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Metal-mediated dearomatization leading to 2-azaspiro[4.5]decanes via tandem nucleophilic aromatic addition–Horner–Wadsworth–Emmons olefination–oxidative demetalation sequences

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ABSTRACT

A ruthenium-mediated dearomatization sequence has been developed that delivers structurally intriguing azaspirolactam products in stereoselective fashion. Treatment of (η^6-arene)Ru(cyclopentadienyl) complexes bearing *N*-benzyl-β-amido phosphonate side chains with excess NaH results in intramolecular nucleophilic aromatic addition to the *ipso* position of the coordinated arenes. Subsequent Horner–Wadsworth–Emmons (HWE) reaction with added aldehydes affords olefinated spirolactam cyclohexadienyl ruthenium complexes. Mild oxidation with $CuCl_2$ or $CuBr_2$ under CO effects removal and recovery of the CpRu(II) fragment. Substituents present on the cyclohexadienyl skeleton influence the outcome of demetalation and products obtained in this study include functionalized 2-azaspiro-[4.5]decanes and tetrahydroisoquinolinones.

1. Introduction

Arene metal complexes are versatile organometallic reactants well recognized as useful synthetic intermediates. Applications of η^6-arene complexes usually capitalize upon the ability to functionalize the coordinated arene via normally unfavorable reaction manifolds. Common transformations of arene complexes include nucleophilic aromatic addition and substitution, arene deprotonation, and benzylic deprotonation.[1] The transition metal fragment plays a dual role in these transformations by activating the arene ligand toward reaction with nucleophiles/bases while also serving as a stereocontrol element. Thus, reactions such as nucleophilic aromatic addition and benzylic deprotonation/alkylation proceed with high levels of diastereoselectivity from the face opposite the metal center. This inherent stereoselectivity has been harnessed in asymmetric syntheses employing planar chiral derivatives.[2] The most extensively investigated type of arene metal complex is that incorporating a tricarbonyl chromium fragment, and such complexes have been widely used in organic chemistry for several decades. Aside from chromium(0), metalated arenes of manganese(I), iron(II), and ruthenium(II) have also been examined in the context of organic synthesis.

While the chemistry of (η^6-arene)ruthenium complexes is not as well developed when compared to Cr(0) congeners, these materials exhibit several desirable characteristics that render them potentially attractive as synthetic building blocks. For example, arene ruthenium complexes, particularly (η^6-arene)RuCp cations (Cp=cyclopentadienyl) are readily prepared in high yield using standard bench-top techniques and, in general, are easily handled air- and moisture-stable compounds.[3] Arene ligands coordinated to a CpRu(II) fragment display a convenient level of reactivity toward a wide range of nucleophiles so that processes such as nucleophilic aromatic addition/substitution proceed efficiently under mild conditions.[4] It is also possible to recover the CpRu(II) fragment in a reusable form upon removal from a functionalized arene ligand.

As part of a program aimed at exploiting the largely untapped reactivity of (arene)Ru(II) complexes in synthesis, we have previously reported the ruthenium-mediated dearomatization of *N*-benzyl acetoacetamide complexes (e.g., **1**) to metal-free spirolactams such as **3** using a protocol that entails sequential intramolecular nucleophilic aromatic addition, enolate O-alkylation, and oxidative demetalation (Scheme 1).[5] Dearomatization reactions, particularly metal-mediated variations, possess significant synthetic potential[6] and spirolactams such as **3** represent intriguing heterocyclic building blocks. Consequently, it was disappointing to find that while a number of acetoacetamide-functionalized (η^6-arene)Ru complexes participated in the tandem spirocyclization/enolate trapping process to afford stable (cyclohexadienyl)Ru intermediates (e.g., **2**),[5a] efficient oxidative demetalation was

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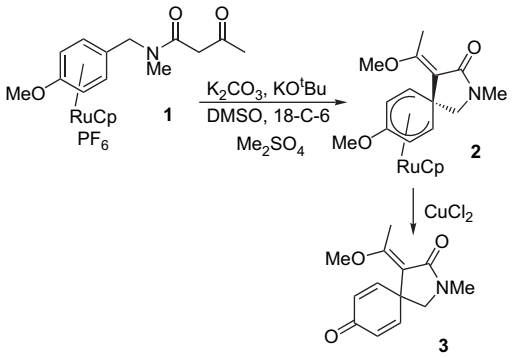
restricted to only certain electron rich derivatives.[5b–d] In addition, the requirement for enolate O-alkylation further limited the range of spirolactams accessible via this methodology. The presence of a peripheral acid-sensitive enol ether group also affects the stability of cyclohexadienyl products (**2**) and may have contributed to our inability to uncover more general demetalation procedures.



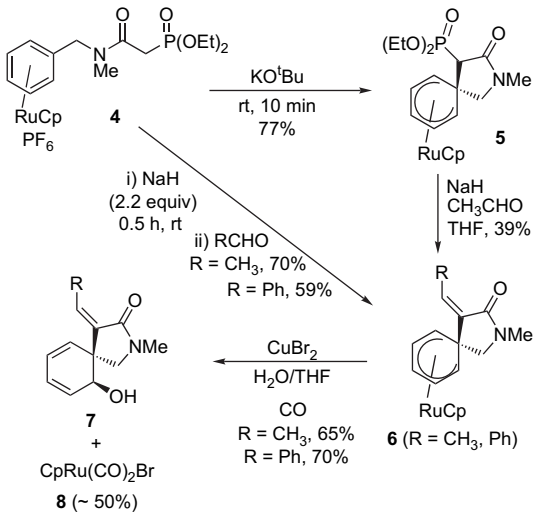
Scheme 1.

With these shortcomings in mind, alternative spirocyclization substrates were designed with the aim of accessing more substituted (hence more versatile) lactams structurally related to **3** in a stereocontrolled fashion. In this context, (arene)Ru complexes possessing β-amido phosphonate side chains were particularly intriguing as it was envisioned that such complexes may participate in intramolecular nucleophilic aromatic addition to produce phosphonate-substituted spirolactams. Subsequent Horner–Wadsworth–Emmons (HWE) olefination could then be used to introduce a variety of substituents onto the periphery of the lactam ring while avoiding generation of acid-sensitive enol ethers. Indirect precedent for the individual steps of the proposed reaction sequence can be found in reports from Müller and Martín that describe the preparation and utilization of relatively simple (η^6-benzyl phosphonate)$Cr(CO)_3$ complexes in side-chain olefination reactions with various aldehyde partners.[7,8] Müller has also reported the synthesis of more elaborate arene-metalated benzyl phosphonates through side-chain manipulations.[9] Additionally, phosphoryl-stabilized carbanions have been found to participate in intermolecular S_NAr reactions with chloroarene iron and chromium complexes, thus these anions appear to be sufficiently nucleophilic for reaction with π-coordinated arenes.[10] The feasibility of performing these individual transformations in tandem on an arene ruthenium platform, however, was unknown at the outset of our studies.

Gratifyingly, the desired reaction sequence described above proved to be largely successful as outlined in Scheme 2.[11] The preparative route was further simplified by application of a two-step/one-pot sequence for the preparation of olefinated spirolactam **6** from (η^6-arene) complex **4** without isolation of the intermediate phosphonate **5**. Moreover, **6** was found to be susceptible to stereoselective nucleophilic oxidative demetalation which, if performed under a CO atmosphere, resulted in recovery of the CpRu(II) fragment.[11] This article presents a complete account of initial investigations into the scope and limitations of these unique Ru-assisted dearomatizations involving *N*-benzyl-β-amido phosphonate complexes. The prospects for developing asymmetric dearomatization sequences are also discussed.

2. Results and discussion

The preparation of arene ruthenium complexes of the type **4** proved to be exceedingly straightforward. *N*-Methyl benzyl amines



Scheme 2.

were first acylated with chloroacetyl anhydride and then subjected to Arbuzov reaction with $P(OEt)_3$. The resulting β-amido phosphonates were then treated with $[(CH_3CN)_3RuCp][PF_6]$[12] in warm 1,2-dichloroethane to afford Ru-coordinated arenes in high overall yields. An initial concern over the reaction sequence illustrated in Scheme 2 was the fate of the anion generated upon deprotonation of an amido phosphonate side chain. An unfavorable equilibrium between an uncyclized zwitterionic species (i.e., arene ruthenium cation and α-phosphonate anion) and the neutral spirocyclic cyclohexadienyl complex (such as **5**) would jeopardize the success of the overall transformation. Encouragingly, however, exposure of **4** to an equimolar amount of KO^{t}Bu in THF-d_8 rapidly and quantitatively produced the desired spirocycle **5** as evidenced by the disappearance of signals corresponding to arene hydrogens and the appearance of signals consistent with a cyclohexadienyl ligand. Additionally, the Cp hydrogens experienced an upfield shift from ~5.5 ppm in the η^6-complex to ~4.8 ppm in **5**. The phosphonate **5** appears to be relatively stable, although isolation and purification were complicated by the polar nature of the material. The difficulty encountered in purifying **5** may be responsible for the modest efficiency of subsequent HWE olefination with acetaldehyde and NaH. Consequently, a higher yielding and experimentally simpler one-pot reaction was developed. The η^6 complexes (e.g., **4**) were dissolved in THF or DMF and treated with an excess of NaH (2.2 equiv) at room temperature for 30 min. Addition of an aldehyde then produced stable cyclohexadienyl complexes in good yield.[11] As expected, nucleophilic aromatic addition occurred exclusively from the face opposite the CpRu fragment. The subsequent HWE reaction was also stereoselective, giving *Z*-configured exocyclic olefins (geometry was assigned on the basis of 2D NMR experiments).[13]

With an initial procedure for the preparation of olefinated spirolactam complexes seemingly established, suitable methods for completing the dearomatization sequence via removal of the CpRu(II) fragment were next considered. Before exploring the feasibility of nucleophilic oxidative demetalation (shown in Scheme 2) we first sought to build on previous work that had demonstrated the viability of performing oxidative demetalations on electron rich cyclohexadienyl complexes (such as **2**).[5b,c] Toward this end, several 4-methoxy-substituted cyclohexadienyl ruthenium complexes (**9**)[11] (prepared from the corresponding *p*-methoxy benzyl amide derivatives) were treated with $CuCl_2$. In each case conversion to the desired metal-free cyclohexadienone spirolactam was observed and the organic products **10a–f** were isolated in good yield (Table 1). The one exception to this trend is encountered in entry **f**