A Novel Dearomatization of Anilines via Complexation to Pentaammineosmium(II): Synthesis of Highly Functionalized 3-Aminocyclohexenes from Anilines

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Previously, we have reported that dihapto-coordinated aniline complexes of pentaammineosmium(II) show enhanced reactivity toward conjugate addition at C4. In particular, when the complexes $[Os(NH_3)_5(5,6\text{-}\eta^2\text{-L})]^{2+}$ (L = aniline, *N*,*N*-dimethylaniline) are treated with maleic anhydride, para-alkylated anilines are generated as major products.[1] We now wish to report that under appropriate conditions, the α,β-unsaturated iminium intermediates obtained from C4 alkylation can be sufficiently stabilized by the metal that subsequent nucleophilic addition at C3 and electrophilic addition at C2 may be achieved. Thus, through the use of an η^2-complexing agent, anilines become versatile synthons to highly functionalized aminocyclohexenes.[2]

η^2-Aniline and η^2-phenol complexes of pentaammineosmium(II) are readily generated from $Os(NH_3)_5(OTf)_3$ and an excess of the desired ligand with typical yields ranging from 80 to 95%. Recent work in our laboratories has shown that the η^2-phenol complexes readily undergo conjugate addition at C4 with a variety of Michael acceptors to yield stabilized 2,5-dienone species.[3] Although this reaction is quite facile for phenol, the η^2-aniline analogs have proven to be sufficiently less reactive; ligand substitution or metal oxidation by the electrophile usually preempts conjugate addition.[4] However, we have found that silylating agents such as TMSOTf or TBSOTf greatly accelerate conjugate addition of η^2-aniline complexes at C4, thereby providing a high-yielding route to cyclohexadieniminium complexes. For example, treatment of $[Os(NH_3)_5(5,6\text{-}\eta^2\text{-}N,N\text{-dimethylaniline})]^{2+}$ [5] (**1**), with an excess of methyl acrylate affords no reaction over the lifetime of **1**. However, in the presence of 1 equiv of TBSOTf(CD_3CN), the iminium silyl ketene acetal **2** is generated in 90% yield along with ~8–10% of the protodesilylated product **3** (Figure 1).[6] A 6% NOE enhancement of H4 for **3** upon irradiation of the *cis* ammines is consistent with the *anti* stereochemistry. Subsequent hydrolysis of **2** to **3** followed by base-promoted rearomatization and substitution of the iminium ligand cleanly affords the para-substituted aniline **4**.[7] Alternatively, the conjugated iminium species **3** may be reduced by borohydride at C3 (~5:1 regioselectivity, *vide infra*), protonated at C2, and reduced again by hydride at C1 to form the allylamine complex **5**.[8] The allylamine ligand **6** is readily displaced from the osmium by either oxidation or heat.[9] The *trans* stereochemistry of the free allylamine **6** is consistent with both the Michael addition at C4 and hydride reduction at C1 occurring *anti* to the osmium.[10] Preliminary experiments indicate that in the presence of TBSOTf, C4 conjugate addition for the η^2-aniline complex **1** is quite general; stable cyclohexadieniminium complexes analogous to **3** have been prepared from reaction **1** with dimethylfumarate, 2-cyclohexen-1-one, acrylonitrile, and methyl 2,4-pentadienoate (1,6 addition).

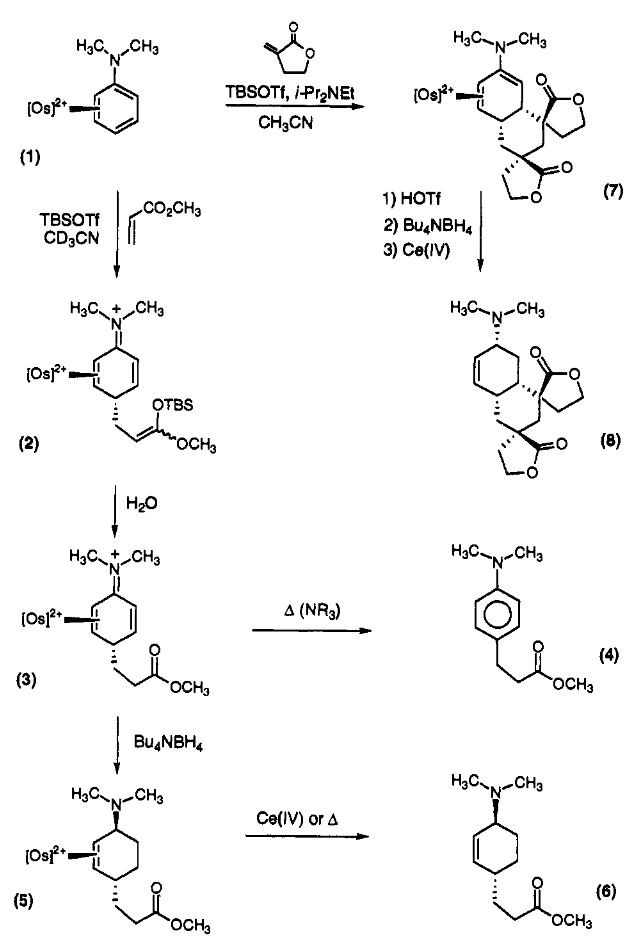

Figure 1. Reaction scheme for the η^2-aniline complex **1**, demonstrating facile conjugate addition to C4. ($[Os]^{2+} = [Os(NH_3)_5]^{2+}$; triflate anions are not shown).

[†] 1992 Camille and Henry Dreyfus Teacher-Scholar, 1993 NSF Young Investigator.

(1) Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 8972.

(2) For a review on the use of arenes as synthons in organic synthesis, see: Mander, L. N. *Synlett* **1991**, 134.

(3) Typical electrophiles include α,β-unsaturated ketones and esters, acrolein, acrylonitrile, maleic anhydride, and *N*-methyl maleimide.

(4) Gonzalez, J.; Harman, W. D., unpublished results.

(5) The synthesis of $[Os(NH_3)_5(5,6\text{-}\eta^2\text{-}N,N\text{-dimethylaniline})]^{2+}(OTf)_2$ (**1**) from $[Os(NH_3)_5(OTf)]^{2+}(OTf)_2$ has been reported: Harman, W. D.; Sekine, M.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 5725. The triflate starting material was prepared from osmium tetroxide as described: Lay, P. A.; Magnuson, R. H.; Taube, H. *Inorg. Synth.* **1986**, *24*, 269.

(6) The silyl ketene acetals **2**, present in a 1:6 ratio, were identified on the basis of ^{13}C resonances for SiO—C=CH. For the major isomer, these are at 159 and 70 ppm (see Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650). Addition of water converts **2** to **3**, which was then isolated in 92–97% yield as a purple solid by precipitation of the reaction mixture with ether.

(7) A solution of **3** (from 0.2 mmol of **1**) was heated with *N*,*N*-diisopropylethylamine at 80 °C for 1 min. Methyl 3-(4-(dimethylamino)-phenyl)propionate (**4**) was obtained as a clear oil (22 mg, 56%) after an aqueous workup, followed by a prep-TLC purification (0.25 mm silica plate; CH_2Cl_2; $R_f = 0.6$). ^1H NMR ($CDCl_3$): δ 7.08 (d, $J = 8.5$ Hz, 2H), 6.70 (d, $J = 8.5$ Hz, 2H), 3.67 (s, 3H, CH_3O), 2.92 (s, 6 H, $(CH_3)_2$-N) 2.87 (t, $J = 8.0$ Hz, 2H), 2.59 (t, $J = 8.0$ Hz, 2H). The ^{13}C NMR resonances are consistent with those reported for this compound: Radeglia, R.; Spassov, S. L.; Stefanova, R.; Simova, D. D. *Z. Naturforsch.* **1980**, *35B*, 934.

(8) This reaction sequence was carried out in one step using an excess of tetrabutylammonium borohydride in methanol, followed by acidification. Precipitation of the reaction mixture from ether yielded an ~85:15 mixture of protonated **5** and its major regioisomer (resulting from 1,2 attack of hydride at C1) in a combined yield of 93–98%.

(9) A solution of **5** was oxidized with ceric ammonium nitrate under acidic conditions (HOTf) in CH_3CN, yielding a mixture containing **6** in 48–51% overall yield from **1** by ^1H NMR integration. The mixture was separated by preparative TLC (performed five times in tandem using 1:1:4 hexamethyldisilazane/methanol/methyl *tert*-butyl ether), yielding the following: (1) methyl 3-phenylpropionate (2%) ($R_f = 0.85$); (2) 3-(dimethylamino)-6-(2-(carbomethoxy)ethyl)-1,4-cyclohexadiene (3%) ($R_f = 0.56$); and (3) 3-(dimethylamino)-6-(2-(carbomethoxy)ethyl)cyclohexene (**6**) (40%) ($R_f = 0.48$). Data for **6**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 2H, H2 and H3), 3.59 (s, 3H, CH_3O), 3.17 (m, $w_{h/2} = 20$ Hz, 1H, H1), 2.24 (s, t overlap, 8H, CH_3N and CH_2CO_2), 1.8–1.0 (overlapping m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (CO), 133.5 (CH), 129.5 (CH), 60.7 (CHN), 51.4 (CH_3O), 39.9 (CH_3), 35.0 (CH), 31.0 (CH_2), 30.8 (CH_2), 27.7 (CH_2), 22.0 (CH_2).

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In some cases, an enolate generated (directly or indirectly) from the Michael acceptor may serve as the nucleophile that adds to C3. Thus, when the aniline complex **1** is treated with an excess (3 equiv) of α-methylene-γ-butyrolactone, a [2 + 2 + 2] Michael-Michael-ring-closure (MIMIRC) sequence is achieved across the 3,4 double bond of the aniline ligand. In the presence of Hunig's base, the spirolactone enamine **7** is produced as the major diastereomer (62% de) in ~50% isolated yield.[11,12] The crystal structure of **7** was determined, and the ORTEP for the cation (Figure 2) confirms the expected *cis* stereochemistry which results from bond formations at C3 and C4 *anti* to the bulky pentaammineosmium moiety.[13] The enamine ligand of **7** is converted cleanly to the cyclic allylamine **8** via protonation/borohydride reduction and decomplexation from the metal.[14] Here, in contrast to that observed in the formation of the less-hindered allylamine complex **5**, hydride attack on **7** occurs *syn* to the metal center, an observation demonstrating that the steric bulk of Os(NH_3)$_5$ does not always preclude the formation of bonds from the β face.[15] Inspection of the ORTEP diagram for **7** reveals that the β face is actually the less sterically congested face of the organic ligand.

In summary, η^2-coordination of pentaammineosmium(II) not only activates the aniline toward a C4-selective electrophilic addition but also plays the important role of stabilizing the resulting dieniminium intermediate, such that nucleophilic addition at C3 is possible. Finally, the metal sets the stereochemistry of the reaction directing both electrophilic (C4) and nucleophilic addition (C3) *anti* to the site of metal coordination. This methodology, which appears to be general for anilines,[16] is complementary to existing dearomatization methods in both regiochemistry and types of C–C bonds formed.[17] The scope of this chemistry is the topic of an ongoing investigation.[18]

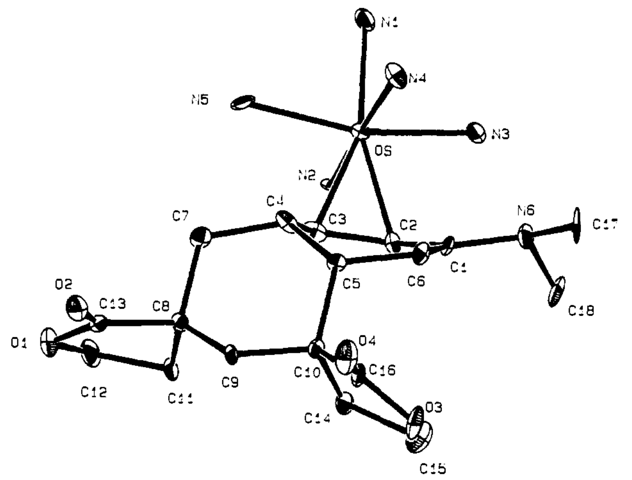

Figure 2. ORTEP drawing for the cation of the MIMIRC product **7**, showing 30% thermal ellipsoids. Selected bond lengths (Å) and angles (deg) are as follows: Os–C2 = 2.15(2); Os–C3 = 2.16(1); C2–C3 = 1.41(2); C1–C6 = 1.35(2); N6–C1 = 1.42(2); C1–C2–C3 = 120(1); C3–C4–C5 = 114(1); C4–C5–C6 = 111(1); C1–C6–C5 = 122(1).

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Supplementary Material Available: Additional information on the synthesis and characterization of compounds **1**–**8** and minor products; tables of experimental details, atomic position parameters, thermal parameters, bond distances and angles, and ORTEP drawings for compounds **7** and **8** (20 pages). Ordering information is given on any current masthead page.

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(10) The stereochemistry of the dimethylamino substituent for compounds **6** and **8** was assigned on the basis of vicinal coupling between the aliphatic and olefinic methine resonances. For **6**, $J_{12} \sim J_{34} \sim 0$ Hz is consistent with both H1 and H4 having axial orientations. For **8**, $J_{12} \sim 0$ Hz and $J_{34} = 3.5$ Hz are consistent with axial and pseudoequatorial H1 and H4, respectively (see Jackman, L. M.; Sternhell, S. *Applications of NMR in Organic Chemistry*; Pergamon Press, New York, 1969; p 288.). The structure of **8** was confirmed by X-ray crystallography: $C_{18}H_{25}NO_4$, $M = 319.40$; monoclinic, space group $P2_1/n$ (No. 14); $a = 6.958(2)$ Å, $b = 9.555(3)$ Å, $c = 24.410(7)$ Å, $\beta = 91.99(3)°$, $V = 1621(1)$ Å^3, $Z = 4$. The structure was solved by direct methods applying TEXSAN 5.0 and refined to $R(F) = 0.059$ and $R_w(F) = 0.07$ for 853 reflections with $I > 3\sigma(I)$ measured up to $2\Theta = 46.0°$ on a Rigaku AFC6S diffractometer (Mo Kα radiation, $\lambda = 0.710\,69$ Å, $T = 25$ °C).

(11) For reviews of multicomponent, one-pot annulations, see (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225.

(12) Complex **1** (695 mg, 1.0 mmol) and *N*-ethyldiisopropylamine (517 mg, 4.0 mmol) were dissolved in 4 g of CH_3CN, the solution chilled to –10 °C, and a likewise-cooled solution of α-methylene-γ-butyrolactone (294 mg, 3.0 mmol), and *tert*-butyldimethylsilyl triflate (317 mg, 1.2 mmol) in 1 g CH_3CN was added. The dark mixture was allowed to warm to room temperature and after 15 min is added dropwise to 50 mL of ether, yielding 916 mg of tan material. Recrystallization from acetone yielded analytically pure **7** (463 mg, 52%) as a canary yellow crystalline solid. ^{1}H NMR (CD_3CN): δ 4.59 (d, $J = 5.4$ Hz, 1H, CH=CN), 4.4–4.1 (m, 6H, 2CH_2O and CH–Os), 4.09 (s, 3H, *trans*-NH_3), 3.35 (dd, 1H), 3.11 (s, 12H, *cis*-NH_3), 2.8 (m, 1H), 2.55 (m, 1H), 2.50 (s, 6H, $(CH_3)_2N$), 2.33 (m, 1H), 2.3–2.2 (m, 2H), 2.0–1.9 (m, 2H), 1.7 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 182.8 (CO), 182.5 (CO), 156.1 (=C—N), 121.1 (q, $CF_3SO_3^-$), 99.0 (CH=), 67.4 (CH_2O), 66.0 (CH_2O), 46.9 (C), 45.3 (CH), 42.5 (CH_3–N), 42.0 (CH), 41.7 (C), 40.7 (CH), 38.5 (CH_2), 37.3 (CH_2), 35.5 (CH_2), 31.1 (CH), 29.6 (CH_2). Anal. Calcd for ($C_{23}H_{44}N_6O_{11}S_2F_6Os\cdot(CH_3)_2CO$): C, 29.11; H, 4.67; N, 8.86. Found: C, 29.16; H, 4.67; N, 8.90. The mother liquors from the recrystallization contain a mixture of products, including a para-alkylated aniline and several minor diastereomers. The diastereoselectivity of this reaction is based on the isolated yields of all organic diastereomers obtained in the synthesis of **8** (*vide infra*) using crude **7**.

(13) Crystallographic data: $C_{20}H_{38}F_6N_6O_{10}OsS_2\cdot0.5(CH_3)_2CO$, $M = 914.87$; triclinic, space group $P\bar{1}$ (No. 2); $a = 12.748(6)$ Å, $b = 16.040(8)$ Å, $c = 10.048(3)$ Å; $\alpha = 103.58(3)°$, $\beta = 95.39(3)°$, $\gamma = 67.67(3)°$; $V = 1847(3)$ Å^3; $Z = 2$. The structure was solved by heavy-atom techniques applying TEXSAN 5.0 and refined to $R(F) = 0.067$ and $R_w(F) = 0.083$ for 4471 absorption-corrected reflections with $I > 3\sigma(I)$ measured up to $2\Theta = 50°$ on a Rigaku AFC6S diffractometer (Mo Kα radiation, $\lambda = 0.710\,69$ Å, $T = -120$ °C).

(14) Compound **7** (1.0 mmol) was reduced with excess tetrabutylammonium borohydride in acidic acetonitrile. Oxidation of the resulting complex with ceric ammonium nitrate and HOTf in acetonitrile followed by an aqueous workup and column chromatography on basic alumina (1:1:3 hexamethyldisilazane/methanol/methylene chloride; $R_f = 0.5$ on silica TLC) yielded 247 mg (77%) of **8**. Two recrystallizations from ethyl acetate yielded analytically pure material, mp 188–190 °C. ^{1}H NMR ($CDCl_3$): δ 5.72 (d, $J = 9.4$ Hz, 1H, H2), 5.57 (ddd, $J = 9.4$, 3.5 Hz, 2.5 Hz, 1H, H3), 4.25 (m, 4H, 2CH_2O), 3.15 (m, 1H, CH–N), 2.80 (m, 1H), 2.43 (d, $J = 14.4$ Hz, 1H), 2.4 (m, 2H), 2.24 (s, m overlap, 8H, $(CH_3)_2N$ and CH_2), 1.98 (dt, $J = 12.6$ Hz, $J' = 6$ Hz, 1H), 1.82 (dd, $J = 14.0$ Hz, 2.2 Hz, 1H), 1.51 (d, $J = 14.4$ Hz, 1.5 (m, 1H), 1.29 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 181.4 (CO), 180.5 (CO), 131.9 (CH), 130.7 (CH), 65.6 (CH_2O), 65.0 (CH_2O), 61.1 (CH–N), 45.8 (C), 41.5 (C), 41.1 (CH_3), 40.6 (CH_2), 37.3 (CH), 36.8 (CH_2), 34.8 (CH_2), 31.7 (CH_2), 30.0 (CH), 22.3 (CH_2). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.71; H, 7.78; N, 4.35.

(15) Here we define the β-face of the organic ligand as that which is coordinated by osmium.

(16) For instance, the osmium(II) complexes of *N*-ethylaniline and *N*,*N*-dimethyl-*p*-toluidine undergo Michael additions exclusively at C4 with methyl acrylate and methyl vinyl ketone. See ref 18.

(17) Classical organometallic η^6-arene complexes (e.g., in which the metal center is $Cr(CO)_3$), are activated toward ring *nucleophilic* attack, *meta* to the electron-donating substituent. For a review, see: Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 517.

(18) Gonzalez, J.; Kolis, S. P.; Harman, W. D., work in progress.