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## Exploiting Phosphonate Chemistry in Metal-Mediated Dearomatization: Stereoselective Construction of Functionalized Spirolactams from Arene Ruthenium Complexes

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 $\eta^6$ -Arene metal complexes are well recognized as versatile synthetic intermediates due to the facility with which the arene ligand can be functionalized.<sup>1</sup> In recent years, developing stereo-contolled methods suitable for efficiently converting such complexes into nonaromatic (alicyclic) products has attracted renewed interest.<sup>2</sup> Recent examples of diastereoselective metal-mediated dearomatization involving tricarbonyl Cr(0) and Mo(0) arene complexes have been reported.<sup>3,4</sup> More reactive cationic arene Mn(CO)<sub>3</sub> complexes have also been elaborated to substituted cyclohexadienes.<sup>5</sup>

Arene ruthenium complexes, particularly those incorporating a CpRu(II) fragment, are easily prepared in high yield using conditions compatible with functionalized arene ligands.<sup>6</sup> Their use as synthetic building blocks, however, has not been extensively explored, and aside from our own work, reaction manifolds leading to nonaromatic products are virtually unknown.<sup>7</sup> In this context, we have found that readily available benzyl amide ruthenium complexes can be converted to diastereomerically pure metal-free spirolactam derivatives. This net Ru-mediated dearomatization is accomplished via intramolecular nucleophilic aromatic addition of a phosphonate anion to an electrophilic (arene)Ru moiety followed by HWE olefination. The resulting cyclohexadienyl ruthenium products are then subjected to stereocontrolled nucleophilic demetalation performed under oxidative conditions.

Previously, we have reported the preparation of spirolactams exhibiting the 2-azaspiro[4.5]decane framework (e.g., 1) from methoxy-substituted ( $\eta^6$ -*N*-benzyl acetoacetamide)RuCp<sup>+</sup> complexes (2).<sup>8</sup> The conversion  $2 \rightarrow 1$  entails tandem nucleophilic aromatic addition/enolate O-alkylation, followed by oxidative demetalation. While effective, the procedure suffers from several



shortcomings, notably the modest isolated yields sometimes encountered in the enolate alkylation step, the necessary inclusion of an acid-sensitive enol ether in the lactam periphery, and the requirement of a strategically positioned methoxy substituent in order to achieve controlled demetalation. We have largely ameliorated these drawbacks through the use of *N*-benzyl- $\beta$ -amido phosphonates as spirolactam precursors.

The decision to examine  $\beta$ -amido phosphonates as spirocyclization substrates was predicated upon the following considerations: generation of a nucleophilic phosphonate anion capable of participating in aromatic addition reactions should be straightforward; the

3498 J. AM. CHEM. SOC. 2006, 128, 3498-3499

 Table 1.
 Construction of Olefinated Spirocyclic Lactam Ruthenium Complexes



products of such a reaction (i.e., cyclohexadienyl complexes) would retain a phosphonate group, thereby potentially allowing further elaboration via inter alia olefination reactions; the enamide products obtained after olefination would be devoid of acid-sensitive enol ether groups. This last feature was viewed as particularly desirable as it was hoped that the added stability of such complexes would facilitate development of truly general demetalation procedures.

The preparation of arene ruthenium substrates possessing  $\beta$ amido phosphonate side chains (3, 4) was accomplished in high yield using standard organic/organometallic procedures (see Supporting Information). Gratifyingly, treatment of 3 or 4 in THF (or DMF) with excess NaH at room temperature for  $\sim$ 30 min followed by addition of aldehyde afforded the desired azaspirocyclic ruthenium complexes (Table 1). Several aliphatic and aromatic aldehydes were employed in this reaction, and all were found to provide Z-configured olefinated lactams stereoselectively. Acetone and cyclohexanone, however, were not effective participants, and other ketones were not investigated. Deprotonation of the activated methylene group in the arene ruthenium side chain presumably leads to rapid spirocyclization with nucleophilic aromatic addition occurring exclusively from the face opposite the RuCp fragment. It is noteworthy that incorporation of an electron-donating methoxy group para to the amido phosphonate side chain (i.e., 4) has no noticeable effect upon the efficiency of this process. A second in situ deprotonation then generates a reactive phosphonate anion that

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participates in Horner–Wadsworth–Emmons olefination after addition of the aldehyde component. Cyclohexadienyl complexes 5-14 (Table 1) were obtained as air-stable materials in yields ranging from good to excellent after isolation via conventional purification techniques (recrystallization and/or silica gel chromatography).

Methoxy-functionalized cyclohexadienyl ruthenium products display reactivity similar to their enol ether-derived counterparts (vide supra)<sup>8b</sup> in that direct oxidative demetalation could be accomplished simply by treatment with a mild oxidant such as CuCl<sub>2</sub>. Thus, exposure of **10** to the conditions indicated in eq 1 afforded the corresponding metal-free azaspirocyclic dienone **15** in good yield. Significantly, *unsubstituted* cyclohexadienyl complexes also proved to be viable substrates for demetalation under slightly modified reaction conditions. As illustrated in eq 2,



treatment of **5** with CuBr<sub>2</sub> in MeOH under a CO atmosphere resulted in clean conversion to methoxy-substituted diene **16**. Moreover, **16** was obtained as a single diastereomer exhibiting the relative stereochemistry shown. In addition, the CpRu(II) fragment was also recovered from the reaction in the form of bromodicarbonyl adduct **17**.<sup>9</sup>

Methoxy diene **16** is envisioned to evolve from nucleophilic addition of methanol to one terminus of a cyclohexadienyl cationlike species generated via oxidation of **5**. The stereochemical outcome reflects nucleophilic addition to the dienyl ligand from the face opposite the Ru fragment.<sup>10</sup> Performing the transformation under a blanket of CO (as compared to Ar) resulted in higher isolated yields of **16** (presumably through decomplexation of an  $\eta^4$  intermediate) and provided a convenient means of recovering the transition metal center. Cupric bromide proved to be a more efficient oxidant than CuCl<sub>2</sub> in this transformation, an effect that we ascribe to the better solubility of CuBr<sub>2</sub> in organic solvents.

The scope of the nucleophilic oxidative demetalation depicted in eq 2 has been briefly investigated. Performing the reaction in a mixture of THF/H<sub>2</sub>O leads to dienol products as shown in Scheme 1. In each case a single diastereomer exhibiting the relative stereochemistry indicated is obtained. Facile addition of H<sub>2</sub>O to the cyclohexadienyl ligand in substrates such as **5** and **9** not only

## Scheme 1





provides access to potentially synthetically versatile heterocyclic building blocks but also presents an opportunity for development of asymmetric versions of this spirocyclization method. Our initial approach toward achieving this latter objective entails utilization of a chiral nonracemic  $\alpha$ -substituted benzylamine as a ruthenium ligand precursor and is illustrated in Scheme 2. Conversion of (*S*)-(-)- $\alpha$ -methyl benzylamine (>98% ee) to arene ruthenium complex **20** was easily accomplished. Tandem intramolecular nucleophilic aromatic addition/intermolecular HWE olefination afforded cyclohexadienyl complex **21** in high yield. It was anticipated that the presence of the  $\alpha$ -methyl substituent would influence the regioselectivity of nucleophilic addition to the diastereotopic cyclohexadienyl ligand. This, indeed, proved to be the case as exposure of **21** to conditions of nucleophilic oxidative demetalation gave dienol (-)-**22** as a single diastero- and enantiomerically pure stereoisomer.

In conclusion, an experimentally mild and stereoselective ruthenium-mediated dearomatization procedure has been developed in which simple and readily available (arene)Ru(II) complexes are converted to unique and heavily functionalized 2-azaspiro[4.5]-decane derivatives. This approach has coupled activating and stereodirecting effects of a CpRu(II) fragment with organophosphonate chemistry in order to access this pharmacologically intriguing heterocyclic ring system.<sup>11</sup> We are currently exploring the utilization of azaspirodecanes as synthetic building blocks while also investigating other Ru-promoted dearomatization reaction manifolds

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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