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One-Pot Formation of Substituted Cyclopentadienyl and Indenyltricarbonyl Rhenium Complexes through in Situ Generation of Cyclopentadienyl- and Indenyltributylstannanes

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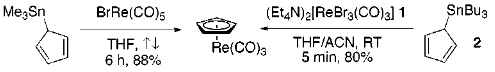
The extensive use of metallic radionuclides in nuclear medicine is dominated by technetium-99m (γ, $t_{1/2} = 6$ h), and radiopharmaceuticals labeled with this isotope are used in approximately 80% of all diagnostic imaging procedures.[1] For tumor radiotherapeutic purposes, rhenium-186 (β, $t_{1/2} = 91$ h) and rhenium-188 (β, $t_{1/2} = 17$ h) have shown great promise.[2] Recently, a large number of publications have appeared describing the synthesis of low-valent technetium and rhenium (i.e., $M(CO)_3^+$) and their use for the preparation of new radiopharmaceuticals.[3] Our own interest has been focused on the development of novel methods for the generation of stable substituted η^5-cyclopentadienyltricarbonyl rhenium and technetium ($CpRe(CO)_3$ and $CpTc(CO)_3$) complexes for radiolabeling biologically interesting molecules, especially small molecule ligands for receptors.[4] However, until recently, the preparation of these organometallic species has required harsh conditions and multistep procedures.[5] Herein we describe the utility of trialkyltin-substituted cyclopentadienes in the efficient synthesis of substituted $CpRe(CO)_3$ complexes.

Reactions of trialkylstannylcyclopentadienes with Group VII pentacarbonyl halides [$MX(CO)_5$] for the preparation of unsubstituted $CpRe(CO)_3$ complexes have been reported.[6] Most reactions utilized the trimethyltin derivative and were complete within 3−7 h, with manganese, as expected, exhibiting a higher rate of reaction than rhenium. However, for this chemistry to be useful for radiolabeling receptor ligands, we needed to be able to include additional functionality in the cyclopentadienyl ring.

Our initial studies focused on the reaction of tributylstannylcyclopentadiene (CpTBT) with $(Et_4N)_2[ReBr_3(CO)_3]$ (**1**)[3a] as the source of $Re(CO)_3^+$, an approach analogous to that which we used in a related three-component condensation.[7] Because the metal precursor **1** is insoluble in THF, it was dissolved in acetonitrile (MeCN). CpTBT, being insoluble in MeCN, was dissolved in THF, which was used as reaction cosolvent. When a solution of **1** in MeCN was treated with a THF solution of CpTBT at room temperature, formation of $CpRe(CO)_3$ was complete *within 5 min*, and this material could be obtained in 80% yield, after isolation and chromatography (Scheme 1). The corresponding reaction with $BrRe(CO)_5$ required *6 h* at reflux in THF to achieve a similar yield. It should be noted that under analogous conditions, neither of the other Cp donors, nickelocene nor trimethylsilyl-cyclopentadiene, produced any significant amount of $CpRe(CO)_3$.

Scheme 1. Comparison of Reactivity of Rhenium Sources



With this promising result in hand, we attempted to prepare a variety of substituted cyclopentadienyl- and indenyltributyltin compounds. Unfortunately, we were unable to isolate most of these compounds, because of the facility with which they underwent protonolysis (destannylation). To circumvent this hydrolysis problem, we chose not to isolate the tributyltin species, but rather to generate them in situ, and use them directly in the reaction with the addition of the metal precursor **1**.

Recently, tin-amines have been used in palladium-catalyzed amination reactions of aryl halides.[8] However, the tin-amines have long been known for their ability to react with protic solvents, such as alcohols, thiols, and other amines, to form the corresponding tin-alkoxides, sulfides, or amines under mild conditions.[9] They also are known to react with the relatively acidic protons of cyclopentadiene and indene to form the corresponding enyltin species.[6b,10]

Our initial attempt to utilize the tin-amines was in the preparation of unsubstituted $CpRe(CO)_3$. When we treated a THF solution of freshly cracked cyclopentadiene with diethylamino-tributyltin at room temperature for 2 h, added this mixture to a solution of **1** in a minimal amount of MeCN, and refluxed the resulting solution, we indeed saw formation of $CpRe(CO)_3$ by TLC analysis. After 1 h, $CpRe(CO)_3$ was isolated, as above, in 81% yield.

To extend this reaction to other ring systems, we attempted to carry out the analogous reaction using indene rather than cyclopentadiene. In this experiment, a THF solution of indene was treated with diethylamino-tributyltin at reflux for 1 h. TLC showed complete consumption of the indene starting material and formation of a new, higher R_f, compound. However, upon addition of the MeCN solution of **1** at room temperature, TLC analysis showed the rapid reappearance of free indene, with no detectable formation of the desired indenyltricarbonyl rhenium (InTR) complex. It is unlikely that adventitious water can account for this complete protonolysis. Rather, because the pK_a values of indene and the solvent MeCN are comparable, it is more likely that the indene anion is being protonated by this solvent, although it is not clear why this same protonation would not happen with the more basic Cp-tin species. In any case, we developed as an alternative a strictly aprotic system in THF solvent.

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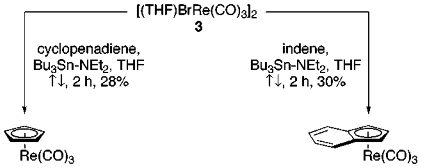
Scheme 2. Studies on in Situ Generation of Enyl-Stannanes



A simple form of the metal precursor that is soluble in THF is $[(THF)BrRe(CO)_3]_2$ (**3**), which is a halide-bridged dimer in the solid state that becomes a monomer $[(THF)_2BrRe(CO)_3]$ in THF solution.[11] It should be noted that the related technetium complex, $[^{99m}Tc](THF)_2ClTc(CO)_3$, can be produced by the reduction of $[^{99m}Tc]NH_4TcO_4$ by $BH_3{\cdot}THF$ in the presence of a chloride source, according to the methods developed by Alberto.[3b] Our hope was that precursor **3** would offer similar reactivity in THF as did precursor **1** in MeCN.

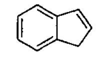
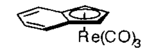
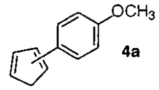
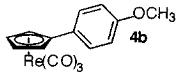
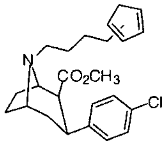
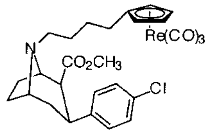
For this study, we attempted to generate the CpTBT in the presence of the $Re(CO)_3^+$ source, as this would simplify the in situ, two-step procedure used above. We were pleased to find that treatment of a solution of the metal precursor **3** and cyclopentadiene in THF with diethylamino-tributyltin at reflux for 2 h afforded $CpRe(CO)_3$ in 28% yield. More importantly, when we performed the analogous procedure with indene, we successfully isolated InTR, although in a relatively modest 30% yield (Scheme 2). To our knowledge, this result represents the first *one-pot* synthesis of $CpRe(CO)_3$ and InTR, using an in situ generated enyl-stannane.

Several aspects of this reaction deserve comment. First and foremost is that $CpRe(CO)_3$ was not formed under the reaction conditions in the absence of the tin reagent. It is also of note that the yields of both reactions improved somewhat with extended reaction times, although the yields were lower than expected when compared to the results obtained from metal precursor **1** in MeCN. We believe that the different reaction temperatures used in the two cases are not as important as the greater polarity and ionizing potential of MeCN compared to THF. These factors may become more apparent in future mechanistic studies.

To demonstrate the utility of this reaction, we wished to extend it to more complex substrates. Our results are summarized in Table 1. When the substituted cyclopentadiene **4a** is subjected to the reaction conditions described above, the corresponding *p*-methoxyphenyl-substituted $CpRe(CO)_3$ (**4b**)[4b] was formed in 65% yield: In three separate trials, the yields of this compound consistently averaged 65%. Similarly, the phenyl-tropane **5a** gave the highly functionalized alkyl-substituted $CpRe(CO)_3$ **5b** in 26% yield. Although the reaction worked with these substrates, it did not work with several others (e.g., other diarylindenes). Efforts to make more complex rhenium tricarbonyl complexes, specifically those with estrogenic cores, are currently underway in our laboratories.[12]

The mechanism of this reaction is not known; however, the transmetalation to rhenium appears to be the rate-limiting step. During this transmetalation, attack of halide at tin can occur in an inter- or intramolecular fashion, but the exact nature of this transition state is unknown. Based on literature precedent,[6b] it is likely that the reaction occurs through initial olefin coordination to form an η^2-intermediate, then directly to a η^3-intermediate, and finally to the η^5-product.

Table 1. Structures and Isolated Yields in the Reaction of **3** with Various Cyclopentadienes and Indenes

Entry	Reactant	Yield (%)	Product
1		28	
2		30	
3		65	
4	 **5a**	26	 **5b**

In summary, the reaction herein reported has proved to be a mild and efficient method for the preparation of substituted $CpRe(CO)_3$ complexes.[13] The reaction is quite complementary to other protocols developed in our laboratories. It is not limited by the need for an electron-withdrawing substituent as in the double ligand transfer reaction, and it does not require the isolation of a reactive cyclopentadienyl source as in the three-component condensation. The reaction can be extended to the use of indenyl ring systems and shows tolerance of a variety of functional groups. The main limitation of the reaction is the yield, which is modest, when the reaction times need to be kept short to achieve efficient radiochemical synthesis with a short-lived radionuclide (e.g., the Tc-99m half-life is 6 h). The solvent MeCN gives the best yields of $CpRe(CO)_3$, although this solvent proved to be incompatible with the indenyl ring system. In THF, the reaction can be carried out in a single pot, and in this solvent it can be extended to more complex systems. We feel that the reaction should provide a powerful extension of the recent work by Jaouen, who has shown that substituted cyclopentadienes can be produced cleanly by irradiation of cyclopentadienyltricarbonyl manganese complexes.[14]

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Supporting Information Available: Complete experimental procedures and spectral data for compounds **4a**, **4b**, **5a**, and **5b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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