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Studies on the Applications of Arene-Ruthenium Complexes in Synthetic Approaches to Vancomycin: a Mild Procedure for the Selective Formation of Chlorinated Aryl Ethers and Triaryl Diethers

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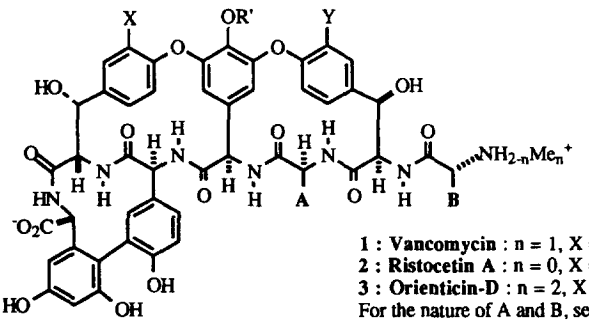
Abstract: Reactions of (η^6-1,3-dichlorobenzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate and (η^6-1,3-dichloro-2-methoxy-benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate with ortho-chlorinated phenolates were found to proceed with excellent selectivity to generate monoarylated ethers under mild conditions. The second halogen may be displaced allowing the synthesis of unsymmetrical and symmetrical triaryl diethers. Methodology for sequential selective displacement of both chlorides by different nucleophiles and a photochemical method for demetallation of the arene-Ruthenium-Cp (η^5-cyclopentadienyl) complexes are reported.

The selective formation of diaryl ethers with sensitive functional groups under mild conditions is an important step in the total synthesis of cyclic peptide/aryl ethers, exemplified by the complex glycopeptides vancomycin (**1**), ristocetin (**2**) or orienticin-(D) (**3**).[1] These molecules present a challenge to the synthetic organic chemist because of the presence of the arylglycine subunit that is sensitive towards racemization. There exist very few methods for diaryl ether formation by direct coupling of two aryl amino acid derivatives. Evans,[2] Yamamura,[3] Boger,[4] Chakraborty,[5] Rao[5] and Zhu[6] groups have reported elegant solutions by using a methodology including Ullmann[7] and cycloamidation coupling reactions but no successful total synthesis of vancomycin has been reported. None of the approaches so far reported allow facile incorporation of the mono-chloro substituants (X and Y = Cl in structure) without difficult multistep operations.

We have already reported new methods by using chloroarene-metal π (metal = Fe, Mn, Ru) complexes as reactive intermediates for the selective formation of diaryl ethers and triaryl diethers under very mild conditions.[8] Use of arene-manganese complexes is limited to monochloro substitution,[9] whereas [arene-FeCp]$^+PF_6^-$ and [arene-RuCp]$^+PF_6^-$ are known to undergo mono and disubstitution.[8] We report herein the first studies for the selective monoarylation and diarylation of [arene-RuCp]$^+PF_6^-$ with *ortho*-chlorinated phenoxides. Our method allows use of protected amino acid derivatives and synthesis of a new class of triaryl diethers that promise to give methodology for the synthesis of molecules in the vancomycin group.

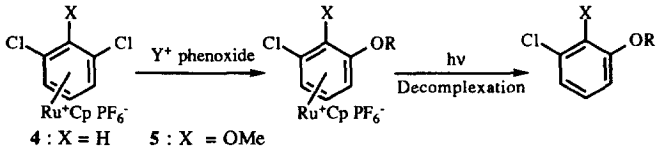


1 : Vancomycin : n = 1, X = Y = Cl (R' = sugar unit)
2 : Ristocetin A : n = 0, X = Y = H (R' = sugar unit)
3 : Orienticin-D : n = 2, X = Y = Cl (R' = sugar unit)
For the nature of A and B, see references 1 and 8

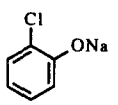
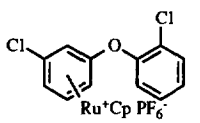
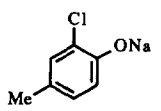
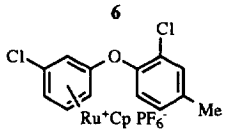
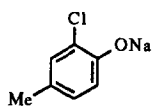
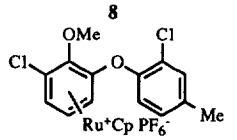
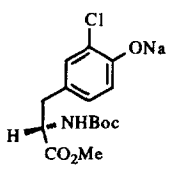
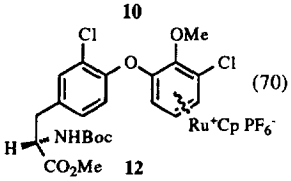
(η^6-1,3-Dichlorobenzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**4**) was prepared by the literature procedure[10] and synthesis of analogue **5** was accomplished by similar procedure in 82% yield. The reactions of **4** and **5** with nucleophiles were investigated in order to obtain pure monoarylated ruthenium

complexes. The selective monoarylation of **4** with *o*-chlorophenol sodium salt under mild conditions (1.15 equiv NaH, THF, -78°C) was problematic and low yielding (25%) because of the presence of the electron-withdrawing chlorine substituent. It was then decided to use a more reactive phenolate with an electron-donating substituent in the *para* position. The monoarylation of **4** with 2-chloro-4-methyl-phenol sodium salt (1.5 equiv NaH, THF, 2 hrs -78°C, 2 h RT) provided **8** in 54% yield whereas monoarylation of **5** with 1.5 equiv sodium phenolate gave the diaryl ether **10** in 92% yield. Monoarylation of **5** with chiral nucleophile, 1 equiv of (L)-3-chloro-N-*tert*-butoxycarbonyl-tyrosine methyl ester[11] sodium salt gave incomplete reaction and a mixture of mono and diarylated ruthenium complexes. After optimization of the reaction conditions (1.4 equiv NaH, 2 hrs -78°C, 1 h RT), we obtained **12** in 70% yield (after purification of the cationic complexes on neutral alumina) as a mixture of diastereoisomeres. ^{1}H NMR showed a mixture of monoarylated and diarylated complexes in a 10:1 ratio (estimated by integration of the cyclopentadienyl protons). Use of n-butyllithium as base gave no reaction. Decomplexation of complexes **6, 8, 10, 12** under mild conditions (irradiation in acetonitrile, General Electric 275W Sun Lamp) under nitrogen at RT for one day)[8d], resulted in complete decomplexation to give the diaryl ether derivatives **7**,[12] **9**, **11** and **13** ($[\alpha]^{24}_D$ = +33.6° (c = 0.5, CH_2Cl_2)) whose structures have been rigorously established.

Table 1. Selective Formation of Chlorinated Aryl Ethers



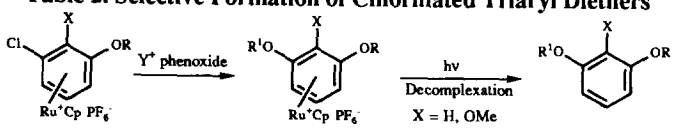
4 : X = H **5** : X = OMe

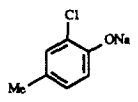
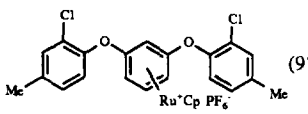
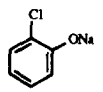
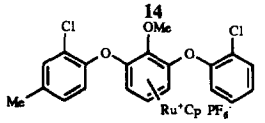
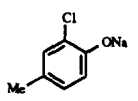
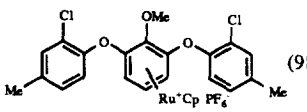
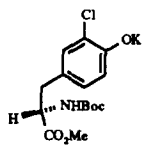
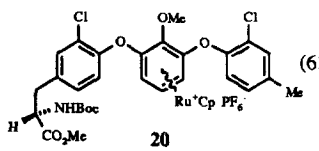
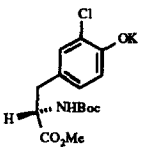
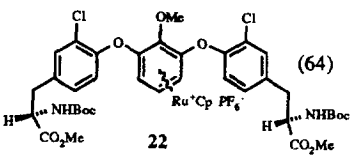
Entry 4 or 5	Phenoxide	Product (%)		Decomplexation product (%)	
4		 **6**	(25)	**7**	(70)
4		 **8**	(54)	**9**	(58)
5		 **10**	(92)	**11**	(85)
5		 **12**	(70)	**13**	(72)

After showing it was possible to generate a new class of chlorinated aryl ethers with monochlorinated phenolates with good selectivity, we investigated the substitution of the second chlorine. Synthesis of the symmetric triaryl diether **14** was attempted using complex **8** and 2-chloro-4-methyl, phenol sodium salt (1.1

equiv in THF); unfortunately, it was impossible to synthesize **14** because of the insolubility of **8** in THF. We finally succeeded by using acetone as solvent, providing **14** in 97% yield. By coupling the complex **10** with *o*-chlorophenol sodium salt, we obtained a mixture of unreacted complex **10** and small quantity of the required product **16**. This mixture was directly decomplexed and **16** was obtained in 20% overall yield. We can say in this case that the presence of an electron-donating group in *para* position is very important. Complex **18** was synthesized with 1.1 equiv of sodium phenolate and by increasing the reaction time (2 h -78°C and 1 day RT) as the reaction was sluggish. Synthesis of complexes **20** and **22** with sodium hydride never gave a total diarylation (either after increasing the base and reaction time) and required modifications to the above conditions. The electron-rich systems **10** and **12** were unreactive towards substitution of the second chlorine. So, we increased the reactivity of the nucleophile by using more reactive phenoxides. Use of 18-crown-6 allowed complete diarylation but it was not possible to separate the ruthenium complexes from 18-crown-6. Finally, the use of 2 equiv of potassium *tert*-butoxide under mild conditions (2 h, -78°C, 2-3 hrs RT) afforded **20** and **22**[13] in 63% and 64% yield respectively (after chromatography on neutral alumina). All complexes **14**, **18**, **20** and **22** were photolytically demetallated as previously to give the triaryl diethers **15**, **19**, **21** $[\alpha]^{24}_D$ = +28.6° (c = 0.5, CH_2Cl_2) and **23** $[\alpha]^{24}_D$ = +39.0° (c = 0.6, CH_2Cl_2) in high yield (88-94%) after chromatography.

Table 2. Selective Formation of Chlorinated Triaryl Diethers



Complex	Phenoxide	Product (%)		Decomplexation product (%)	
8		 **14**	(97)	**15**	(88)
10		 **16**		**17**	Total Yield (20)
10		 **18**	(98)	**19**	(98)
10		 **20**	(63)	**21**	(92)
12		 **22**	(64)	**23**	(94)

The model studies described above have demonstrated it is possible to synthesize selectively monoarylated ruthenium complexes in good yields with *ortho*-chlorinated phenolates. We have shown the phenolate had to contain a *para*-electron donor substituent. The first monoarylation occurs rapidly and uses bases like sodium hydride whereas second arylation needed longer times because of the electron-rich system that did not favor second chlorine substitution. This problem was solved by using potassium *tert*-butoxide which produces a more reactive potassium phenoxide. Our approach allows synthesis of a novel series of chlorinated symmetrical and unsymmetrical triaryl diethers. Yields are acceptable and decomplexation reactions proceed in good yields. These results are promising for synthesis of northern part of vancomycin. Future work will be directed towards the application of this chemistry in synthesis of subunits found in vancomycin.

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13. In cases where the mixtures of products complexes could not be separated, the decomplexation products have been rigorously purified and identified.

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