Leaving Group Placement to Control the Stereoselective Organoiron-based Synthesis of Regioisomeric Tetrahydrophenanthridine Derivatives

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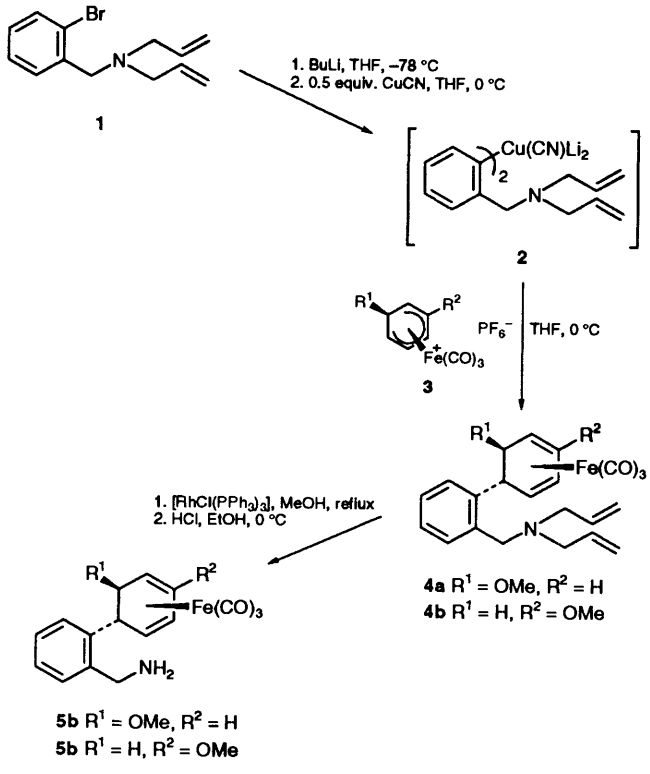
Stereo- and regio-specific cyclisation of the complexes **4a** and **4b** gives high yield access to the tricyclic ammonium complexes **7a** and **7b**.

The stereocontrolled formation of fused six-membered heterocyclic rings is an important objective in asymmetric synthesis. Annulation procedures that use nucleophilic additions to electrophilic organometallic π-complexes [1] are especially attractive because of the complete stereo- and regio-control generally available in such reactions. We have recently applied these concepts in a lactonization procedure [2] to build the central three rings of the alkaloid hippeastrine, a process that ensures the *cis* relative stereochemistry of the ring junction. This methodology makes double use of the control action of a tricarbonyliron complex, and employs a C-6 alkoxy leaving group [3] in the organometallic precursor to provide reactivation to promote the second nucleophile addition. Rearrangement of the binding position of the tricarbonyliron group in η^4-diene complexes provides the possibility that a substituent at a metal-bound sp^2-hybridised carbon atom can function as a leaving group, following rearrangement. Such reactions give convenient regiocontrolled access to η^5-dienyl complexes.[4] When applied to the problem of polycyclic ring construction required in alkaloid synthesis, the rearrangement process offers the prospect of a versatile method in which the nature of the annulation product is controlled by the placement of the leaving group on the cationic η^5-dienyl precursor.

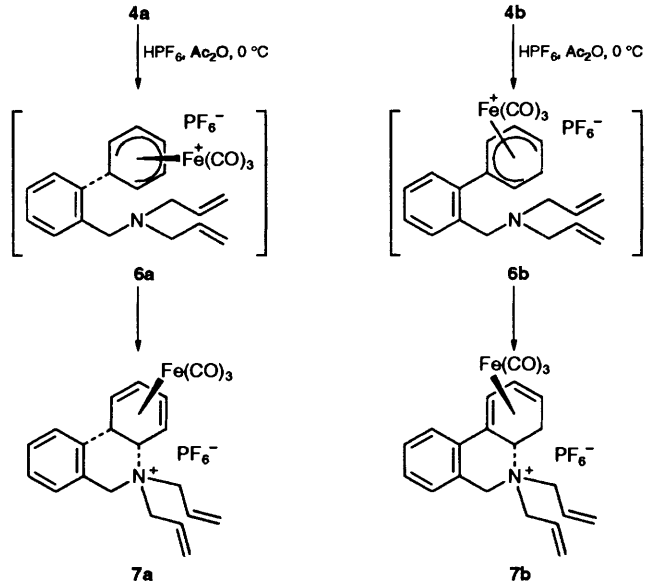
We report here the results of preliminary experiments to test this hypothesis and compare the C-6 leaving group method with the rearrangement approach (C-2 leaving group) in the case of novel C–N formative 6-membered ring closures. Metallated *O*-substituted arenes have previously been shown [5] to react stereo- and regio-selectively with cationic tricarbonyl-(η^5-cyclohexadienyl)iron(1+) complexes. Thus, the cuprate **2**, obtained by addition of 0.5 equiv. of CuCN after lithiation of the protected amine **1**, was allowed to react with the cations **3** to form stereoselectively the iron complexes **4a** (90%) and **4b** (73%). Treatment of **4** with [$RhCl(PPh_3)_3$] and subsequent hydrolysis [6] liberated the free amine complexes (**5a**, 62%; **5b** 68%) (Scheme 1).

Reformation of the dienyl bonding mode by removal of the C-6 methoxy group from **4a** was performed using HPF_6 in acetic anhydride. In this way, the expected η^5-dienyl intermediate **6a** was formed *in situ*, and spontaneously cyclised to the tricyclic ammonium salt **7a** (74%) (Scheme 2). When the C-2 methoxy substituted complex **4b** was treated with acid in the same manner, the tricyclic ammonium salt **7b** (84%) was formed *via* the rearranged cationic intermediate **6b** (Scheme 2).

The structure of **7b** has been confirmed by X-ray analysis.[7] This reaction demonstrates the utility of the leaving group control methodology and provides feasible access to regioisomeric tricyclic tetrahydrophenanthridine tricarbonyliron complexes. The cyclisations were followed by FT-IR examination of the characteristic metal carbonyl bands.† The cationic inter-



Scheme 1

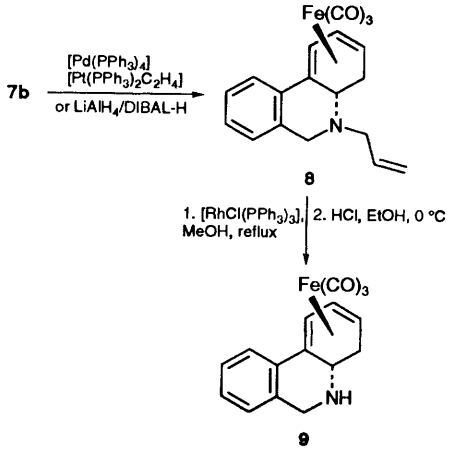


Scheme 2

† Typical carbonyl absorptions of $Fe(CO)_3$-cyclohexadiene/dienyl complexes: neutral Fe^0 ν_{max}/cm^{-1} *ca.* 2040 and 1970; cationic Fe^+ ν_{max}/cm^{-1} *ca.* 2150 and 2050.

mediate **6a** was detected by the presence of high frequency carbonyl bands (ν_{max}/cm^{-1} 2120 and 2072), which disappeared over a period of 3 h. The corresponding IR absorbances of the intermediate **6b** were not detected, indicating the rapid cyclisation of **4b** to the conjugated rearranged product **7b**. Reaction of the sensitive free amine complex **5b** under identical conditions, however, proved to be ineffective; use of a protected amine precursor is needed for the success of acid-promoted cyclisation.

For products of type **7** to be of value as synthetic intermediates, deprotection following the cyclisation step is necessary. At first, transition metal-mediated deprotection reactions were examined. One allyl group was selectively detached by treatment of the ammonium salt **7b** with either $[Pd(PPh_3)_4]$[8] or $[Pt(PPh_3)_2C_2H_4]$[9] to give the mono-allyl amine complex **8** in 60 and 65% yield, respectively. The mixed hydride reagent $LiAlH_4$/DIBAL-H proved more effective and afforded the same mono-deallylated product **8** (73%), whereas the separate use of these reagents gave only unchanged starting material. The fully deprotected tricyclic amine complex **9** (68%) was obtained after treatment of **8** with $[RhCl(PPh_3)_3]$ followed by hydrolysis (Scheme 3).[6]



Scheme 3

Oxidative cyclisations have proved to be particularly effective for the closure of 5-membered nitrogen-containing heterocyclic ring systems.[10] However, the Knölker-type cyclisation procedure (reaction of **5b** with very active MnO_2)[11] was ineffective in our 6-membered ring example. Starting material was recovered (83%) together with a small amount of metal-free material. Two significant differences distinguish our example from the wide range of MnO_2-mediated cyclisations reported by the Knölker group. Successful examples so far employ arylamines to form 5-membered rings. Six-six fused ring systems have not previously been examined. However, since cyclisations of alkylamines to 5-membered rings proceed in low yields[12] it is possible that the lack of an arylamine is the source of the difficulty in our case.

In summary, we have shown that a sequence of two metal-mediated nucleophile additions to tricarbonyliron complexes offers an effective strategy for the formation of 6-membered nitrogen-containing rings. Cyclisation should precede deprotection, and the leaving group-based method appears to be more suitable than the oxidative cyclisation approach for the development of synthetic routes to alkaloids containing six-six nitrogen-fused heterocyclic ring systems.

Experimental

Cyclisation of the Iron Complex **4b**.—HPF_6 (1 cm^3) was added dropwise to a solution of **4b** (316 mg, 0.7 mmol) in acetic anhydride (1 cm^3) under a nitrogen atmosphere at 0 °C. The resulting yellow cloudy solution was stirred for 2 h at 0 °C. Acetonitrile (1 cm^3) was then added and the resulting brown solution was transferred dropwise into ether (100 cm^3). The solid which separated was collected and was washed with water and dry ether to give **7b** (335 mg, 84%) as a lemon-yellow crystalline solid, m.p. 171 °C (decomp.) (from $MeCN/Et_2O$) (Found: C, 48.2; H, 3.9; N, 2.5. Calc. for $C_{22}H_{22}F_6FeNO_3P$: C, 48.1; H, 4.0; N, 2.55%); ν_{max}(MeCN)/cm^{-1} 2057vs and 1989vs (Fe-CO); δ_H(400 MHz; [$^2H_6$]acetone; Me_4Si) 2.31 (1 H, dd, *J* 14.9, 6.2), 2.62 (1 H, ddd, *J* 15.1, 10.3, 4.8), 3.33 (1 H, ddt, *J* 7.9, 4.8, 1.6), 3.79 (1 H, dd, *J* 13.5, 7.1), 3.87 (1 H, dd, *J* 13.5, 7.1), 4.20 (1 H, dd, *J* 13.5, 7.1), 4.29 (1 H, dd, *J* 13.5, 7.0), 4.55 (1 H, d, *J* 15.9), 4.70 (1 H, dd, *J* 0.3, 6.3), 5.18 (1 H, d, *J* 15.9), 5.48 (1 H, dd, *J* 17.1, 1.2), 5.61 (1 H, d, *J* 9.9), 5.79 (1 H, d, *J* 10.7), 5.87 (1 H, dd, *J* 16.7, 1.2), 6.09 (2 H, m), 6.33 (2 H, m), 7.25 (1 H, d, *J* 7.5), 7.41 (2 H, m) and 7.56 (1 H, dd, *J* 8.1, 1.0); δ_C(100 MHz, [$^2H_6$]acetone; Me_4Si) 21.84, 51.54, 55.53, 60.24, 64.31, 69.51, 70.68, 83.75, 93.29, 125.57, 125.80, 127.43, 127.59, 128.61, 128.92, 129.14, 129.45, 129.68, 136.06, 206.44 and 210.96 [Found: *m/z* (FAB) 404.095. Calc. for (M^+ − 145): 404.095].

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