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Intramolecular Addition of Stabilized Enolates to (η^6-Arene)ruthenium Complexes: Synthesis of Ru-Coordinated Azaspirocycles

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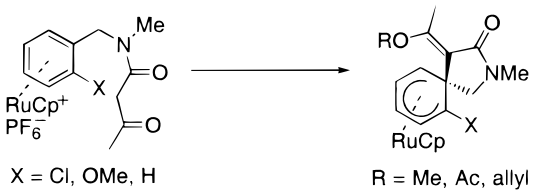
ABSTRACT



Stabilized enolates attached to cationic (arene)Ru^{II}Cp complexes via an amide linkage were found to participate in nucleophilic aromatic addition reactions resulting in the formation of novel cyclohexadienyl–Ru azaspirocycles. Enolate addition to the activated arene ring was found to proceed with complete stereoselectivity.

Arene−metal complexes are well-recognized as versatile intermediates in organic synthesis. The reactivity of an arene ring is dramatically altered upon coordination to a transition metal fragment and normally unfavorable processes, such as nucleophilic aromatic substitution and benzylic deprotonation, are greatly facilitated.[1] Moreover, the metal center is oftentimes capable of acting as a stereocontrol element during synthetic manipulations. Of the (η^6-arene)metal complexes that have been characterized, those involving coordination of a tricarbonylchromium fragment are the most thoroughly investigated and numerous synthetic applications have been reported.[2] Arene complexes incorporating cyclopentadienyl (Cp) iron[3] and tricarbonylmanganese[4] fragments also have received considerable attention. In contrast, (η^6-arene)Ru^{II}Cp cations have been scarcely utilized in organic synthesis although these complexes are easily prepared and exhibit excellent air and moisture stability.[5] Furthermore, methods are available to recover the CpRu^{II} moiety in a reusable form upon removal of the arene ligand.[5a] To date, however, the most significant synthetic applications of (arene)RuCp complexes have been for the preparation of the biaryl ether functionality found in the vancomycin class of antibiotics.[6]

In connection with ongoing efforts aimed at expanding the utility of arene−Ru(II) complexes in synthesis,[7] a potentially versatile means of preparing tetrahydroisoquino-

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(2) (a) Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 517−549. (b) Uemura, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press Ltd.: Greenwich, CT, 1991; Vol. 2, pp 195−245.

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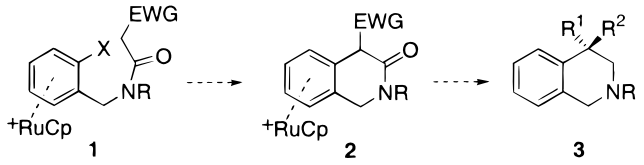
line derivatives that would exploit both the activating and stereodirecting effects of a $CpRu^{II}$ fragment was devised. The approach (Scheme 1) was envisioned to proceed via

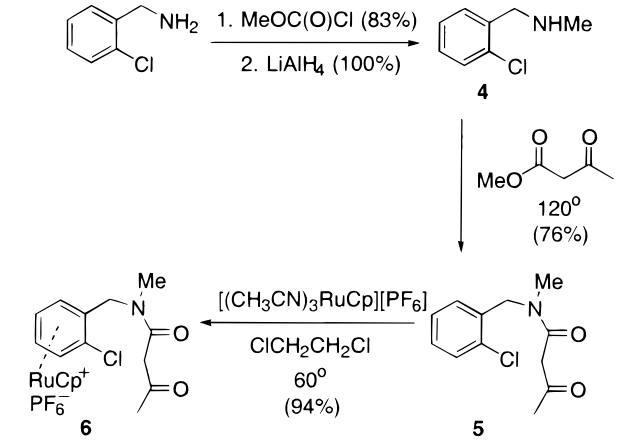
Scheme 1



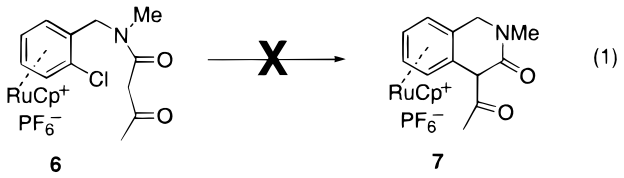
intramolecular nucleophilic aromatic substitution between a stabilized enolate and a haloarene functional group present in complex **1** to provide complex **2**. Stereoselective alkylation at the benzylic position[7] and functional group manipulation (including decomplexation) would ultimately yield **3**.

To determine the feasibility of this approach, a $CpRu^{II}$ complex of the type **1** was required. A suitable arene ligand (**5**) was prepared in high yield via routine functional group manipulation starting from 2-chlorobenzylamine (Scheme 2).

Scheme 2



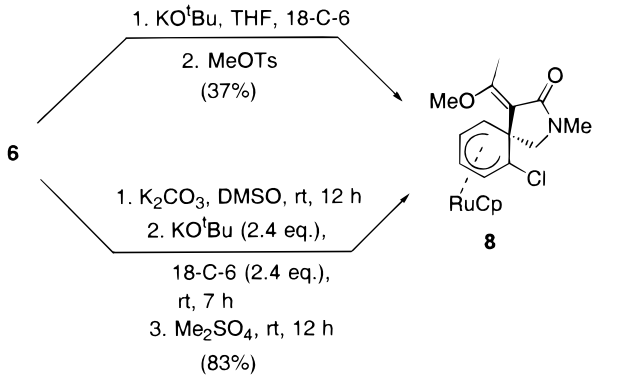
Successful η^6-coordination of **5** to a $CpRu^{II}$ moiety using Mann's procedure[5a] was not, however, a forgone conclusion given the presence of a potentially competitive β-dicarbonyl ligand.[8] Gratifyingly, treatment of **5** with $(CH_3CN)_3RuCp^{\bullet}PF_6$ in warm 1,2-dichloroethane resulted in smooth complexation of the aromatic ring and **6** was isolated as a crystalline solid in excellent (94%) yield.[9] Stabilized enolates generated from β-dicarbonyl compounds are known to participate in *inter*molecular nucleophilic aromatic substitution reactions with (haloarene) transition metal complexes;[10] consequently, the *intra*molecular substitution of the chlorine atom in **6** was not anticipated to be a difficult transformation. Unfortunately, all attempts to convert **6** to **7** (eq 1) resulted



in either formation of intractable mixtures or recovery of unreacted starting material. This reaction was attempted under both basic (K_2CO_3/DMSO; NaH/THF; NaH/DMF; Ag_2CO_3/THF; KO^{t}Bu/^{t}BuOH; KOH/H_2O/DMSO) and acidic (TFA/THF) conditions at various temperatures, all to no avail.

Unwilling to accept that the activated arene present in **6** was unreactive, an effort was made to trap any intermediate species formed by initial nucleophilic addition to the aromatic nucleus. Thus, a THF suspension of **6** was treated with KO^{t}Bu and 18-crown-6 (18-C-6) and heated to reflux (Scheme 3). After several hours, methyl tosylate (MeOTs)

Scheme 3



was added, and the reaction was maintained at reflux several additional hours. Analysis of the reaction mixture by thin-layer chromatography revealed the presence of a new UV-active compound. Isolation and purification of this material using flash column chromatography (SiO_2) afforded a colorless crystalline solid assigned the novel structure **8** on the basis of extensive 1D and 2D-NMR spectroscopic

(9) All new compounds exhibited spectral (^{1}H-NMR, ^{13}C-NMR, and IR) and analytical (combustion analysis) data consistent with the assigned structures.

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(11) All crystallographic data will be deposited in the Cambridge Structural Database.

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(14) Complexes **9** and **10** were prepared from the corresponding benzylamines using a route analogous to that shown in Scheme 2.

analysis.[9] Confirmation of this structural assignment was secured through single-crystal X-ray diffraction and the molecular structure of **8** is shown in Figure 1.[11] Evidently,

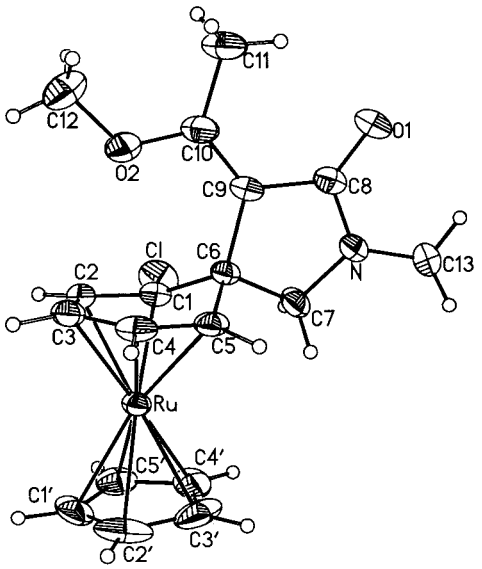


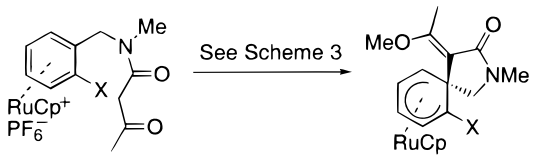
Figure 1. X-ray structure of cyclohexadienyl Ru complex **8**.

under these reaction conditions the stabilized enolate generated by deprotonation of **6** adds regio- and stereoselectively to the *ipso* carbon from the face opposite the Ru center to form the observed neutral spirocyclic cyclohexadienyl−cyclopentadienyl−Ru(II) complex. Further deprotonation of the initially formed spirocycle results in production of a second stabilized enolate that is then trapped via O-alkylation to afford the *E*-enol ether exclusively. Currently, it is not known whether the spirocyclic ring system represents the thermodynamically favored arene addition product or whether subtle conformational effects operative in the benzylamide substituent are responsible for the observed regioselectivity. Whatever the underlying reason for the formation of **8**, this organometallic complex possesses an intriguing structure that merits further discussion. First, **8** exhibits remarkable stability as a solid and in solution. Crystals of **8** can be stored at room temperature open to the air for extended periods of time with no evidence of decomposition. The complex also is amenable to purification by flash column chromatography. Finally, while simple cyclohexadienyl cyclopentadienyl complexes of Ru(II) have been prepared and spectroscopically characterized by addition of nucleophiles (hydride, RLi) to arene complexes,[5b,12] **8** appears to be the first such complex structurally characterized via X-ray crystallography.

While the formation of **8** was unexpected, the transformation depicted in Scheme 3 may represent a potentially general route to important azaspirocyclic ring systems. Moreover, the formation of spirocycles via intramolecular nucleophilic addition to arene−metal complexes is a rarely observed reaction manifold. In fact, it appears the only other notable examples of such a process involve formation of carbocyclic spirocycles via nucleophilic addition to certain arene−chromium complexes as first reported by Semmelhack nearly 20 years ago.[13] Thus, efforts were directed toward optimizing conditions leading to spirocyclic products and toward obtaining an initial indication of the generality of the reaction. A number of reaction conditions were screened in the course of this study, and the best isolated yield of **8** (83%) was obtained using the protocol illustrated in Scheme 3 (lower arrow). Dimethyl sulfoxide proved to be a superior solvent as compared to THF, DMF, and CH_3CN. The use of KO^{t}Bu as well as K_2CO_3 and the addition of 18-C-6 also were important for obtaining high yields of **8**. Finally, dimethyl sulfate (Me_2SO_4) proved to be a more effective electrophile than methyl tosylate.

With the identification of an acceptable set of reaction conditions, the influence of substituents on the arene nucleus was next examined. As shown in Scheme 4, neither the

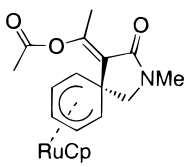
Scheme 4



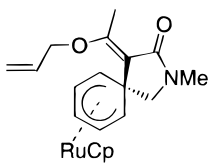
9 X = OMe
10 X = H

11 X = OMe (67%)
12 X = H (68%)

presence of a strong electron-donating substituent in the *ortho* position (**9**, X = OMe) nor the absence of a substituent (**10**, X = H) had a profound effect on the efficiency of spirocycle formation.[14] In each case the spirocyclic products (**11** and **12**) were isolated as single stereoisomers, the structures being assigned on the basis of extensive NMR spectroscopic measurements and by analogy to **8**.[9] The modest decrease in isolated yield observed in the preparation of **11** and **12** relative to **8** may be indicative of a small electronic substituent effect and experiments are underway to determine if this is the case.[15] Complex **10** was chosen to assay the suitability of alternative electrophiles in the reaction. Substituting Ac_2O for Me_2SO_4 in Scheme 4 resulted in stereoselective formation of enol acetate **13** in 64% yield, whereas use of allyl tosylate led to isolation of allyl vinyl ether **14** in somewhat more modest (27%) yield, again as a single stereoisomer.[9] Allyl bromide was found to be an ineffective reaction partner.



13 (64%)



14 (27%)

In conclusion, a novel, stereoselective, and potentially general route for the preparation of stable azaspirocyclic

cyclohexadienyl−cyclopentadienyl−Ru(II) complexes has been uncovered. Significantly, removal of the azaspiro[4,5]-decane ligand from the metal center would provide access to highly functionalized compounds structurally related to several classes of biologically active natural products, such as the triticones,[16] spirostaphylotrichins,[17] histrionicotoxins,[18] and certain *Nitraria* alkaloids.[19] Studies aimed at achieving this goal are underway. Additionally, the scope and limitations of this methodology, particularly as a means of accessing alternative spirocyclic ring systems, is also being examined. Finally, it is noteworthy that *ortho*-disubstituted arene−Ru complexes (e.g., **6** and **9**) potentially are available as optically pure planar−chiral materials which would allow for the construction of azaspirocyclic ring systems with control of absolute stereochemistry.

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Supporting Information Available: Complete crystallographic details for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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