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# Neighboring Group Participation by Chromium in Substitution Reactions of ($\eta^6$-Arene)tricarbonylchromium Complexes

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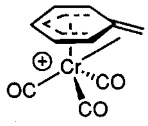
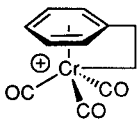
*Summary: ($\eta^6$-Arene)tricarbonylchromium complexes with leaving groups at the $\beta$- or $\gamma$-positions undergo nucleophilic substitution reactions with net retention of stereochemistry via neighboring group participation from the coordinatively saturated chromium atom.*

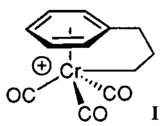
Neighboring group participation is an important mode of chemical reactivity whereby interaction of neighboring groups with reactive centers can alter the regiochemical or stereochemical outcome and rates (anchimeric assistance) of reactions.[1] In organometallic chemistry, such interactions are common at allylic and benzylic positions, but less so at remote positions. ($\eta^6$-Arene)tricarbonylchromium complexes[2] with leaving groups at the benzylic position are known to undergo substitution reactions with net retention of stereochemistry[3] and at faster rates than their noncomplexed counterparts.[4] These properties are central to many recent synthetic applications of arene complexes,[5] and a detailed theoretical picture of the complexed benzylic cation **I** responsible for the observed chemistry is now available.[6] Intriguingly, ($\eta^6$-arene)tricarbonylchromium complexes with $\beta$-position leaving groups also undergo solvolytic substitution reactions with net retention of stereochemistry[7] and enhanced rates.[8,9] In these studies, only an oxygen nucleophile (solvent) was employed. Bly initially proposed and then rejected, on the basis of conflicting rate data,[8b,c] the chromacyclic cation **II** to explain reaction rates and stereochemistry resulting from solvolyses of methanesulfonates $\beta$ to chromium-complexed arenes. Our results from experimental and theoretical studies strongly support the existence of complexed $\beta$-cations and provide a detailed picture of the parent chromacyclic intermediate cation **II** responsible for the observed chemistry.[10] Structures **I** and **II**, which can be viewed as the result of neighboring group participation to ionization by chromium, have closed-shell electron configurations at both chromium and the reactive carbons. These results led us to question whether intermediate **II** might be utilized for formation of carbon−carbon bonds and if neighboring group participation by chromium[11] in substitution reactions might be a more general phenomenon: for example, extending to the $\gamma$-position as in **III**. We report herein that (a) carbon nucleophiles are effective for substitution reactions at the $\beta$-position under ionizing conditions, (b) substitutions with carbon nucleophiles at the $\beta$-position are regioselective and stereoselective for net retention, and (c) substitutions at the $\gamma$-position can also be stereoselective for net retention.



**I**



**II**



**III**

***β*-Position.** As an initial test of chromium, as opposed to phenyl, neighboring group participation for substitution reactions at the $\beta$-position, a simple labeling study was explored, employing a $CD_2$ unit as a regiochemical marker. Under ionizing conditions, 2-phenylethyl substrates react with phenyl group participation via phe-

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10.1021/om000980w CCC: $20.00
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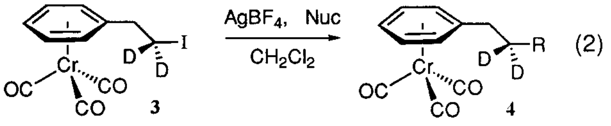
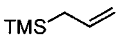
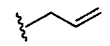
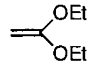
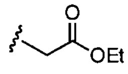
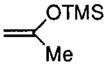
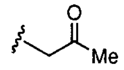
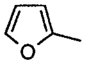
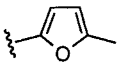
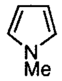
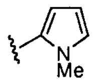
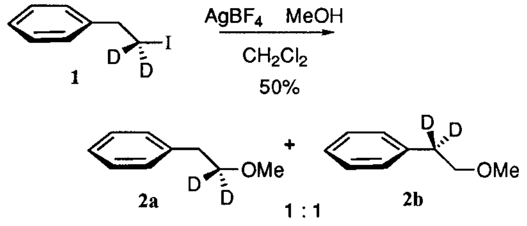
**Table 1**



| Entry | Nucleophile | R | Yield[a] |
|---|---|---|---|
| 1 | MeOH | OMe | 49% (63%) |
| 2 | Et$_3$SiH | H | 61% (75%) |
| 3 |  |  | 68% |
| 4 |  |  | 19% (35%) |
| 5 |  |  | 55% |
| 6 |  |  | 53% |
| 7 |  |  | 39% (60%) |

[a] Yields in parentheses based on recovered starting material.

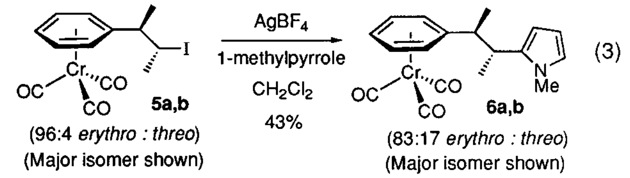
nonium ion intermediates to yield products where the side-chain carbons are scrambled,[12] and this was confirmed with substrate **1** (eq 1).



(1)

In marked contrast to **1**, reaction of complexed iodide **3** under the same reaction conditions (1.1 equiv of AgBF$_4$, 5 equiv of MeOH, CH$_2$Cl$_2$) provided methyl 1,1-dideuterio-2-($\eta^6$-phenyltricarbonylchromium)ethyl ether (Table 1, entry 1) in 49% yield. Notably, the reaction was twice as fast and occurred with *no positional scrambling*.[13] To explore the scope and synthetic utility of this reaction, in particular for carbon–carbon bond formation, a variety of nucleophiles were examined and found to be successful in substitution reactions (Table 1). The yields were modest, but consistent, and rearrangement products were not detected by $^1$H and $^{13}$C NMR analysis. Of particular interest are entries 6 and 7, in which we demonstrate the compatibility of this primary iodide to participate in Friedel–Crafts alkylation reactions.

To test the stereochemical outcome of substitution reactions at the $\beta$-position employing carbon nucleophiles, **5a**,**b** (96:4 *erythro*:*threo*) was prepared by starting from *cis*-2,3-epoxybutane.[14] It is interesting that the stereochemistry of **5a** had to be confirmed by an X-ray structural analysis, since the $^1$H NMR coupling constants between the two methine protons in this and related systems are ambiguous.[15] Treatment of **5a**,**b**, under the same reaction conditions as for **3** above, afforded **6a**,**b** (83:17 *erythro*:*threo*). X-ray structural

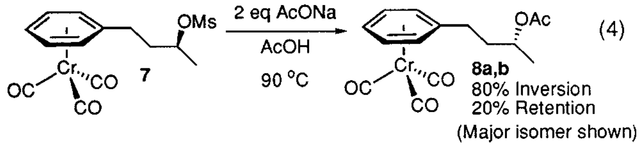


(3)

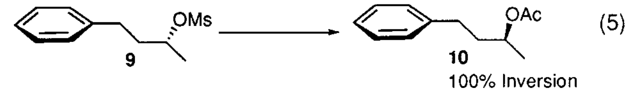
analysis of **6a** determined that the reaction proceeded with 86% *retention of stereochemistry*. While stereoselective Friedel–Crafts reactions are known, most occur with net inversion of stereochemistry.[16]

Presumably, the silver ion in these reactions complexes to the iodine and activates it for d-orbital electrons on chromium to interact with the $\beta$-carbon center. The chromacyclic intermediate **II** is then captured by the nucleophile, producing the substituted product. The regiochemistry, stereochemistry, and qualitative rate enhancements are evidence for neighboring group participation by chromium for ionization of leaving groups at the $\beta$-position and a direct metal–carbon interaction.

**$\gamma$-Position.** These results, coupled with detailed computational studies on chromium centers interacting with remote cations as in chromacyclic intermediates **II** and **III**,[10] led us to propose that participation by chromium in substitution reactions is a more general phenomenon. To test this prediction, optically active substitution substrate **7**, prepared via an enzymatic resolution,[17] reacted under solvolytic conditions (2 equiv of AcONa, AcOH, 90 °C) to give acetates **8a**,**b**. Analysis found that substitution occurred with 80% inversion and 20% retention of configuration (eq 4).[14] As a control reaction, noncomplexed substrate **9** reacted to give substitution with 100% inversion of stereochemistry (eq 5). This latter result was expected from the results of Winstein, who demonstrated that phenyl groups do not participate in solvolyses of leaving groups at the $\gamma$-posi-



(4)



(5)

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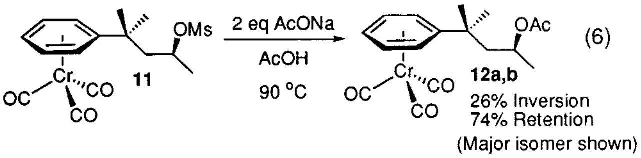
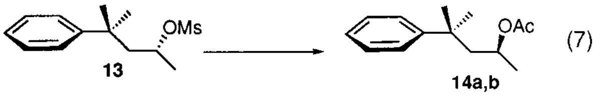
tion.[18] We propose that the 20% of substitution with retention in eq 4 occurred by ionization with net inversion using neighboring group participation from chromium followed by nucleophilic displacement of chromium, also with inversion.[19] Thus, the chromium tricarbonyl moiety *does* participate in the remote substitution reaction, but the rate of reaction in this case is a factor of 4 less than the rate of the competing direct $S_N2$ reaction.

To enhance chromium participation by employing the *gem*-dialkyl effect,[20] substrate **11**[14] was examined (eq 6). Solvolysis (2 equiv of AcONa, AcOH, 90 °C) resulted in substitution with 74% *retention of configuration*. As a control reaction, noncomplexed substrate **13** reacted to give substitution with 91% inversion of stereochemistry (eq 7).[21] These results demonstrate that the chromium atom of an ($\eta^6$-arene)tricarbonylchromium complex can provide neighboring group participation in solvolytic reactions at the $\gamma$-position and that this interaction with a remote cation leads to net retention of configuration in substitution reactions. It is also interesting to point out that, with regard to the phenonium ion, there are no examples of phenyl participation at the $\gamma$-position[12,18] and only a few at the $\delta$-position;[22] thus, these results provide access to a unique mode of reactivity. To obtain 100% retention, further refinements are currently under examination. First, to reduce the rate of the competing direct $S_N2$ reaction, a less nucleophilic system might be used. Second, the chromium atom might be tuned[23] to be more nucleophilic by replacing a CO with a phosphine ligand or by substituting the aromatic ring with electron-donating substituents.



**11** → **12a,b** (6)

26% Inversion
74% Retention
(Major isomer shown)



**13** → **14a,b** (7)

91% Inversion
9% Retention
(Major isomer shown)

Reactions of electrophiles with organometallic complexes at either the ligands or the metal are certainly well-known,[24] especially for protons.[25] However, here we begin to address the question of whether participation by a metal center in a distal ligand-centered reaction can impart changes in the rate, regiochemistry, and stereochemistry of the reaction. We contend that just as benzylic positions exhibit cationic stabilization via direct coordination to chromium (**I**), so can cations at the $\beta$- and $\gamma$-positions (**II** and **III**), barring strong steric demands or cation stabilization,[26] and that this interaction can be utilized for formation of carbon–carbon bonds and control of stereochemistry. Further, this should extend to other metal systems. For example, α-substituted ferrocene complexes undergo substitution with retention of configuration via an intermediate analogous to **I**,[27] and we predict that substitutions at the $\beta$- and $\gamma$-positions could involve metal participation.[28] Studies on the mechanistic implications and synthetic applications of these phenomena are presently underway in our laboratories.

**Supporting Information Available:** Complete experimental procedures and spectral characterization for all compounds and full X-ray structural details for compounds **5a** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Control reaction (7) might be interesting in its own right. Since $\gamma$-phenyl rings do not participate in solvolyses of simple systems,[11,16] one interpretation is that the *gem*-dialkyl effect[18] promotes phenyl participation and the 9% retention results from a double-inversion process rather than a simple racemization. Support for this idea comes from cyclization reactions, where four-membered-ring closure did not occur without *geminal* substituents: (a) Park, S.-U.; Varick, T. R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975–2978. (b) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719–6722.

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