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Highly Stereoselective Substitution Reactions of Functionalized η^4-[3(E),5(E)-Heptadien-2-ol]iron Tricarbonyl Complexes

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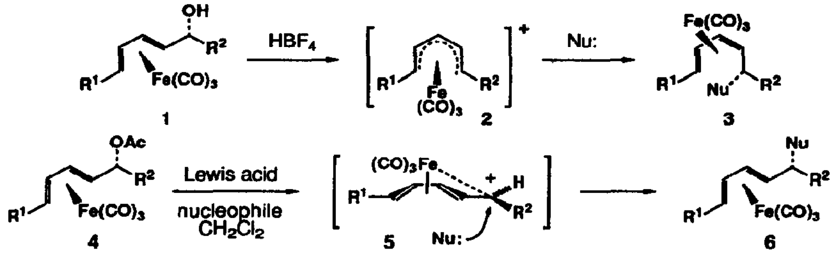
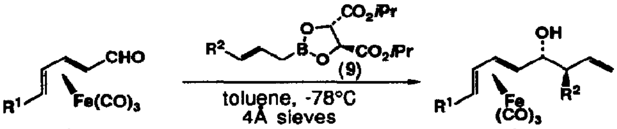
Abstract. Substituted η^4-[3(E),5(E)-heptadien-2-ol)Fe(CO)$_3$ complexes **10a,b**, **11a,b** or the corresponding acetate derivatives **14**, **20**, **23**, **25** and **28** undergo highly stereoselective Lewis acid mediated substitution reactions with various nucleophiles, including R_3Al reagents, ketene silyl acetals, allyltributylstannane, allyltrimethylsilane, and trimethylsilylazide. Evidence is presented that these reactions proceed with retention of configuration.

η^4-Diene iron(tricarbonyl) complexes have found numerous applications in organic synthesis.[1] Of particular interest are the η^5-(pentadienyl)-Fe(CO)$_3$ cation complexes 2 and 5 that are conveniently generated from the corresponding alcohol or acetate complexes.[1-4] The stable, isolable, cisoid cation complex 2 is well known to react with various nucleophiles to give substitution products 3.[2,3] It is believed that the transoid cation 5 is an intermediate in the formation of the cisoid cation 2.[2-4] Uemura and co-workers have generated and trapped the transoid cation complex 5 in the presence of several carbon nucleophiles, and have demonstrated that these reactions are stereospecific, in that the substitution products obtained from the Ψ_{exo} alcohol diastereomers are different than those obtained from the Ψ_{endo} alcohol isomers.[4] Lillya had previously established that the solvolysis reactions of the diastereomeric Ψ_{exo} and Ψ_{endo} η^4-[3(E),5(E)-heptadien-2-yl]Fe(CO)$_3$ dinitrobenzoates proceed with retention of configuration,[5] and based on the results of the Lillya study it has been assumed that substitution reactions of 4 (via 5) with carbon nucleophiles also proceed with retention of configuration.[1,4] We report herein additional studies of the substitution reactions of functionalized η^4-[3(E),5(E)-heptadien-2-ol]Fe(CO)$_3$ complexes and provide concrete experimental evidence that these reactions indeed proceed with retention of configuration.



Our interest in the use of complexes 1 in organic synthesis originated with our observation that racemic diene aldehyde-Fe(CO)$_3$ complexes **7/8** undergo highly efficient kinetic resolution with the tartrate ester modified allylboronates **9a** and **9b**, and that the fast reacting enantiomer of **7/8** is transformed with high diastereoselectivity into the Ψ_{exo} alcohols **10/11**.[6] Moreover, meso complex **12** was found to be an exceptional substrate for the asymmetric allylboration reaction, providing **13a,b** (c.f., **10/11**, R^1 = CHO) with ≥98% e.e. and ≥50 : 1 d.e. The (E)-crotylboration of **12** was recently applied in our synthesis of the *as*-hydrindacene nucleus of ikarugamycin.[7]



7, R^1 = Me
8, R^1 = CO_2Me
12, R^1 = CHO

10, R^1 = Me
11, R^1 = CO_2Me
13, R^1 = CHO

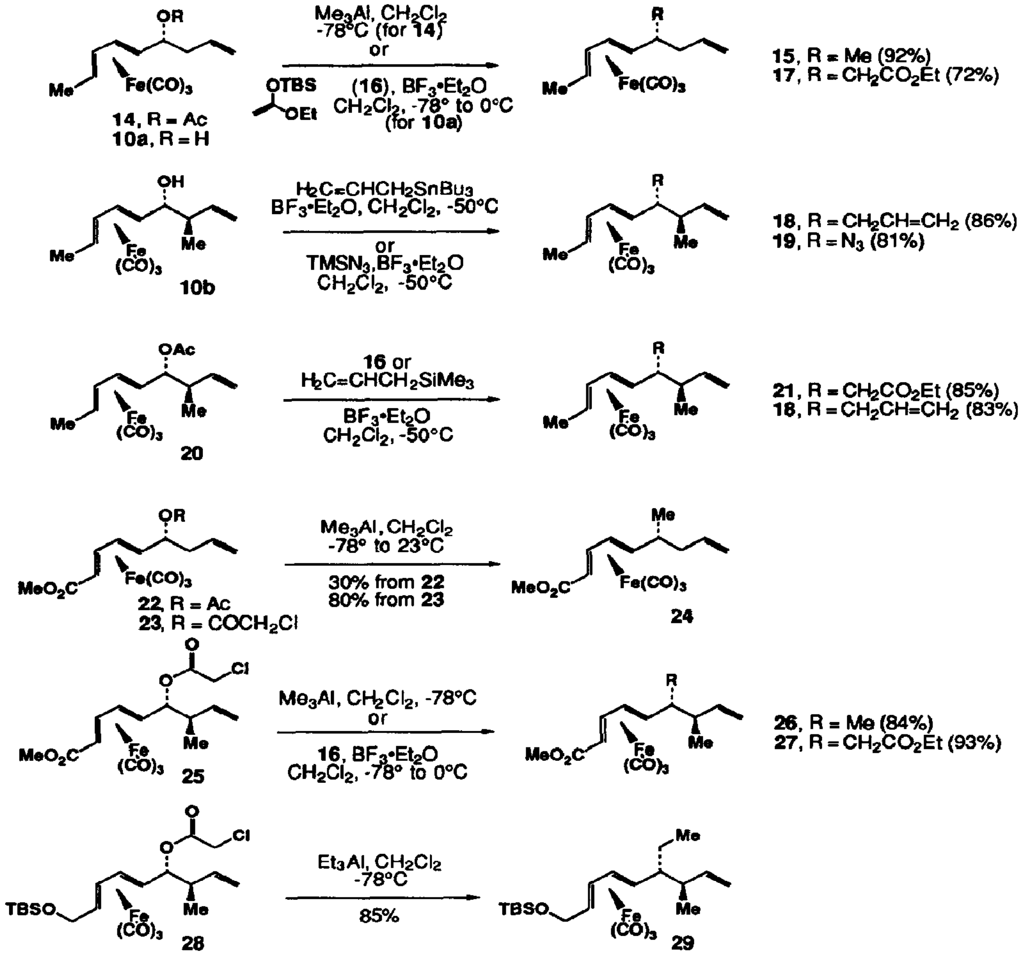
a, R^2 = H
b, R^2 = Me

In planning to use complexes like **10** and **11** in synthesis, it was important to establish unambiguously the stereochemistry of the Uemura substitution process. There was also reasonable concern that the branching methyl substituent of **10b/11b** might slow the rate of the substitution reactions by increasing the steric congestion of the substitution transition state, thereby allowing E_1 processes to compete. These issues were addressed in the studies that are summarized below.

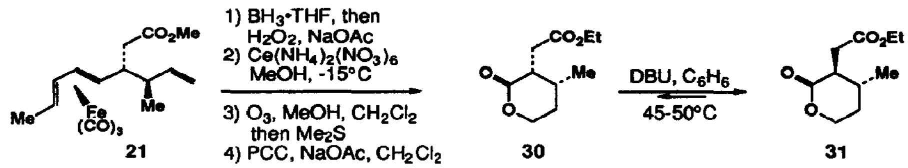
Initial substitution experiments were performed with acetate **14**, prepared from alcohol **10a** under standard conditions. Thus, treatment of **14** with Me_3Al (2 M in toluene, 2 equiv.) in CH_2Cl_2 at -78°C for 30 min provided the alkylation product **15** in 92% yield as the only diastereomer observed by 500 MHz ^1H NMR analysis of the crude reaction mixture.[8] It was of interest to determine if it is necessary to activate the alcohol as an acetate derivative for the substitution reaction. Although alcohols **10a** and **10b** react sluggishly with Me_3Al or Et_3Al, they are excellent substrates for reactions that are performed in the presence of $BF_3 \cdot Et_2O$. For example, treatment of **10a** with ketene silyl acetal **16** (1.5 equiv.) and $BF_3 \cdot Et_2O$ (3 equiv.) at -78°C with warming to 0°C over 30 min provided **17** in 72% yield, again as a single observed diastereomer. Similarly, the reactions of **10b** with either allyltributylstannane (2 equiv.) or trimethylsilylazide ($TMSN_3$; 2 equiv.) in CH_2Cl_2 at -50°C in the presence of 2-3 equiv. of $BF_3 \cdot Et_2O$ provided **18** and **19**, respectively, as the only observed products in 81-86% yield. While the reaction of **10b** with ketene silyl acetal **16** provided ester **21** in 53% yield, much better efficiency (85% yield of **21**) was achieved by using the acetate derivative **20** as the substrate for the substitution reaction. The $BF_3 \cdot Et_2O$ promoted reaction of **20** and allyltrimethylsilane was also highly selective, providing **18** in 83% yield.

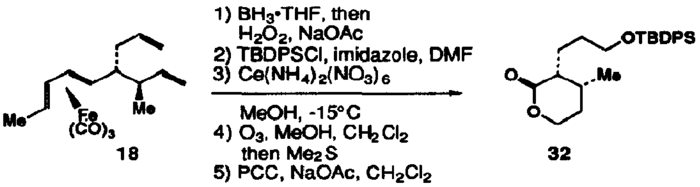
While excellent results were obtained in the substitution reactions of **10a**, **10b**, and/or the corresponding acetate derivatives **14** and **20**, acetate **22** prepared from alcohol **11a** reacted only sluggishly with Me_3Al at -78°C. Reaction occurred at ambient temperature, but provided the desired substitution product **24** in only 30% yield. Suspecting that the electron withdrawing carbomethoxyl substituent was interfering with carbocation formation, the chloroacetate derivative **23** was prepared and shown to react smoothly with Me_3Al at -78°C with warming to ambient temperature, thereby providing **24** in 80% yield. The more hindered chloroacetate derivative **25** (from **11b**) similarly reacted smoothly with Me_3Al or with ketene silyl acetal **16** to give **26** (84%) and **27** (93%) in excellent yield. Finally, use of the chloroacetate leaving group strategy with **28** facilitated the synthesis of the ethyl substitution product **29** (85% yield). The corresponding acetate derivative reacted with Et_3Al at -78°C, but the rate was slowed to the presence of the electron withdrawing TBS ether substituent and competitive displacement of the TBS ether was also observed.

It is clear from these results that the presence of the branching methyl substituents in **10b**, **20**, **25**, and **28** does not compromise the efficiency of the substitution reactions. Product yields (72-95%) are excellent in the majority of cases, and elimination products are very minor, if observed at all. Most importantly, only one diastereomeric substitution product was observed in every example studied. Thus, the substitution reactions of complexes of general structure **1** and **4** appear to have considerable synthetic potential.



The first evidence that the Uemura substitution reaction proceeds with retention of stereochemistry was provided in our synthesis of the *as*-hydrindacene nucleus of ikarugamycin.[7] Additional supporting evidence was obtained as follows. Substitution products **21** and **18** were converted to the lactones **30** and **32** by hydroboration of the terminal vinyl groups and oxidation of the diene system. The ^1H-^1H coupling constants between H(2) and H(3) determined by 500 MHz ^1H NMR analysis were $J_{2,3}$ = 5.7 Hz for **30** and $J_{2,3}$ = 4.2 Hz for **32**, indicative of *cis* stereochemical relationships. This was confirmed by treatment of **30** with DBU in benzene at 45-50°C for 48 h which gave a 2.3 : 1 mixture favoring the 2,3-*trans* lactone isomer **31** which exhibited $J_{2,3}$ = 10.2 Hz. These data require that **18** and **21** have anti stereochemistry at the C(3)-C(4) centers as depicted, and therefore that the substitution reactions that produced **18** and **21** from **10b** and **20** proceeded with retention of configuration. Finally, the stereostructure of azide substitution product **19** was confirmed by a single crystal X-ray analysis.[9] Collectively, these data support the conclusion that these highly stereoselective substitution reactions proceed with retention of configuration, presumably by way of the -Fe(CO)3 stabilized carbocation **5**.





In summary, we have established that highly stereoselective substitution reactions of η^4-(2,4-dienol)-$Fe(CO)_3$ complexes may be achieved with ketene silyl acetal **16**, allyltributylstannane, allyltrimethylsilane, and trimethylsilylazide by using $BF_3 \bullet Et_2O$ to promote ionization of the alcohol leaving group, and that the presence of a branching methyl substituent in substrates like **10b** does not interfere with the substitution process. With less Lewis acidic reagents like Me_3Al and Et_3Al, it is necessary to use acetate leaving groups to achieve acceptable results in the C-C bond forming event. With less reactive substrates like **11a,b** which have substituents that interfere with carbocation formation, use of a chloroacetate leaving group allows substitution to occur readily at -78°C. Finally, evidence has been provided that these reactions proceed with retention of configuration, a result best accommodated by the -$Fe(CO)_3$ stabilized carbocation intermediate **5**. The data summarized herein should facilitate additional applications of this methodology in organic synthesis.

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8. The spectroscopic properties (^1H NMR, ^{13}C NMR, IR, HRMS and/or C,H combustion analysis) of all new compounds were in complete agreement with the assigned structures.
9. We thank Dr. J. C. Huffmann for performing the X-ray structure analysis of **19**. Details are provided in the Indiana University Molecular Structure Center Report No. 94089.

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