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Intramolecular nucleophilic aromatic substitution reactions of (η^6-arene)ruthenium complexes: preparation of substituted 2-tetralones

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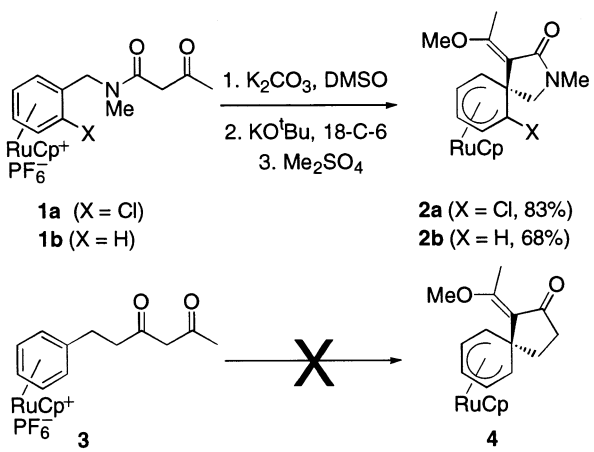
Abstract—A stabilized enolate attached with a carbon tether to a cationic (η^6-arene)Ru^{II}Cp moiety was found to participate in an intramolecular S_NAr reaction to deliver Ru-coordinated 1-acetyl-2-tetralone. Nucleophilic aromatic substitutions involving substituted β-dicarbonyl nucleophiles proceeded with concomitant deacetylation to afford 1-alkyl-2-tetralone derivatives. The 2-tetralone products were found to be amenable to further stereocontrolled elaboration via benzylic alkylation. © 2000 Elsevier Science Ltd. All rights reserved.

Cationic (η^6-arene)ruthenium(II) complexes are easily prepared air and moisture stable materials. The coordinated arene ring in this organometallic species exhibits a unique and potentially useful reactivity pattern due to the activating effect exerted by the $CpRu^{II}$ fragment.[1] In the context of organic synthesis, (chloroarene)RuCp (Cp = cyclopentadienyl) moieties have been shown to be excellent electrophilic partners for nucleophilic aromatic substitution reactions. This property has led to the development of (arene)ruthenium-based approaches for the construction of macrocyclic biaryl ethers, an intriguing structural motif found in the vancomycin family of antibiotics.[2] Aside from this application, however, arene–Ru complexes have not been extensively utilized in synthesis relative to isoelectronic arene complexes of chromium,[3] manganese,[4] and iron.[5] While the cost associated with employing stoichiometric amounts of ruthenium may serve as a deterrent, this expense is somewhat mitigated by the availability of methods to recover the $CpRu^{II}$ fragment in a form suitable for reuse after removal of the arene ligand.[6]



Scheme 1.

As part of a study aimed at expanding the synthetic utility of arene–ruthenium complexes, we recently uncovered a means to prepare ruthenium-coordinated azaspiro[4,5]decane derivatives (e.g. **2**) from (*N*-benzylacetoacetamide)Ru precursors (**1**). The reaction entails regioselective intramolecular nucleophilic aromatic addition of a stabilized enolate to the *ipso* position and was accomplished using the protocol shown in Scheme 1.[7] It is noteworthy that an *ortho*-chloro substituent (present in **1a**) is compatible with spirocyclization and is not displaced as part of a potentially competitive intramolecular S_NAr process. In an effort to extend the scope of this novel spirocyclization reaction, the conversion of **3** to the corresponding carbocyclic spirocycle **4** was subsequently examined. Unfortunately, all attempts to effect the desired transformation returned either starting complex **3** or intractable mixtures. Apparently, for reasons that are currently unknown, replacement of the *N*-methyl group in **1** with a methylene unit alters the regioselectivity of nucleophilic addition (vide infra).

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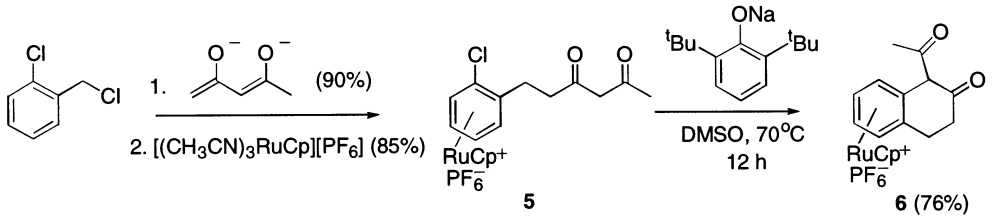
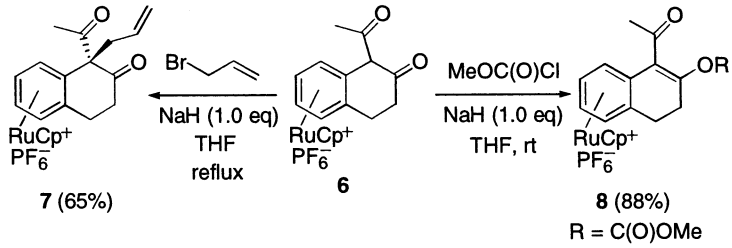
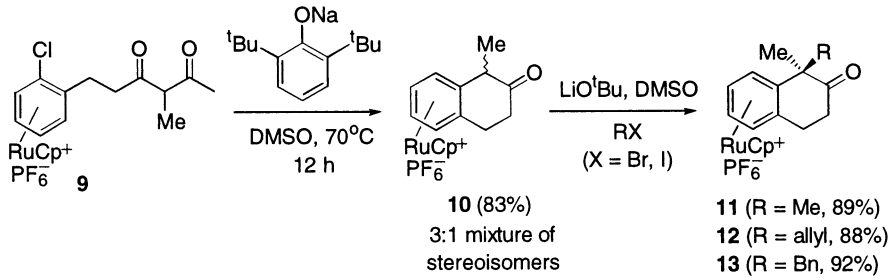


Scheme 2.



Scheme 3.



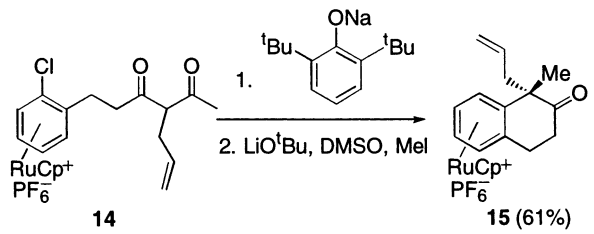
Scheme 4.

As the enolate generated upon deprotonation of **3** failed to react productively at the *ipso* position, we next turned our attention to the possibility of effecting an intramolecular S_NAr by displacement of an *ortho*-chloro substituent despite the apparent absence of such a reaction manifold in complex **1a**. Significantly, while stabilized enolates generated from β-dicarbonyl compounds are known to be viable participants in *inter*-molecular S_NAr reactions involving arene–ruthenium substrates,[8] intramolecular variations have not been reported. Moreover, the successful realization of such transformations may ultimately provide a new means of accessing synthetically versatile substituted 2-tetralone derivatives. The route used to prepare an (arene)Ru substrate potentially capable of undergoing intramolecular S_NAr is shown in Scheme 2.[9] Alkylation of the dianion of acetylacetone with 2-chlorobenzylchloride followed by introduction of the $CpRu^{II}$ fragment using $[(CH_3CN)_3RuCp][PF_6]$ as a ruthenium transfer reagent[6] proceeded smoothly to give **5**. In line with previous results, the CpRu moiety was found to coordinate to the arene ring exclusively despite the presence of an alternative chelating acac-type ligand.[7] After screening several sets of reaction conditions, it was found that the desired intramolecular cyclization could be conveniently effected by exposing **5** to an excess (~ 5 equiv.) of sodium 2,6-di-*tert*-butylphenoxide in warm (70°C) DMSO. Such treatment resulted in isolation of acetyl-substituted 2-tetralone complex **6** in good yield. The identification of **6** by NMR was somewhat complicated by the existence of keto–enol tautomerism; however, single crystals of **6** were easily obtained from an ether/CH_2Cl_2 solution and the molecular structure was confirmed by X-ray analysis.[10]

With a relatively straightforward route to Ru-coordinated 2-tetralones seemingly in hand, the ability to further manipulate complex **6** was briefly examined. It was anticipated that alkylation at the 1-position would proceed with a high level of stereocontrol given the presence of the CpRu fragment.[11] Indeed, treatment of **6** with NaH/allyl bromide in refluxing THF afforded the *C*-alkylated derivative **7** in reasonable yield (65%) as a single stereoisomer (Scheme 3).[9] Thus, the CpRu fragment does serve as an effective stereodirecting group. Unfortunately, attempts to functionalize the benzylic position of **6** with other electrophiles were unsuccessful, presumably a consequence of the stabilized nature of the corresponding benzylic anion. *O*-Alkylation of **6**, however, was much more facile as evidenced by conversion to the enol carbonate **8** in excellent yield.

In an effort to extend the scope of the ruthenium-mediated cyclization to include direct access to β-tetralones possessing a quaternary center at the 1-position,

(arene)Ru complex **9** was prepared and exposed to the cyclization conditions described previously (Scheme 4).[9] In addition to smooth intramolecular S_NAr, however, the reaction was found to occur with concomitant deacetylation and **10** was isolated as a 3:1 mixture of stereoisomers.[12] At the present time, it is speculated that this deacetylation is the result of a retro-Claisen process triggered by the presence of water (either adventitious water or water introduced during the work-up). Unlike acetyl-substituted 2-tetralone **6**, complex **10** (as a mixture of isomers) was found to undergo C-1 alkylation in high yield and with complete stereocontrol with the reactive electrophiles examined thus far. Treatment of **10** with LiO^{t}Bu in DMSO resulted in formation of a deep red solution. The red color was discharged upon addition of the alkyl halide and **11**–**13** were isolated as stereoisomerically pure crystalline solids. As expected, the intermediate benzylic anion reacts at the face opposite the metal. Further proof of stereoselective benzylic alkylation was secured by conversion of allylated complex **14** to β-tetralone **15**—material that is stereoisomeric to **12** (Scheme 5).[9]

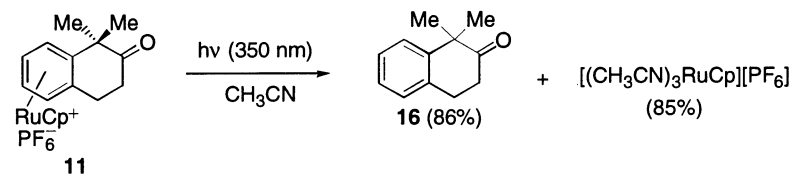


14 **15** (61%)

Scheme 5.

Finally, an important consideration when developing synthetic methods that rely on applications of arene–metal complexes is the ease with which the ligand can be liberated from the metal center. In the case of (arene)ruthenium complexes, removal of the $CpRu^{II}$ fragment can be achieved under mild photochemical conditions.[6] To demonstrate the ability to access metal-free 2-tetralone derivatives from Ru-coordinated precursors, **11** was subjected to typical decomplexation conditions. As indicated in Eq. (1), irradiation (350 nm) of an acetonitrile solution of **11** at rt in a Rayonet photochemical apparatus did indeed lead to isolation of **16** in excellent yield. Significantly, the $CpRu^{II}$ fragment also was recovered in a reusable form (as the tris(acetonitrile) salt) in 85% yield.

In conclusion, a new approach for the synthesis of 2-tetralone derivatives has been described. A heretofore unprecedented intramolecular C–C bond forming S_NAr reaction between an (arene)Ru moiety and an attached stabilized enolate constitutes the key transformation. Importantly, 2-tetralone derivatives have been utilized as versatile intermediates in the synthesis of structurally more elaborate and/or biologically active materials.[13] It is envisioned that the ruthenium-based method described above may ultimately provide a convenient means of preparing substituted β-tetralones that are difficult to obtain by other routes. Moreover, the use of optically pure planar-chiral (arene)Ru complexes analogous to **6** and **10** would serve to extend this protocol into the realm of asymmetric synthesis. Studies along these lines are currently in progress. In addition, experiments designed to discern the underlying reason(s) for the reaction dichotomy observed between benzylamide-derived complexes such as **1a** and benzyl acetylacetone derivatives (e.g. **5**) are underway.



11 **16** (86%) (1)

Acknowledgements

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