hz, 1 H), 5.60 (dd, *J* = 5.1, 5.1 Hz, 1 H), 5.09 (s, 2 H), 4.79 (m, 1 H), 3.98 (br s, 1 H, *O*H), 3.55 (ddd, *J* = 12.0, 7.2, 4.8 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.0, 154.0, 142.2, 137.3, 128.4, 128.1, 128.0, 110.2, 109.2, 67.0, 66.9, 45.4; IR (thin film) 3384, 3032, 2941, 1700, 1526, 1451, 1255, 1147, 735 cm$^{-1}$; HRMS (CI, $NH_3$) accurate mass calcd for $(C_{14}H_{16}NO_4+H)^+$ requires *m/z* 262.1079; found *m/z* 262.1078. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.34; H, 5.79. Found: C, 64.52; H 5.83.

**1-(Furan-2-yl)-2-nitroethanol (6)**.

To an oven-dried 500 mL flask was added $LiAlH_4$ (380 mg, 10 mmol, 10 mol %) and dry THF (200 mL) under a nitrogen atmosphere. The mixture was stirred for 30 min at 0 °C for 30 min, at with time nitromethane (30.5 g, 27.1 mL, 500 mmol) was added via syringe. The reaction was stirred for another 30 min at 0 ºC, followed by addition of furfural (9.60 g, 8.28 mL, 100 mmol) via syringe. The reaction was monitored by removal of aliquots followed by analysis of the $^1$H NMR spectrum (aldehyde proton disappearance at δ 9.68). After 30 h, less than 1% furfural remained by crude $^1$H NMR analysis. The crude reaction mixture was vacuum filtered through filter paper and washed with sat. aqueous $NaHCO_3$. The mixture was again vacuum filtered through filter paper and the phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($Na_2SO_4$), and then concentrated under reduced pressure to give a dark yellow oil (15.15 g). The crude reaction mixture was purified by flash chromatography (optional) to yield furan **6** as a colorless oil (13.38 g, 85.1 mmol, 85% yield): $R_f$ 0.21 (hexanes / EtOAc, 17 : 3); $^1$H NMR (200 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 1.6, 1.0 Hz, 1H), 6.42-6.37 (m, 2H), 5.49 (ddd, *J* = 8.8, 5.2, 3.6 Hz, 1H), 4.79 (dd, *J* = 13.6, 8.6 Hz, 1H), 4.69 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.76 (d, *J* = 5.0 Hz, 1H, *OH*); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 150.7, 143.1, 110.6, 108.1, 78.3, 64.7; IR (thin film): 3458, 2969, 2930, 1552, 1379 cm$^{-1}$; MS (EI) mass calcd for $(C_6H_7NO_4)^+$ requires *m/z* 157, found *m/z* 156 ($M^+$-1), 139 ($M^+$-$H_2O$).

**(2-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (1)**.

To a 250 mL flask was added nitroalcohol **6** (7.33 g, 46.7 mmol), MeOH (25 mL) and 10% palladium on carbon (730 mg, 10 mass %) under a nitrogen atmosphere. The headspace of the reaction flask was flushed with hydrogen gas and a hydrogen balloon was attached to the reaction via a needle through a septum. The reaction was stirred for 24 h, at which time the starting material had been consumed as judged by TLC analysis. The reaction mixture was filtered through celite and concentrated under reduced pressure to yield the crude aminoalcohol (5.61 g, 44.1 mmol, 95% yield) as a yellow oil. The oil was dissolved in THF (22 mL). Water (22 mL) and $K_2CO_3$ (18.3 g, 132.4 mmol) were added to the reaction pot, which was cooled to 0 °C. Benzyl chloroformate (8.95 mL, 53.0 mmol) was added to the

reaction dropwise via syringe and the reaction was stirred for 24 h. The reaction was quenched with sat. aqueous $NaHCO_3$ (20 mL) and stirred for 15 min. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to yield a brown oil (12.8 g). Column chromatography yielded the pure protected amine **6** (5.72 g, 21.3 mmol, 47% yield).

**(*R*)-Acetic acid 2-benzyloxycarbonylamino-1-furan-2-ylethyl ester (7).**

To an oven-dried 50 mL screw-cap vial was added racemic alcohol **1** (2.72 g, 10.41 mmol), benzene (32 mL), activated 4 Å molecular sieve (600 mg), vinyl acetate (2.88 mL, 31.2 mmol), and Lipase AK (136 mg, 5 mass %). The sealed vial was slowly rotated with a lab quake for 6 d, during which time the reaction was monitored by $^1$H NMR analysis. After 6 d, the reaction had proceeded to 56% completion. The mixture was filtered though a pad of diatomaceous earth. The pad was rinsed with EtOAc and the filtrate was concentrated. Column chromatography (silica gel, 4 cm × 5 in; gradient elution, hexanes / EtOAc = 1 : 9 to 3 : 7) provided the pure acetate 35 (1.77 g, 5.84 mmol, 56 %) as a white solid (mp 68-69.5 °C; $[\alpha]_D$ +43.3 ° (*c* 1.14, $CH_2Cl_2$); $R_f$ 0.60 (EtOAc / hexane = 3 : 7)) and the pure alcohol ***S*-1** (1.03 g, 3.96 mmol, 38% yield) as a clear solid wax (mp 49-50.5 ºC $R_f$ 0.24 (EtOAc / hexane = 3 : 7); $[\alpha]_D$ –16.7 ° (*c* 1.06, $CH_2Cl_2$). Similar results were found for the resolution of racemic **1** (6 days, 56% conversion to achieve material of equal optical purity, $[\alpha]_D$ –16.5 °).

For the acetate **7**: $^1$H NMR: (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 6H), 6.38 (d, *J* = 3.0 Hz, 1H), 6.34 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.93 (dd, *J* = 7.0, 5.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 5.03 (br s, 1H, *N*-H), 3.78-3.67 (m, 2H), 2.05 (s, 3H); $^{13}$C NMR: (125 MHz, $CDCl_3$) δ 170.0, 156.2, 150.2, 142.9, 136.3, 128.5, 128.2, 128.1, 110.4, 109.4, 67.3, 66.9, 42.7, 20.9; IR (thin film): IR (thin film) 3345, 3050, 2944, 1726, 1527, 1240 cm$^{-1}$; HRMS (CI, $NH_3$) accurate mass calcd for $(C_{16}H_{17}NO_5 + NH_4)^+$ requires *m/z* 321.1450, found *m/z* 321.1441. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 63.36; H, 5.65. Found: C, 63.56; H 5.88.

**(*R*)-(2-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (1).**

A flask was charged with acetate **7** (2.64 g, 8.70 mmol), MeOH (17 mL). A methanolic solution of NaOMe (0.5 M in MeOH, 3.5 mL, 1.74 mmol, 20 mol %) was added dropwise with stirring at 0 °C. The solution turned from light yellow to deep yellow after complete addition of NaOMe. After 10 min, the reaction was deemed compete as judged by TLC analysis. The reaction was diluted with $Et_2O$ (20 mL) and sat. aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous layer was extracted with $Et_2O$ (2 × 20 mL) and EtOAc (2 × 20 mL). The organic layers were combined and dried

over $Na_2SO_4$, followed by concentration under reduced pressure. Silica gel flash chromatography yielded alcohol **5** clear solid (1.95 g, 7.46 mmol, 86 % yield).

**(2-Furan-2-yl-2-oxoethyl)carbamic acid benzyl ester (8)**:

To a 10 mL flask was added alcohol ***rac*-1** (85 mg, 0.32 mmol), $CH_2Cl_2$ (0.6 mL), and Dess-Martin periodinate (204 mg, 0.48 mmol). The reaction was allowed to stir for 3 h, at which time the starting material had been consumed as judged by TLC analysis. The reaction mixture was diluted with $Et_2O$ (5 mL) and was filtered through a pad of diatomaceous earth. The filtrate was washed with sat. aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was then dried over $Na_2SO_4$ and concentrated to a yellow oil. Column chromatography yielded pure ketone **8** (72.6 mg, 0.28 mmol, 88% yield) as a colorless oil: $R_f$ 0.45 (hexanes / EtOAc, 7 : 3); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.39-7.27 (m, 6H), 6.58 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.79 (br s, 1H, *N*-H), 5.22 (s, 2H), 4.57 (d, *J* = 5.1, 2H); $^{13}$C NMR (75 MHz, $CD_3OD$) δ 183.5, [156.9 (major rotamer), 156.2 (minor rotamer)], 150.6, 147.0, 136.1, 128.5, 128.1, 128.0, 118.0, 112.5, 66.8, 47.1; IR (thin film) 3358, 3063, 3033, 2954, 1717, 1599 cm$^{-1}$; HRMS (CI, $NH_3$) accurate mass calcd for $(C_{14}H_{13}NO_4 + H)^+$ requires *m/z* 260.0923, found *m/z* 260.0932.

**(1*R*)-(2-Furan-2-yl-2-hydroxyethyl)carbamic acid benzyl ester (1):**

To a 10 mL flask was added ketone **8** (154 mg, 0.59 mmol), $CH_2Cl_2$ (1.1 mL), $Et_3N$ (164 μL, 1.18 mmol), formic acid (116 μL, 2.95 mmol) the Noyori asymmetric transfer hydrogenation catalyst[19b] (*S*)-Ru($\eta^6$-mesitylene)-(*R,R*)-TsDPEN (17.6 mg, 0.03 mmol, 5 mol %). The resulting orange solution was heated to 50 °C for 1 h, at which time the reaction was complete as judged by TLC analysis. The reaction was diluted with water (5 mL) and was extracted with EtOAc (4 × 10 mL). The organic layers were combined, washed with sat. aqueous $NaHCO_3$, dried over $Na_2SO_4$, and were concentrated under reduced pressure to give the crude alcohol (155 mg). Column chromatography (silica gel, hexanes / EtOAc, 7 : 3) yielded pure **(*R*)-1** (142.5 mg, 0.545 mmol, 92% yield) as a colorless oil with spectral properties identical to those described above for **1**. Optical rotation was of the same sign and of greater magnitude: $[\alpha]^{23}_D$ +16.7 ° (*c* 1.04, $CH_2Cl_2$). Examination of Mosher ester $^1$H and $^{19}$F spectra confirmed high optical purity (> 96% ee).

**(2-Furan-2-yl-2-oxoethyl)carbamic acid *tert*-butyl ester (11):**

*N*-Boc-glycine **10** (3.5 g, 20 mmol) was dissolved in 100 mL of THF. The solution was cooled to −30 °C and *n*-BuLi (8 mL, 2.5 M, 20 mmol) was added dropwise to the solution. The resulting white suspension was cooled to −78 °C and then 2-lithiofuran (0.5 M, 120 mL, 60 mmol) was added slowly. The red

solution formed was stirred 30 min at −78 °C followed by warming and stirred at 0 ºC for an additional 4h. The reaction mixture was poured into cold aqueous $NaH_2PO_4$ (10%, 200 mL) and extracted with $Et_2O$ (2 x 100 ml). The organic layers were combined, washed with cold aqueous NaOH (1 N, 30 ml) and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. Flash chromatography (30% EtOAc/hexane) on silica gel yielded 2.53 g (11.2 mmol, 56%) of ketone **11** as a light yellow solid: mp 122-124 ºC; $R_f$ (50% EtOAc/hexanes) = 0.58; IR (thin film, $cm^{-1}$) 3338, 3119, 2975, 1714, 1666, 1530, 1279, 1253, 909; $^1$H NMR (270 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.7 Hz, 1H), 7.26 (d, *J* = 3.0 Hz, 1H), 6.55 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.39 (br/s, 1H), 4.49 (d, *J* = 5.0 Hz, 2H), 1.44 (s, 6H); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 183.9, 155.7, 150.8, 146.9, 117.7, 112.4, 77.5, 46.9, 28.3; ESI HRMS Calcd for $[C_{11}H_{15}O_4 + Na]^+$: 248.0893, Found: 248.0888.

**(2*S*)-(2-Furan-2-yl-2-hydroxyethyl)carbamic acid *tert*-butyl ester (12):**[23]

To a 10 mL flask was added ketone **12** (0.27 g, 1.2 mmol), formic acid-triethylamine (1:1, 3 mL), $CH_2Cl_2$ (1 mL), and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η$^6$-Mesitylene)-(*S*,*S*)-TsDPEN • HCl (**9**) (3.5 mg, 0.5%mol). The resulting solution was stirred at rt for 24 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with sat. aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (30% EtOAc/hexane) on silica gel yielded 0.25 g (1.1 mmol, 92%) of alcohol **12** as a light yellow oil: $R_f$ (30% EtOAc/hexanes) = 0.62; $[\alpha]^{25}_D$ −14 º (*c* 1.02, MeOH); IR (thin film, $cm^{-1}$) 3356, 2980, 2940, 1695, 1520, 1367, 1252, 1172, 739; $^1$H NMR (270 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.7 Hz, 1H), 6.33 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.02 (s, br, 1H), 4.80 (ddd, *J* = 8.2, 4.2, 4.2 Hz, 1H), 3.62-3.37 (m, 2H), 3.31 (d, *J* = 4.2 Hz, 1H), 1.43 (s, 9H); $^{13}$C NMR (68 MHz, $CDCl_3$) δ 156.8, 154.3, 142.2, 110.2, 106.7, 79.9, 67.6, 45.2, 28.3.

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