Reactivity of (η^6-Arene)tricarbonylchromium Complexes with Carbenoids: Arene Activation or Protection?

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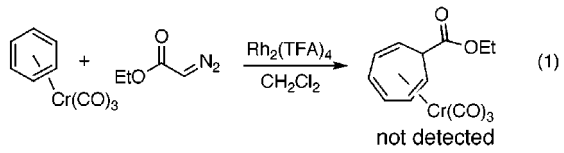
Received July 20, 2001

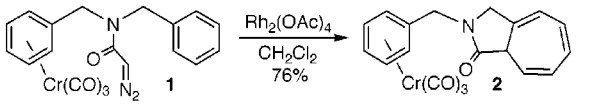
Rhodium-catalyzed reactions of α-diazocarbonyl compounds access a wide range of synthetically important products via electrophilic carbenoid intermediates.[1] Modes of reactivity include cyclopropanation, C−H insertion, heteroatom-H insertion, and ylide generation. Arene substrates, in particular, participate in cyclopropanation, benzylic C−H insertion, and aryl C−H insertion reactions, and this methodology has been elegantly applied in natural product synthesis.[1,2] Chromium complexation dramatically alters the reactivity of aromatic systems.[3] The electron-withdrawing chromium tricarbonyl moiety enhances nucleophilic addition[3a,e] to complexed arenes and also acts to increase the acidity of aryl[3b,f] and benzylic[3c,4] hydrogens. In addition, complexation activates the ring toward radical addition,[5,6] provides a new pathway for electrophilic addition,[5,7] stabilizes benzylic cations,[3e,8,9] and provides for stereoselective radical reactions at the benzylic position,[10] while not modifying the electronic nature of benzylic radicals.[8,9] However, despite numerous investigations on the fundamental reactivity of chromium arene complexes and their application in organic synthesis,[11] their reactivity with carbenes has not been explored. Indeed, consideration of the reactivity of complexed arenes with carbenes leads to several mechanistically intriguing and synthetically important questions: (1) Will the enhanced acidity of aryl and benzylic protons activate C−H insertion at these positions, or will complexation protect the arene? (2) Will cyclopropanation be observed or will complexation prohibit reactivity with electrophilic carbenoids? We report herein selected experiments that address these issues, as well as demonstrate diastereoselective and enantioselective C−H insertions of arene complexes.

In 1885, Buchner and Curtius reported the synthesis of cycloheptatrienes from thermal and photochemical reactions of ethyl diazoacetate with benzene via arene cyclopropanation, followed by electrocyclic ring opening of the intermediate norcaradiene.[12] Nearly a century later, Noels, Hubert, and co-workers discovered that rhodium(II) trifluoroacetate catalysis provided a single isomer of the cycloheptatriene in 98% yield.[13] To investigate the reactivity of arene chromium complexes in the Buchner reaction, benzenechromium tricarbonyl was treated with ethyl diazoacetate and rhodium(II) trifluoroacetate. Unlike benzene, complexed benzene did not yield any addition products (eq 1). Electron-rich *p*-dimethoxybenzenechromium tricarbonyl also failed to react, suggesting that chromium complexation protects arenes from intermolecular carbene addition.



(1)

Intramolecular Buchner reactions are also reported in the literature.[2a,e,14] In particular, Doyle and co-workers used rhodium-catalyzed reactions of *N*-benzyldiazoacetamides to synthesize fused 5,7-ring systems.[15] These substrates inspired an intramolecular competition experiment to compare directly the effect of chromium tricarbonyl complexation on cyclopropanation using pseudo-C_2 symmetric substrate **1**. Reaction of diazoacetamide **1** with rhodium(II) acetate afforded exclusive addition to the noncomplexed ring, with no addition to the complexed ring detected (eq 2). *Thus, in both inter- and intramolecular Buchner reactions, chromium complexation protects arenes from cyclopropanation.*



(2)

One explanation for the protection of complexed arenes from addition is the electron-withdrawing nature of the chromium tricarbonyl moiety which is comparable to that of a nitro substituent.[3a] Carbene additions to electron-poor arenes show

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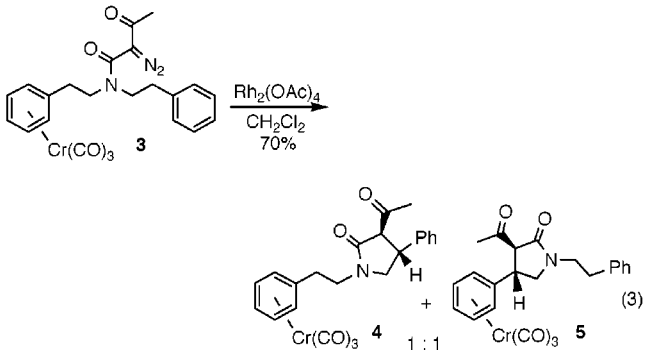
10.1021/ja011767+ CCC: $20.00
Published on Web 10/12/2001

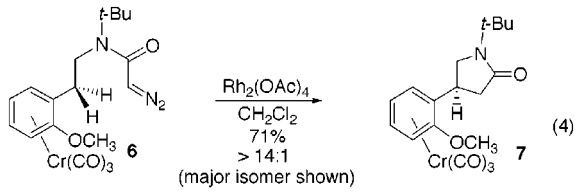
minimal, if any, formation of desired product, with a propensity for benzylic C−H insertion instead.[15,16] This electronic effect is intuitive, after considering the electrophilic nature of the rhodium carbenoid,[1h] and is substantiated by the vast number of electron-rich arenes that undergo cyclopropanation.

The mode of carbenoid reactivity is dependent on the structure of the diazoacetamide, as substrates lacking a β-keto group readily undergo addition to aromatic systems, while benzylic C−H insertion is favored for substrates possessing β-carbonyl groups.[2c,16,17] Since chromium complexation activates benzylic hydrogens for deprotonation, we were curious whether this would also correlate with a preference for benzylic C−H insertion. However, reaction of intramolecular competition substrate **3** resulted in a 1:1 ratio of γ-lactams **4** and **5** (eq 3). Thus, the influence of chromium complexation on benzylic C−H insertion appears to have little, if any, visible effect.



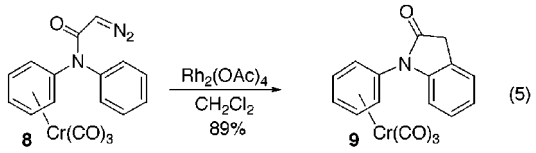
(3)

Since insertion benzylic to a chromium complexed arene is feasible, this methodology can be utilized advantageously in stereoselective synthesis. For example, the diastereotopic nature of benzylic protons in ortho substituted chromium complexed arenes can be exploited to achieve stereoselective benzylic C−H insertion. Thus, *o*-methoxy substrate **6** underwent rhodium-catalyzed benzylic C−H insertion (eq 4) in 71% yield and *>14:1 diastereoselectivity!*[18] In addition, the noncomplexed diazoacetamide analogue of **6** primarily underwent cyclopropanation (67%), with a minor amount of insertion product formed (31%). Thus, this example demonstrates two exciting consequences of chromium complexation: highly diastereoselective benzylic C−H insertion *and* a reversal in reactivity from predominant addition to exclusive insertion.



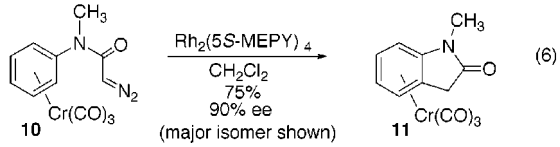
(4)

In the final phase of our investigation, we examined aryl C−H insertion. Previously, Doyle et al. utilized rhodium catalysis for the synthesis of substituted indolinones from *N*-aryldiazoacetamides.[19] This suggested another intramolecular competition experiment to determine the effect of complexation. Due to the increased acidity of aryl hydrogens upon chromium complexation, as well as the enhanced oxidative addition of complexed aryl chlorides in palladium catalyzed coupling reactions,[20] we anticipated a bias for insertion on complexed arenes. In contrast to our predictions, however, treatment of **8** with rhodium(II) acetate provided insertion into the noncomplexed ring as the only observed product (eq 5). *Thus chromium complexation also acts to protect the arene from aryl C−H insertion.* This novel result may have important implications for C−H activation of complexed arenes by transition metal complexes in general.[21]



(5)

To examine the extent of protection, diazoacetamide **10** was reacted with rhodium(II) acetate, as well as with rhodium(II) trifluoroacetate, but both reactions furnished a mixture of products, with the desired indolinone formed in less than 10% yield. Use of a more electron-rich and chiral rhodium catalyst in this system would allow for the synthesis of planar chiral compounds, since the ortho protons are enantiotopic.[22] To our delight, use of Doyle's Rh_2(5*S*-MEPY)$_4$ carboxamide catalyst[23] (eq 6) afforded indolinone **11** in 75% yield and *90% ee!* [18,24] This exciting result leads the way for enantioselective synthesis of chromium complexed arenes via aryl C−H insertion.[25]



(6)

In summary, we demonstrated the dramatic effect of chromium complexation in rhodium-catalyzed reactions of arenes in six modes of reactivity. Complete protection from cyclopropanation was observed in both inter- and intramolecular reactions. Protection was also observed in a rhodium(II) acetate-catalyzed intramolecular aryl C−H insertion competition. However, direct C−H insertion on complexed rings is indeed feasible, and an electron-rich and chiral rhodium catalyst allows for enantioselective formation of planar chiral complexes. Finally, no significant preference between free and complexed arenes was found for benzylic C−H insertion, thus allowing for highly diastereoselective insertions in arene complexes. These results add carbenes to the list of reactive intermediates that show exciting differential reactivity toward free and chromium complexed arenes.

Acknowledgment. We thank Dr. Jennifer Albaneze-Walker of Merck for determining the enantiopurity of **11** and Professor Michael P. Doyle for his generous donation of Rh_2(5*S*-MEPY)$_4$ catalyst.

Supporting Information Available: Experimental procedures and characterization data for all reported compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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