Notes

A Simple Asymmetric Synthesis of 4-Arylphenylalanines via Palladium-Catalyzed Cross-Coupling Reaction of Arylboronic Acids with Tyrosine Triflate

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4-Phenylphenylalanine is present as a structural element in certain biologically active compounds; for example, the potent, long-acting angiotensin II antagonist.[1] A biphenyl residue is also present in the cyclic tripeptide antibiotic WS-43708A.[2] To our knowledge, the only chiral synthesis of 4-arylphenylalanines is that reported by Yabe[3] via enzymatic resolution. Tilley[4] has shown that (carboalkoxyalkyl)phenylalanines are obtained in high optical yield from the palladium(0)-catalyzed cross-coupling of tyrosine triflate and organostannanes. Huth[5] and Snieckus[6] have reported that achiral diaryl compounds were synthesized by palladium-catalyzed reaction of aromatic triflates with arylboronic acids. Since the cross-coupling reaction of a CHIRAL aryltriflate with a boronic acid has not yet been reported, we decided to investigate these reactions for the synthesis of chiral 4-arylphenylalanines.

Our process begins with *N*-Boc-(*S*)-tyrosine triflate **1** (Scheme I), which was readily available in excellent yield from *N*-α-Boc-(*S*)-tyrosine methyl ester and trifluoromethanesulfonic anhydride. The palladium-catalyzed, cross-coupling reaction of tyrosine triflate **1** with phenylboronic acid **2a** was first investigated using tetrakis(triphenylphosphine)palladium(0) (3 mol %) and anhydrous potassium carbonate in DMF at 90 °C for 16 h, conditions described by Suzuki.[7] Although the isolated yield of **3a** was high (90%), we found (HPLC) that there was 17% of the undesired *R* isomer in **4a**, indicating some racemization occurred during reaction. However, we did not observe any racemization under a homogeneous condition (triethylamine, DMF, 90 °C) even though this reaction took 2 days for completion. It is clear that both the rate and degree of racemization depend on the conditions used. After considerable experimentation,[8] we found that the cross-coupling reaction works extremely well under heterogeneous conditions: 3 mol % of tetrakis(triphenylphosphine)palladium(0) and anhydrous potassium carbonate (2 equiv) in toluene at 90 °C for 2 h. Under these conditions, the isolated yield of **3a** was high (94%), and the optical purity was determined to be >99% (HPLC).

Scheme I

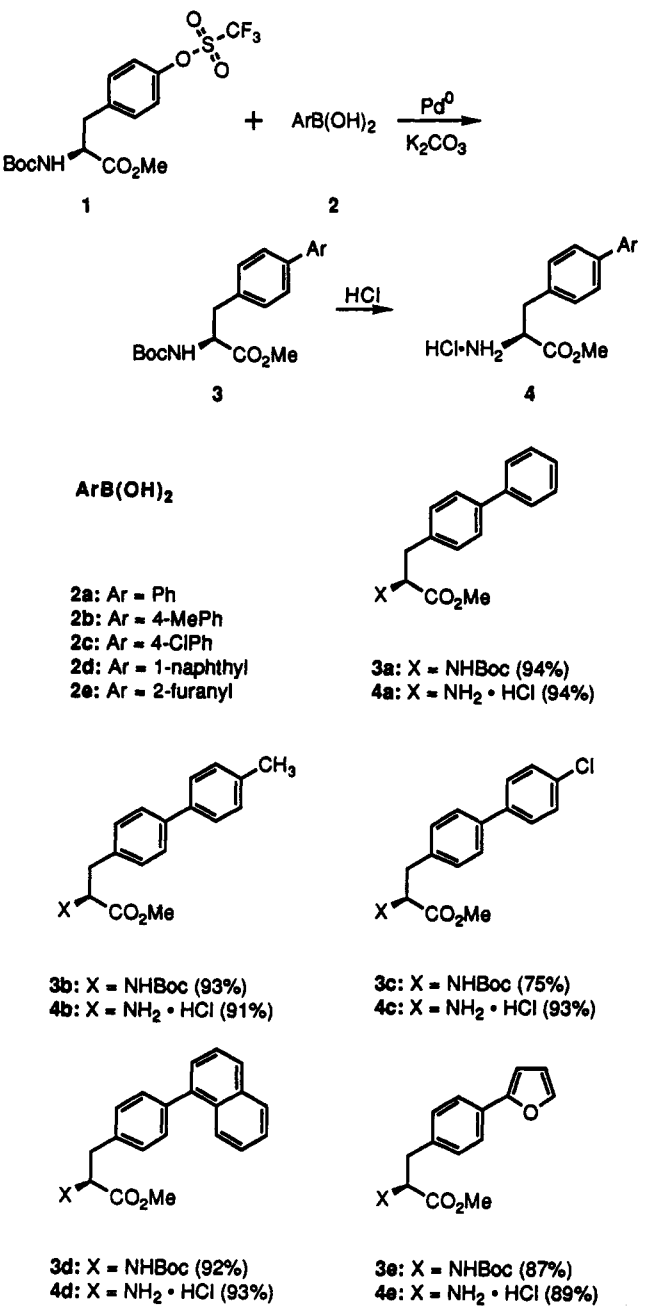

Figure 1. Preparation of (*S*)-4-arylphenylalanine methyl ester hydrochloride salts.

For the preparation of **3b** and **3d**, the cross-coupling reactions of **1** with **2b** and **2d** were fast (3 h) in the presence of 3 mol % of palladium(0) at 90 °C (Figure 1). Under the same conditions, reaction of **1** with either **2c** or **2e** was slow (incomplete after 48 h). However, when we increased the catalyst loading to 30 mol %, both reactions were complete in 3 h.

In order to examine the optical purity of the amino esters obtained by this methodology, **3a** was deprotected with anhydrous hydrogen chloride to afford **4a**, which was analyzed by HPLC using a modified Kinoshita method[9]

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(8) We have also attempted Kishi's conditions: $Pd[P(Ph)_3]_4$/10% aqueous TlOH/THF/rt; $Pd[P(Ph)_3]_4/Ag_2O$/THF (*J. Am. Chem. Soc.* **1987**, *109*, 4756). None of the desired **4a** was obtained.

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(see Experimental Section). We employed a buffered solution of aqueous ammonium formate (0.025M, pH = 4) and methanol as the mobile phase. Under these conditions, complete resolution of the diastereomers was obtained and no racemization was detected.

In conclusion, a variety of chiral 4-arylphenylalanines have been efficiently prepared by palladium-catalyzed cross-coupling reactions. Advantages of this methodology include high optical and chemical yields, ease of operation, commercially available arylboronic acids, easily prepared tyrosine triflate, and a short synthetic sequence. In addition, the minimal environmental impact of this sequence makes this process useful for both industrial and research operations.

Experimental Section

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^{1}H NMR) were recorded at 270 MHz on a Bruker AF series FT-NMR spectrometer. Microanalyses were performed by Robertson Laboratory, Inc. of Madison, New Jersey. Chemical ionization mass spectra (CIMS) were measured on a Hewlett-Packard GC-MS 5985B using methane as reactant gas. Column chromatography was performed on silica gel (EM Science, silica gel 60, 230–400 mesh ASTM No. 9385-3). High-performance liquid chromatography (HPLC) was performed on a Waters system equipped with a 300 × 3.9 mm C-18 column. Optical rotations were recorded at 20 °C with a Perkin-Elmer 241 polarimeter. Concentration refers to removal of solvent under reduced pressure using a Buchi rotary evaporator.

N-α-Boc-(*S*)-tyrosine methyl ester was purchased from Schweizerhall Chemicals. Trifluoromethanesulfonic anhydride, phenylboronic acid, and tetrakis(triphenylphosphine)palladium(0) were purchased from Aldrich Chemical Co. 4-Methylbenzeneboronic acid, 4-chlorobenzeneboronic acid, and 1-naphthaleneboronic acid were purchased from Lancaster Synthesis. 2-Furanboronic acid was prepared according to literature procedure.[10] All chemicals and solvents were used as purchased without purification.

(*S*)-α-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-[[(trifluoromethyl)sulfonyl]oxy]benzenepropanoic Acid Methyl Ester (1). A solution of *N*-α-*t*-Boc-(*S*)-tyrosine methyl ester (5.9 g, 20 mmol) and pyridine (8 mL, 100 mmol) in methylene chloride (30 mL) was cooled to 0–5 °C. Trifluoromethanesulfonic anhydride (4 mL, 23 mmol) was added at 0–5 °C, and the resulting mixture was held for another 30 min. The reaction mixture was diluted with water (60 mL) and methylene chloride (100 mL) and washed sequentially with 0.5 N sodium hydroxide solution (1 × 50 mL), water (1 × 60 mL), 10% citric acid solution (2 × 75 mL), and water (1 × 60 mL). The organic phase was dried over $MgSO_4$ and concentrated to an oil. The oil was purified by column chromatography (silica gel, hexane/ethyl acetate (2/1)) to give 7.75 g (91%) of colorless 1 which crystallized on standing: mp 47–48 °C; $[\alpha]^{20}_D$ +33.6° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 4 H, ArH), 5.05 (d, *J* = 7.1 Hz, 1 H, NH), 4.6 (m, 1 H, α-CH), 3.7 (s, 3 H, OCH_3), 3.17 (m, 1 H, CH*H*), 3.03 (m, 1 H, C*H*H), 1.4 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{16}H_{20}F_3NO_7S$: C, 44.97; H, 4.72; N, 3.28; F, 13.34; S, 7.50. Found: C, 45.22; H, 4.82; N, 3.15; F, 13.60; S, 7.21.

General Procedure for the Preparation of *N*-α-Boc-(*S*)-4-arylphenylalanine Methyl Esters 3. Nitrogen was passed through a suspension of 1 (1.75 mmol), arylboronic acid (3.5 mmol), anhydrous potassium carbonate (2.63 mmol), and toluene (17 mL) for 15 min. Tetrakis(triphenylphosphine)palladium(0) was added, and the mixture was heated at 85–90 °C for 2 h. The reaction mixture was cooled to 25 °C, diluted with ethyl acetate (17 mL), and washed sequentially with saturated sodium bicarbonate (1 × 20 mL), water (1 × 20 mL), 10% citric acid (1 × 20 mL), water (1 × 20 mL), and saturated sodium chloride solution (1 × 20 mL). The organic phase was concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate (2/1)). The compounds obtained by this method are listed below.

(*S*)-Methyl α-[[(1,1-dimethylethoxy)carbonyl]amino]-(1,1′-biphenyl)-4-propanoate (3a): mp 83–85 °C; $[\alpha]^{20}_D$ +54.81° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.15–7.65 (m, 9 H, ArH), 5.04 (d, *J* = 8.3 Hz, 1 H, NH), 4.65 (m, 1 H, α-CH), 3.75 (s, 3 H, OCH_3), 3.02 (m, 2 H, CH_2), 1.4 (s, 9 H, $C(CH_3)_3$); CIMS *m*/*z* (relative intensity) 356 ($M^+ + 1$) (18), 300 ($M^+ + 1 - C(CH_3)_3$) (69), 256 ($M^+ + 1 - CO_2C(CH_3)_3$) (100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.59; H, 6.90; N, 3.91.

(*S*)-Methyl α-[[(1,1-dimethylethoxy)carbonyl]amino]-4′-methyl(1,1′-biphenyl)-4-propanoate (3b): mp 77–79 °C; $[\alpha]^{20}_D$ +52.24° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50 (t, *J* = 8.2 Hz, 4 H, ArH), 7.2 (dd, *J* = 8.0, 8.2 Hz, 4 H, ArH), 5.02 (d, *J* = 8.0 Hz, 1 H, NH), 4.63 (m, 1 H, α-CH), 3.75 (s, 3 H, OCH_3), 3.13 (m, 2 H, CH_2), 2.4 (s, 3 H, $ArCH_3$), 1.4 (s, 9 H, $C(CH_3)_3$); CIMS *m*/*z* (relative intensity) 370 ($M^+ + 1$) (7), 314 ($M^+ + 1 - C(CH_3)_3$) (52), 270 ($M^+ + 1 - CO_2C(CH_3)_3$) (100). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.70; H, 7.36; N, 3.59.

(*S*)-Methyl α-[[(1,1-dimethylethoxy)carbonyl]amino]-(1,1′-biphenyl)-4-propanoate (3c): mp 94–96 °C; $[\alpha]^{20}_D$ +52.74° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32–7.57 (m, 6 H, ArH), 7.2 (d, *J* = 7.8 Hz, 2 H, ArH), 5.0 (d, *J* = 7.7 Hz, 1 H, NH), 4.62 (m, 1 H, α-CH), 3.75 (s, 3 H, OCH_3), 3.1 (m, 2 H, CH_2), 1.4 (s, 9 H, $C(CH_3)_3$); CIMS *m*/*z* (relative intensity) 390 ($M^+ + 1$) (13), 334 ($M^+ + 1 - C(CH_3)_3$) (74), 290 ($M^+ + 1 - CO_2C(CH_3)_3$) (100). Anal. Calcd for $C_{21}H_{24}ClNO_4$: C, 64.69; H, 6.20; N, 3.59; Cl, 9.09. Found: C, 64.37; H, 6.19; N, 3.43; Cl, 9.28.

(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-(1-naphthalenyl)phenylalanine methyl ester (3d): mp 100–102 °C; $[\alpha]^{20}_D$ +48.16° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85–7.95 (m, 3 H, NapH), 7.22–7.55 (m, 8 H, ArH + NapH), 5.1 (d, *J* = 8.2 Hz, NH), 4.7 (m, 1 H, α-CH), 3.77 (s, 3 H, OCH_3), 3.2 (m, 2 H, CH_2), 1.41 (s, 9 H, $C(CH_3)_3$); CIMS *m*/*z* (relative intensity) 406 ($M^+ + 1$) (9), 350 ($M^+ + 1 - C(CH_3)_3$) (54), 306 ($M^+ + 1 - CO_2C(CH_3)_3$) (100). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.02; H, 6.60; N, 3.28.

(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-(2-furanyl)-phenylalanine methyl ester (3e): mp 72–74 °C; $[\alpha]^{20}_D$ +59.80° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.6 (d, *J* = 8.3 Hz, 2 H, Ar_3H), 7.46 (d, *J* = 1.6 Hz, 1 H, Fur_5H), 7.25 (d, *J* = 8.2 Hz, 2 H, Ar_2H), 6.62 (d, *J* = 3.4 Hz, 1 H, Fur_3H), 6.45 (dd, *J* = 3.3, 1.8 Hz, 1 H, Fur_4H), 5.3 (d, *J* = 7.9 Hz, 1 H, NH), 4.6 (m, 1 H, α-CH), 3.72 (s, 3 H, OCH_3), 3.1 (m, 2 H, CH_2), 1.4 (s, 9 H, $C(CH_3)_3$); CIMS *m*/*z* (relative intensity) 346 ($M^+ + 1$) (28), 290 ($M^+ + 1 - C(CH_3)_3$) (57), 246 ($M^+ + 1 - CO_2C(CH_3)_3$) (100). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.69; H, 6.53; N, 3.90.

General Procedure for the Preparation of (*S*)-4-Arylphenylalanine Methyl Ester Hydrochloride Salts (4). To a solution of 3 (1.25 mmol) in ethyl acetate (2 mL) was added a saturated solution of anhydrous hydrogen chloride in ethyl acetate (4.5 mL). The solution was stirred at room temperature for 3 h. The reaction mixture was concentrated to obtain a white solid. The compounds obtained by this method are listed below.

(*S*)-Methyl α-amino(1,1′-biphenyl)-4-propanoate hydrochloride salt (4a): mp 205–207 °C; $[\alpha]^{20}_D$ +11.8° (*c* = 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 8.8 (s, 3 H, NH_3), 7.3–7.7 (m, 9 H, ArH), 4.3 (t, *J* = 6.6 Hz, α-CH), 3.7 (s, 3 H, OCH_3), 3.2 (m, 2 H, CH_2); CIMS *m*/*z* (relative intensity) 256 ($M^+ + 1 - HCl$) (100). Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80; Cl, 12.15. Found: C, 65.51; H, 6.29; N, 4.73; Cl, 12.47.

(*S*)-Methyl α-amino-4′-methyl(1,1′-biphenyl)-4-propanoate hydrochloride salt (4b): mp 207 °C dec; $[\alpha]^{20}_D$ +11.83° (*c* = 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 3 H, NH_3), 7.67 (dd, *J* = 7.6, 7.8 Hz, 4 H, ArH), 7.28 (dd, *J* = 7.9, 7.8 Hz, 4 H, ArH), 4.28 (t, *J* = 6.2 Hz, 1 H, α-CH), 3.67 (s, 3 H, OCH_3), 3.17 (t, *J* = 6.3 Hz, 2 H, CH_2), 2.31 (s, 3 H, $ArCH_3$); CIMS *m*/*z* (relative intensity) 270 ($M^+ + 1 - HCl$) (100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58; Cl, 11.59. Found: C, 66.65; H, 6.53; N, 4.50; Cl, 11.71.

(*S*)-Methyl α-amino-4′-chloro(1,1′-biphenyl)-4-propanoate hydrochloride salt (4c): mp 206–208 °C; $[\alpha]^{20}_D$ +12.80° (*c* = 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 3 H, NH_3), 7.67 (dd, *J* = 8.6, 8.2 Hz, 4 H, ArH), 7.52 (d, *J* = 8.3 Hz, 2 H, ArH), 7.35 (d, *J* = 8.2 Hz, 2 H, ArH), 4.3 (t, *J* = 6.1 Hz, 1 H, α-CH), 3.70 (s,

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3 H, OCH_3), 3.2 (m, 2 H, CH_2); CIMS m/z (relative intensity) 290 ($M^+ + 1 - HCl$) (100). Anal. Calcd for $C_{16}H_{17}Cl_2NO_2$: C, 58.91; H, 5.25; N, 4.29; Cl, 21.73. Found: C, 58.79; H, 5.25; N, 4.04; Cl, 22.05.

(*S*)-4-(1-Naphthalenyl)phenylalanine methyl ester hydrochloride salt (4d): mp 176-177 °C; $[\alpha]^{20}_D$ +9.41° (c = 1, CH_3OH); ^1H NMR ($CDCl_3$) δ 8.77 (s, 3 H, NH_3), 8.0 (dd, J = 8.1, 8.2 Hz, 2 H, NapH), 7.8 (d, J = 8.0 Hz, 1 H, NapH), 7.35-7.6 (m, 8 H, ArH + NapH), 4.35 (t, J = 6.2 Hz, 1 H, α-CH), 3.72 (s, 3 H, OCH_3), 3.26 (m, 2 H, CH_2); CIMS m/z (relative intensity) 306 ($M^+ + 1 - HCl$) (100). Anal. Calcd for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.90; N, 4.10; Cl, 10.37. Found: C, 70.27; H, 5.90; N, 4.10; Cl, 10.56.

(*S*)-4-(2-Furanyl)phenylalanine methyl ester hydrochloride salt (4e): mp 207-208 °C; $[\alpha]^{20}_D$ +16.36° (c = 1, CH_3OH); ^1H NMR ($CDCl_3$) δ 8.67 (s, 3 H, NH_3), 7.75 (d, J = 1.6 Hz, 1 H, Fur_5H), 7.67 (d, J = 8.1 Hz, 2 H, Ar_3H), 7.27 (d, J = 8.1 Hz, 2 H, Ar_2H), 6.95 (d, J = 3.2 Hz, 1 H, Fur_3H), 6.57 (dd, J = 3.1, 1.8 Hz, 1 H, Fur_4H), 4.3 (t, J = 6.4 Hz, 1 H, α-CH), 3.68 (s, 3 H, OCH_3), 3.15 (m, 2 H, CH_2); CIMS m/z (relative intensity) 246 ($M^+ + 1 - HCl$) (100). Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 59.47; H, 5.60; N, 4.86; Cl, 12.37.

Typical Procedure for the Determination of the Enantiomeric Purity of Amino Ester. The amino ester **4a** was derivatized with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) by the procedures reported by Kinoshita[9] to form thio urea diastereomers. A 5-μL aliquot was injected directly into the Waters HPLC system equipped with a C-18 column (Waters μBondapak, 300 × 3.9 mm). The sample was eluted with an isocratic solution of aqueous ammonium formate (0.025M, pH = 4) and methanol, 40/60 (v/v), at a constant flow rate of 1.2 mL/min at room temperature and was monitored at 254 nm. A typical retention time for an (*S*)-**4a** derivative is 33 min and for an (*R*)-**4a** derivative is 40 min. The limit of detection of each diastereomer monitored at 254 nm is less than 1% by weight.

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Registry No. **1**, 112766-18-4; **2a**, 98-80-6; **2b**, 5720-05-8; **2c**, 1679-18-1; **2d**, 13922-41-3; **2e**, 13331-23-2; **3a**, 137255-86-8; **3b**, 137255-87-9; **3c**, 137255-88-0; **3d**, 137255-89-1; **3e**, 137255-90-4; **4a**, 63024-30-6; **4b**, 137255-91-5; **4c**, 137255-92-6; **4d**, 137255-93-7; **4e**, 137255-94-8; Boc-Tyr-OMe, 4326-36-7; $O(SO_2CF_3)_2$, 358-23-6; Pd, 7440-05-3.

Chromium(VI) Oxidation of Tertiary Unsaturated Alcohols. Oxidative Fragmentation of 2-Substituted Bicyclo[2.2.1]hept-5-en-2-ols

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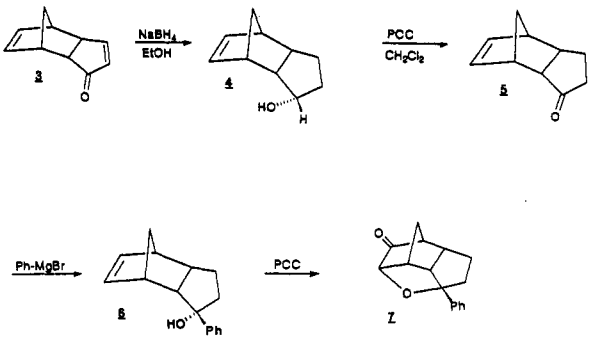
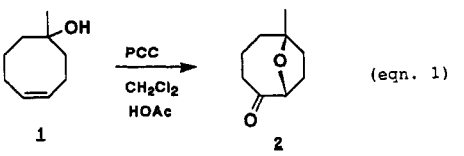
Tertiary alcohols are generally inert toward oxidation by Cr(VI) reagents.[1] Some exceptions, however, have been reported such as strained cyclopropanols[2] and bicyclic [2.2.1] tertiary alcohols[3] which react with chromic acid to yield ketones resulting from C-C bond cleavage. When an alkene double bond is suitably disposed near the tertiary OH site, Schlecht has observed synthetically useful intramolecular C=C oxidations initiated by pyridinium chlorochromate (PCC), for example **1** → **2**.[4] Furthermore, tertiary allylic alcohols react with PCC to give conjugated ketones through allylic rearrangements.[5] Since the mechanisms of some of these reactions remain in doubt and since the synthetic potential of tertiary alcohol oxidations has not been fully exploited, we became interested in investigating further examples of PCC oxidation of tertiary unsaturated alcohols.

Scheme I





(eqn. 1)

Results and Discussion

One such compound is 3-phenyltricyclo[5.2.1.$0^{2,6}$]dec-8-en-*endo*-3-ol (**6**) prepared from the known ketone **3**[6] according to Scheme I. Thus, $NaBH_4$ reduction of **3** yielded the alcohol **4** in which the conjugated double bond of **3** was also saturated.[7] PCC oxidation of **4** followed by PhMgBr treatment gave **6**, where the endo orientation of the OH group is assured since the nucleophilic Grignard reagent must attack from the least hindered exo face of the tricyclic ketone **5**.[8] Within the carbon framework of **6**, the tertiary OH is positioned in a conformationally fixed orientation with respect to the alkene group (in contrast to **1**). As a consequence, we might expect PCC oxidation of **6** to proceed smoothly to a β keto ether in the manner of the **1** to **2** conversion.[4] Indeed, oxidation of tertiary unsaturated alcohol **6** gave crystalline **7**, $C_{16}H_{16}O_2$, in 70% yield. This compound was fully characterized, and spectral data are listed in the Experimental Section.

The mechanism of this reaction very likely parallels the concept elegantly demonstrated by Schlecht for PCC oxidation of substrates such as **1**. Here, the chromate ester of the OH group rapidly forms and participates in a transannular, intramolecular alkene oxidation.[4] Since the strained double bond of **6** might be more reactive toward PCC than the same group in **1**, we have considered the possibility of an intermolecular attack of PCC on the 8-ene

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