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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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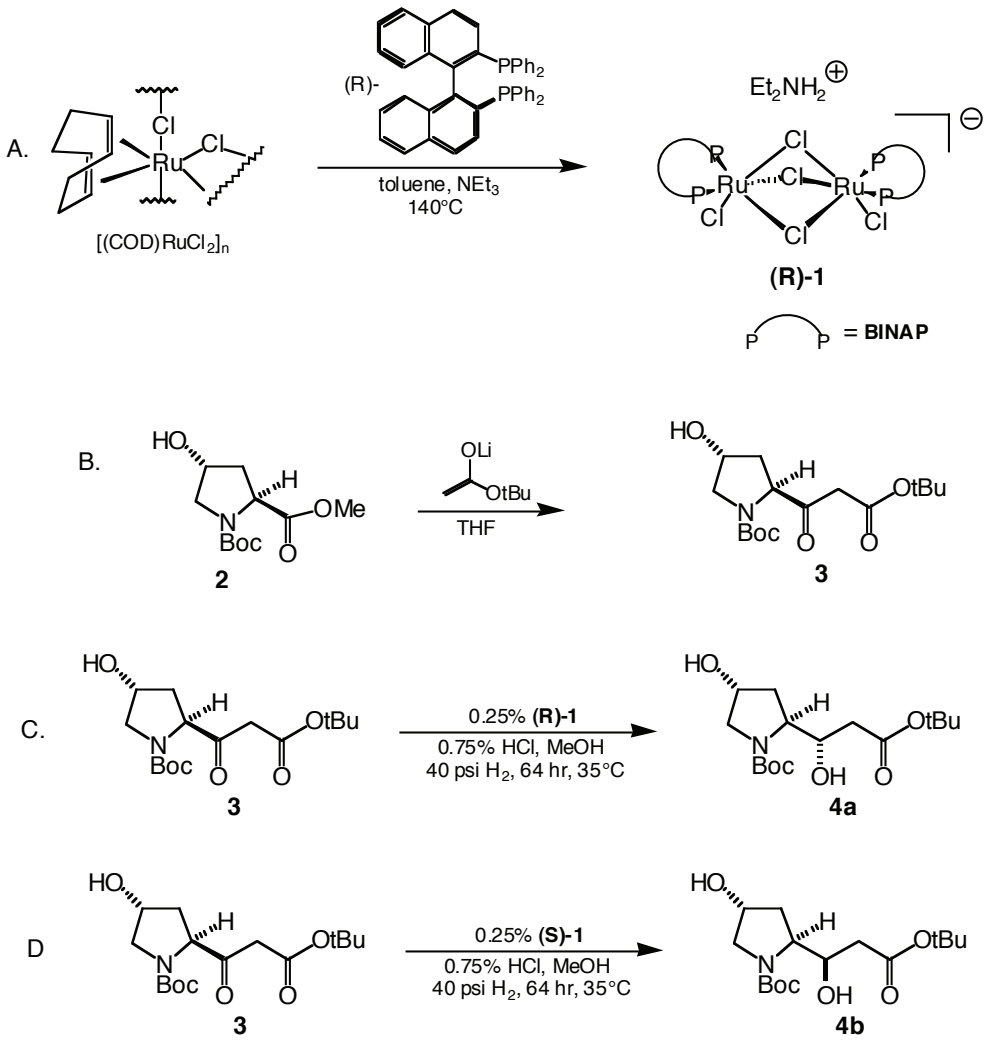
SYNTHESIS AND RU(II)-BINAP REDUCTION OF A KETOESTER DERIVED FROM HYDROXYPROLINE: 2(*S*)-(β-*tert*-BUTOXYCARBONYL-α-(*S*) and α-(*R*)-HYDROXYETHYL)-4(*R*)-HYDROXYPYRROLIDINE-1-CARBOXYLIC ACID, *tert*-BUTYL ESTER

(2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-β,4-dihydroxy-, 1,1-dimethylethyl ester, [2*S*-[2α(*S**),4β]]-)



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Checked by Amos B. Smith, III and Meinrad Brenner.

1. Procedure

A. Preparation of catalyst. Two 100-mL, round-bottomed flasks are connected to a double-ended filter which consists of two chambers, each equipped with a side arm, separated by a glass frit (Note 1). Vacuum grease is used to ensure an air-tight seal and rubber bands are used to secure the flasks to the filter assembly. A magnetic stirbar, (cyclooctadienyl)ruthenium dichloride polymer (0.426 g, 1.5 mmol), and (*R*)-BINAP (1.00 g, 1.60 mmol) (Note 2) are placed in one flask, and the entire apparatus is evacuated and filled with nitrogen. Toluene (34 mL) and triethylamine (3.4 mL) (Note 2), which have been deoxygenated by nitrogen sparging for several min, are added via the lower side arm. The vessel is sealed and the mixture heated to 140 °C producing a deep brick red colored solution (Note 3). After 4 h, the apparatus is allowed to cool to room temperature and the reaction mixture is vigorously stirred while the catalyst precipitates. The apparatus is vented to nitrogen and inverted to filter the product using vacuum on the lower side arm and nitrogen on the upper side arm (Note 4). If the frit cakes with product, slowing down filtration, momentarily reversing the flow of nitrogen will lift the cake away from the frit. The precipitate is washed with 34 mL of deoxygenated toluene and the flask containing the filtrate is replaced with an empty one. The entire apparatus is placed under vacuum and the product is dried overnight to give 0.850 g (67%) of a dark red solid (Notes 5, 6).

B. (2S,4R)-2-tert-Butoxycarbonylacetyl-4-hydroxypyrrolidine-1-carboxylic acid, tert-butyl ester. A 12-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, thermocouple, and nitrogen inlet is charged with 3.3 L (3.82 mol) of 1.15M lithium hexamethyldisilylamide (LHS) solution in THF (Note 7). The solution is cooled to –40 °C, and 514 mL (3.82 mol) of *tert*-butyl acetate is added via the addition funnel over 15 min. A solution of *N*-Boc hydroxyproline methyl ester **2** (187 g, 0.763 mol) in 940 mL of THF (Note 8) is cooled to 0°C and then added slowly via the addition funnel over 20 min while the temperature of the reaction mixture is maintained below –30 °C. The resulting solution is stirred until the reaction is complete (30 min)(Note 9) and then poured over 20 min into an ice cold mixture of 3.8 L of 1M citric acid and 1.7 L of heptanes (Note 10). After stirring for an additional 30 min, the layers are separated (Note 11). The organic layer is concentrated by

distillation under reduced pressure to a volume of 1.1 L (Note 12). Heptanes (3.6 L) are added and the mixture is concentrated by distillation under reduced pressure at 30 °C to a volume of 1.1 L (Note 13). The resulting solution is diluted with 800 mL of heptanes and cooled at 0 °C overnight. The resulting precipitate is filtered, washed with two 800-mL portions of heptanes, and dried overnight in a vacuum oven to provide 227 g (90%) of β-ketoester **3** as white crystals (Note 14).

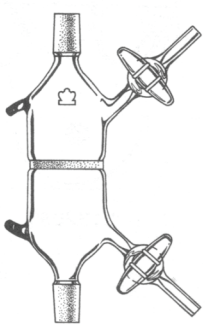
C. 2(S)-(β-tert-Butoxycarbonyl-α-(S)-hydroxyethyl)-4-(R)-hydroxy-pyrrolidine-1-carboxylic acid, tert-butyl ester. A 50-mL Parr shaker bottle capped with a rubber septum was charged with β-ketoester **3** (10.0 g, 30 mmol) and 15 mL of methanol and the solution was deoxygenated by sparging with nitrogen for 15 min. (*R*)-BINAP catalyst **(*R*)-1** prepared as described above (0.064 g, 0.035 mmol) was added followed by 8.7N HCl in methanol (26 μL, 0.23 mmol). The vessel was transferred to a standard Parr shaker apparatus and flushed by evacuating and refilling with nitrogen and then hydrogen several times (Note 15). The apparatus was heated at 35 °C with shaking under 40 psi of hydrogen (Note 16). After 20 min, the reaction mixture became a homogeneous clear yellow solution. After 11 hr, the reaction mixture is transferred to a 250-mL, round-bottomed flask and concentrated to dryness. The residue is suspended in 50 mL of toluene and concentrated to dryness to ensure complete removal of methanol. The product is slurried in 25 mL of toluene/hexane/isopropyl acetate solution (90:5:5) and stirred overnight at room temperature. The precipitate is filtered, washed with 10 mL of toluene, and dried overnight in a vacuum oven (35 °C, <0.5 mmHg) to provide 8.5 g (85%) of (*S*)-hydroxy ester **4a** (Notes 17, 18).

D. 2(S)-(β-tert-Butoxycarbonyl-α-(R)-hydroxyethyl)-4-(R)-hydroxy-pyrrolidine- 1-carboxylic acid, tert-butyl ester. The identical procedure was followed, in this case using the (*S*)-BINAP catalyst **(*S*)-1**. Hydrogenation is conducted for 64 h, and the reaction mixture is then transferred to a 250-mL, round-bottomed flask and concentrated to dryness. The residue is dissolved in 17 mL of methanol and cooled to 15°C. After the slow addition of 7 mL of DI water, the solution is aged for 15 min gradually forming a thin slurry. More DI water (75 mL) is added over 1 hr and the mixture is allowed to stand for an additional 1 hr at 15 °C. The resulting crystals (Note 19) are filtered at 15 °C, washed with 10 mL of 1:4-

MeOH:water, and then dried overnight in a vacuum oven (35 °C, 686 mm) to yield 7.0 g (70%) 0f (*R*)-hydroxy ester **4b** (Note 20).

2. Notes

1. A double-ended filler was purchased from Kontes (catalog #215500-6044) and is shown below.



2. The checkers purchased $[(COD)RuCl_2]_n$ from Fluka (purum quality), BINAP from Aldrich (97 %), and toluene (HPLC grade) and triethylamine (reagent grade) from Fisher Scientific; the latter was distilled from CaH_2 under Ar prior to use. The submitters dried toluene and triethylamine over 4 Å molecular sieves. Karl-Fischer titration indicated <200 μg/mL water.

3. A dark green color of the solution indicates decomposition of the reaction mixture by oxygen.

4. ^{31}P NMR showed that the filtrate contained none of the desired product.

5. The checkers obtained 0.849-0.875 g of catalyst, but ^1H-NMR analysis revealed that the product was of low purity. Reactions run on a 0.75 mmol scale afforded the catalyst in 47-51% yield and in higher purity. Since the reaction is run in a sealed apparatus, the pressure built up in the apparatus (and therefore the boiling point and reaction temperature) may depend on the reaction scale and how far the flask is immersed into the oil bath.

6. ^1H-NMR (CD_2Cl_2, 500 MHz) δ: 1.47 (t, J = 7.4, 6 H), 3.20-3.30 (m, 4 H), 6.52-6.60 (m, 12 H), 6.65 (d, J = 8.6, 2 H), 6.69 (t, J = 7.4, 2 H),

6.74-6.81 (m, 4 H), 6.86 (t, J = 7.4, 2 H); 6.96 (t, J = 7.7, 2 H), 7.18-7.34 (m, 14 H), 7.38 (t, J = 7.2, 2 H), 7.47-7.61 (m, 12 H), 7.63-7.68 (m, 6 H), 7.84 (t, J = 8.3, 2 H), 8.08 (t, J = 8.4, 4 H), 8.57 (s br., 2 H); ^{31}P NMR (CD_2Cl_2, 101 MHz) δ: 52.3 (d, J = 38), 56.5 (d, J = 38).

7. The submitters obtained LHS in THF from Callery Chemical Co. and determined its concentration to be 1.15M by titration according to the method of Ireland (Ireland, R.; Meissner, R. *J. Org. Chem.* **1991**, *56*, 4566-4568). The checkers purchased LHS as a 1M solution in THF from Aldrich Chemical Co.

8. The submitters obtained *N*-Boc-4-hydroxyproline methyl ester from Synthetech, Inc. [Albany, OR, (503) 967-6575] or Bachem California [Torrance, CA, (310) 530-1571] and dried THF over 4Å molecular sieves for two days prior to use (Karl-Fischer titration gave 145 μg/mL water). The checkers purchased N-Boc hydroxyproline methyl ester (97%) and *tert*-butyl acetate (99+%) from Aldrich Chemical Co. and obtained THF (HPLC grade) from Fisher Scientific.

9. The progress of the reaction was followed by HPLC (Zorbax RX-C8 column, 1.5 mL/min, 50:50 CH_3CN:0.01M H_3PO_4 in water, room temperature, detection at 200 nm; retention times: methyl ester **2** 2.343 min, β-ketoester **3** 3.987 min. After 30 min, less than 0.5 area% methyl ester was found to be remaining.

10. There is an exotherm to 10 °C during the quench.

11. GC assay of the organic layer showed no $HN(TMS)_2$ remaining after 15 min of stirring (GC conditions: Restek RTX-1 column (30 m x 0.53 mm, 1 m film thickness), 2.53 mL/min, initial temperature 50 °C, final temperature 300 °C, rate 20 deg/min, injection temperature 200 °C, detector temperature 350 °C, injection volume 1 μL, inject sample neat; retention times: *tert*-butyl alcohol 1.4 min, THF 1.7 min, heptane 2.1 min, $HN(TMS)_2$ 2.6 min, ethylbenzene (present in commercial LHS) 3.1 min, *tert*-butyl acetate 4.0 min). Volume percents were determined based on standard solution counts.

12. The checkers found the product to contain small amounts of citrates. Drying ($MgSO_4$) or washing (H_2O) the organic phase prior to concentration prevents this contamination.

13. The distillation is carried out at ca. 60 mm and at a temperature below 40°C due to the instability of the β-ketoester in the crude solution. It is important to remove all THF prior to crystallization.

14. In smaller scale runs, the checkers obtained the product in 88-93% yield. The product exhibited the following properties: mp 98-99 °C, $[\alpha]_D^{23^\circ}$: –73.2 (c = 0.95, MeOH); ^{13}C NMR (CD_3OD, 500 MHz, rotamers) δ: 28.4, 28.6, 28.7, 38.3, 39.1, 56.0, 56.3, 65.3, 65.6, 70.0, 70.8, 81.7, 82.2, 83.0, 155.9, 156.7, 168.1, 168.3, 204.7, 204.9. IR (film) cm^{-1}: 3439 (br. s), 2979 (s), 2934 (m), 1707 (s), 1395 (s), 1368 (s), 1326 (m), 1258 (m), 1162 (s), 1077 (m), 983 (m), 963 (m), 853 (m), 772 (m). Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.24. Found: C, 58.71; H, 8.52; N, 4.16.

15. Thorough removal of oxygen is imperative to prevent destruction of the catalyst.

16. The progress of the reaction is followed by HPLC (Zorbax RX-C8 column, 1.5 mL/min, gradient elution of 20:80 to 70:30 CH_3CN:0.01 M H_3PO_4 in water over 10 min, held for 20 min, room temperature, detection at 200 nm, retention times: β-keto *t*-butyl ester **2** 8.31 min, hydroxy *tert*-butyl ester **3** 7.10 min, hydroxy methyl ester 4.45 min, β-keto methyl ester 5.47 min).

17. The checkers obtained the product in 73-90% yield. The product exhibited the following properties: mp 99-100 °C; $[\alpha]_D^{23^\circ}$: –50.5 (c = 0.93, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.46 (s, 9 H), 1.47 (s, 9 H), 1.90-2.00 (m, 1 H), 2.00-2.10 (m, 1 H), 2.34 (dd, *J* = 15.7, 9.0, 1 H), 2.41 (dd, *J* = 15.7, 3.3, 1 H), 3.39 (dd, *J* = 12.1, 4.1, 1 H), 3.55-3.70 (m, 1 H), 4.11-4.17 (m, 1 H), 4.40-4.50 (m, 1 H). ^{13}C NMR (CD_3OD, 500 MHz, rotamers) δ: 28.4, 28.7, 36.7, 37.1, 39.3, 40.8, 56.6, 56.9, 61.0, 61.4, 70.1, 70.3, 70.7, 71.9, 81.3, 81.5, 81.8, 156.7, 157.2, 172.9. IR (film) cm^{-1}: 3418 (br. s), 2978 (s), 2933 (s), 1703 (s), 1403 (s), 1367 (s), 1257 (s), 1159 (s), 999 (m), 969 (m), 848 (m), 774 (m), 737 (m). Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.18; H, 9.09; N, 3.98.

18. The submitters determined the crystalline hydroxy esters to be >99.9% diastereomerically pure by supercritical fluid chromatography (EMdiol silica column and a Chiralcel (+) OD-(H) column (Chiral Technologies, Inc.) in tandem (100 bar CO_2; 1.0 mL/min; 8% MeOH, modifier 35°C; retention times: β-ketoester (keto form) **3** 15.83 min, β-

ketoester (enol form) **3** 18.01 min, (*R*)-hydroxy ester **4b** 18.78 min, (*S*)-hydroxy ester **4a** 19.70 min).

19. The checkers found that the product was still slightly brown, indicating that the purification procedure is not effective in removing the catalyst.

20. The product exhibits the following properties: mp 135-137 °C; $[\alpha]_D^{23^\circ}$: –70.2 (c = 0.34, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.46 (s, 9 H), 1.47 (s, 9 H), 1.89-1.94 (m, 1 H), 2.00-2.20 (m br., 1 H), 2.25 (dd, *J* = 15.8, 9.5, 1 H), 2.32 (dd, *J* = 15.8, 3.5, 1 H), 3.40 (dd, *J* = 11.9, 4.0, 1 H), 3.45-3.80 (m br., 1 H), 3.80-4.15 (m br., 1 H), 4.30-4.45 (m, 1 H), 4.45-4.55 (m, 1 H); ^{13}C NMR (CD_3OD, 500 MHz, rotamers) δ: 28.4, 28.8, 34.4, 34.8, 41.1, 41.7, 56.1, 56.7, 61.8, 69.1, 69.2, 70.4, 70.7, 81.0, 81.3, 81.8, 156.7, 157.2, 172.3, 172.6. IR (film) cm^{-1}: 3419 (br. s), 2980 (s), 2919 (s), 1733 (s), 1673 (s), 1477 (m), 1418 (s), 1366 (s), 1244 (m), 1161 (s), 1080 (m), 1049 (m), 1002 (m), 952 (m), 876 (m), 852 (m), 775 (m), 749 (m); Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.33; H, 9.01; N, 3.81.

3. Discussion

The Ru(II)-BINAP complex,[2] $[Et_2NH_2]^+[Ru_2Cl_5(BINAP)_2]^-$,[3] is prepared as a toluene solvate in nearly pure form by this procedure. Typical crystallized product shows no other signals in the phosphorus NMR and gives a good combustion analysis. The material is quite stable and can be routinely handled in air. Storage under nitrogen will extend its shelf life, however.

The Claisen condensation of *t*-butyl acetate with a methyl ester is a general route for the preparation of complex β-ketoesters.[4] The reaction requires an excess of the enolate of *t*-butyl acetate to rapidly deprotonate the product and prevent tertiary alcohol formation. Some workers have also used excess LDA or *t*-butoxide for this purpose.

The reduction of β-ketoesters with Ru(II)-BINAP is the most efficient man-made catalytic asymmetric reaction.[5] Enantioselectivity is nearly always greater than 97% and 1,000 turnovers are typically accomplished in 2-8 hr. In the case of the optically active ketoester shown here, diastereoselectivity is >99:1 in the matched (C.) reaction and 94:6 in the

mismatched (D.) case. Not surprisingly, the matched reaction is also considerably faster. Ketoester reductions are best run as a concentrated solution in methanol. (Methylene chloride/methanol mixtures have also been used; the presence of an alcoholic cosolvent is mandatory.) Reaction mixtures are extremely susceptible to poisoning by the simultaneous presence of hydrogen and oxygen. Thus, thorough degassing is necessary prior to reaction. The addition of a small amount of strong acid (e.g., HCl, H_2SO_4, CH_3SO_3H) is necessary to activate the catalyst; in its absence nearly no reduction occurs. The particular case of *t*-butyl esters demonstrates that the conditions are still quite mild, since acid-catalyzed dealkylation and transesterification are possible side reactions.

1. Merck Research Laboratories, Rahway, NJ 07065.

2. King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

3. This structure is a revision of the originally assigned structure which was $[Ru_2Cl_4(BINAP)_2]\cdot Et_3N$. King, S. A.; DiMichele, L. In "Catalysis of Organic Reactions"; Scaraos, M. G.; Prunier, M. L., Ed.; **1995**, 157.

4. See, for example: Ohta, S.; Shimabayashi, A.; Hayakawa, S.; Sumino, S.; Okamoto, M. *Synthesis* **1985**, 45; Yamaguchi, M.; Nakamura, S.; Okuma, T.; Minami, T. *Tetrahedron Lett.* **1990**, *31*, 3913; Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2279.

5. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856; Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, 23, 345.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

2(*S*)-(β-tert-Butoxycarbonyl-α-(*S*)-hydroxyethyl)-4-(*R*)-hydroxypyrrolidine-1-carboxylic acid, tert-butyl ester: 2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-β, 4-dihydroxy-, 1,1-dimethylethyl ester, [2*S*-[2α(*S**),4β]]-; (167963-30-6).

(2*S*-4*R*)-2-*tert*-Butoxycarbonylacetyl-4-hydroxypyrrolidine-1-carboxylic acid, tert-butyl ester: 2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-4 hydroxy- β-oxo-,1,1-dimethylethyl ester, [2S-4R]-; (167963-29-3).

R-BINAP; Phosphine, (1*R*)-[1,1: binaphthalene]-2,2'-diylbis (diphenyl)-; (76189-55-4).

Triethylamine; Ethanamine, *N,N*-diethyl-; (121-44-8).

Lithium hexamethyldisilylamide: Silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-, lithium salt; (4039-32-1)

tert-Butyl acetate; Acetic acid, 1,1-dimethylethyl ester; (540-88-5).

N-Boc hydroxyproline methyl ester: 1,2-Pyrrolidinedicarboxylic acid, 4-hydroxy, 1-(1,1-dimethylethyl) 2-methyl ester, (2*S*,4*R*); (74844-91-0).