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A New Complex of Palladium–Thiourea and Carbon Tetrabromide Catalyzed Carbonylative Annulation of *o*-Hydroxylarylacetylenes: Efficient New Synthetic Technology for the Synthesis of 2,3-Disubstituted Benzo[*b*]furans

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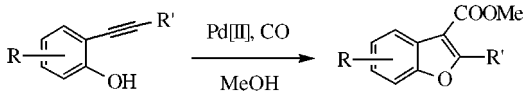
ABSTRACT



A highly effective cocatalysis system (PdI_2–thiourea and CBr_4) was developed for carbonylative cyclization of both electron-rich and electron-deficient *o*-hydroxylarylacetylenes to the corresponding methyl benzo[*b*]furan-3-carboxylates.

During the development of a chemical genetic approach to analyzing biological systems by using small molecules in an appropriate cell-based assay,[1] we became interested in developing a general synthetic method for combinatorial synthesis of a 2,3-disubstituted benzo[*b*]furan library.

Benzo[*b*]furan derivatives are of interest because of their frequent occurrence in nature[2] and their wide range of biological effects.[3]

Although various methods are known in the literature for the synthesis of benzo[*b*]furan,[4] recent research, however, has centered on the use of palladium catalysts for carbon−carbon bond formation leading to the benzofuran structures. Largely due to the efforts of Richard C. Larock and co-workers, an extremely versatile method for the synthesis of a wide variety of heterocycles and carbocycles by the palladium-catalyzed carbo- and heteroannulation of 1,2-dienes,[5] 1,3-dienes,[6] 1,4-dienes,[7] and vinyllic cyclopropanes or cyclobutanes[8] by aromatic halides bearing functional groups in the *ortho* position has been developed.

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For the synthesis of benzo[*b*]furan-3-carboxylates, the palladium-catalyzed carbonylative cyclization of arylacetylenes bearing hydroxyl groups in the *ortho* position (**1**) has proven to be a useful method for the synthesis of these heterocycles (**2**) (Figure 1).[9]

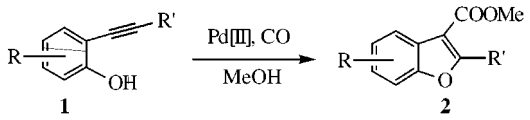

Figure 1. General scheme for palladium-catalyzed carbonylative heteroannulation.

There are however limitations associated with this methodology: (1) low yields of the benzo[*b*]furan-3-carboxylates when electron-deficient substrates are used[9b,c] and (2) the incompatibility of reaction conditions with silyl protecting groups.[10] The later limitation is of particular concern since our proposed library synthesis is to be carried out on a silyl linker to allow efficient high throughput screening. Therefore, we needed to find reaction conditions that will allow us to use both electron-rich and electron-deficient substrates while not cleaving silyl groups.

Mechanistically, the formation of benzo[*b*]furan-3-carboxylates starting from *o*-hydroxylarylacetylenes presumably proceeds via the multistage process shown in Figure 2.[11]

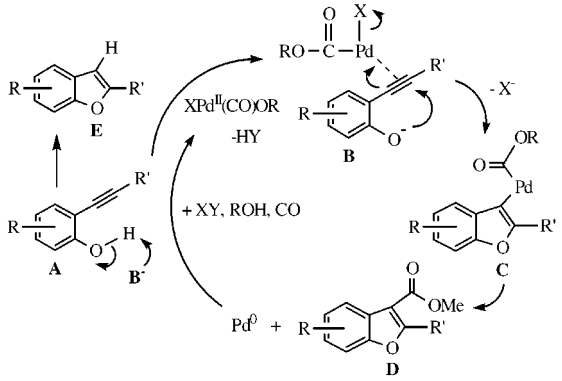

Figure 2. Mechanism of palladium-catalyzed carbonylative cyclization of *o*-hydroxylarylacetylenes.

The overall process may involve attack of a carboalkoxypalladium(II) intermediate on the arylacetylene **A** to generate the complex **B**, followed by nucleophilic addition of the phenolic oxide to the XPd^{II}(CO)OR-activated arylacetylene **B** to give intermediate **C**. Reductive elimination of **C** produces ester **D** and palladium(0). The palladium(0) is then oxidized to palladium(II), completing the cycle.

In this catalytic cycle, the nature of the base (B^-), palladium(II) complex (XPd^{II}(CO)OR), and oxidative agent (XY) [which promotes the turnover of Pd^0 to Pd^{II}] is paramount to the success of the reaction. The base should allow the desired catalytic cycle to proceed while minimizing the unwanted direct cyclization of **A** to **E** (see Figure 2). The XPd^{II}(CO)OR complex has to be active enough to coordinate with acetylene to form **B**, and the oxidative agent (XY) has to efficiently promote the turnover of the palladium catalyst from Pd^0 to Pd^{II} without disrupting the carbonylative cyclization.

The palladium-catalyzed carbonylative cyclization of *o*-hydroxylarylacetylenes to generate benzo[*b*]furan-3-carboxylates has been recently utilized by Scammells in his synthesis of XH_{14}.[9a,b] Unfortunately, we were not able to reproduce the cyclization reported in ref 9a utilizing the published conditions. The best yields we could obtain were in the range of 10−15% due to decomposition of starting material and autocyclization, where Scammells reports a 68% yielding.

We then carried out a systematic study to identify the appropriate base (B^-), catalyst (XPd^{II}(CO)OR), and oxidative agent (XY) that would effect carbonylative heteroannulation of electron-deficient substrates and tolerate silyl-protecting groups. We evaluated palladium catalysts, such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, PdI_2, and PdI_2−thiourea.[11] All the catalysts tested gave low yields when electron-deficient substrates were used with $CuCl_2$ as an oxidative agent. In addition, the silyl protecting group was cleaved under the reaction conditions ($CuCl_2$, MeOH).

We finally focused our attention on oxidative agents (XY in Figure 2). Our goal was to find a reagent that not only efficiently converts the Pd^0 to Pd^{II} but also promotes the annulation of electron-deficient substrates while tolerating silyl groups. Some oxidative agents can convert the Pd^0 to Pd^{II},[9c,12] but they are not compatible with the conditions of our 2,3-disubstituted benzo[*b*]furan synthesis. Although organic halides, such as bromobenzene and iodobenzene, have been used effectively to reoxidize palladium(0),[13] they cannot be applied to our catalytic process owing to competitive reductive elimination of the phenyl group.[14]

After considerable experimentation, it was found that electron-deficient substrates **3** could be carbonylatively heteroannulated with PdI_2−thiourea, CBr_4, and Cs_2CO_3 as the base, in methanol at 40 °C and balloon pressure of CO

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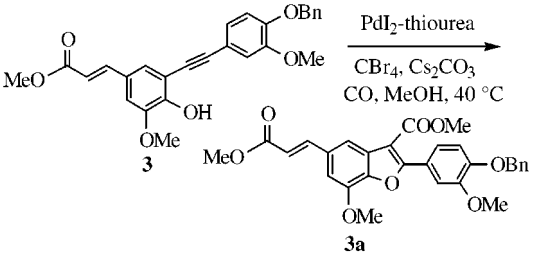
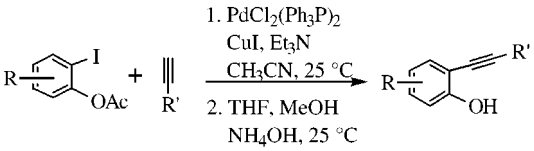
Scheme 1. Synthesis of Benzo[*b*]furan-3-carboxylate **3a**



(Scheme 1), to give 84% yield of the desired product **3a**. The reaction was also complete in less than a half-hour.

To assess the generality of this procedure, other *o*-hydroxylarylacetylenes were prepared by Sonogashira coupling[15] [Scheme 2] and annulated. The detailed experimental

Scheme 2. Synthesis of *o*-Hydroxylarylacetylenes from the Corresponding Iodolphenol Acetates and Acetylenes



data are summarized in the Supporting Information.

Remarkably, with all the substrates (both electron-rich and electron-deficient) the reaction gave satisfactory yields (see Table 1) and went to completion in less than a half-hour using the same conditions as described above. Furthermore, the TBS protecting group (see compound **5a** in Table 1) was found to be stable under these reaction conditions.

In summary, we have developed a highly effective cocatalysis system (PdI_2−thiourea and CBr_4) for carbonylative cyclization of both electron-rich and electron-deficient *o*-hydroxylarylacetylenes to the corresponding methyl benzo[*b*]furan-3-carboxylates. We have introduced, for the first time, carbon tetrabromide (CBr_4) as a superior oxidative agent for the turnover of palladium(0) to palladium(II). This result has the potential to be used in other types of palladium chemistry, such as oxidation of an alcohol to an aldehyde or a ketone.[13]

The application of this cocatalyst system to a silyl linker-based solid-phase benzo[*b*]furan-3-carboxylate synthesis

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Table 1. Palladium−Thiourea-Catalyzed Carbonylative Annulation of *o*-Hydroxylarylacetylenes

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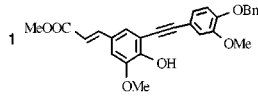
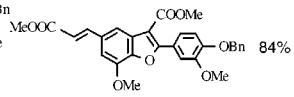
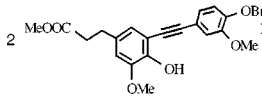
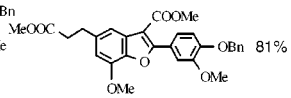
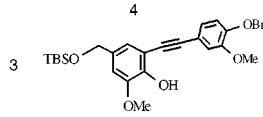
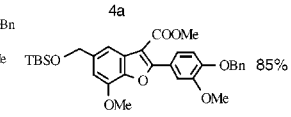
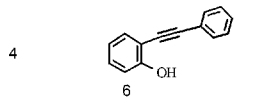
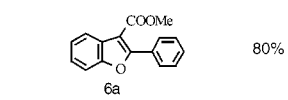
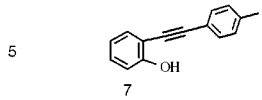
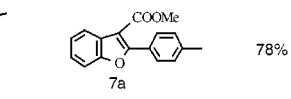
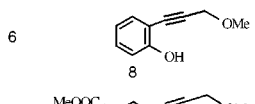
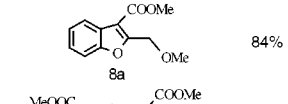
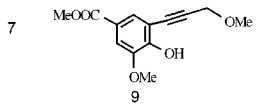
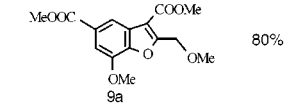
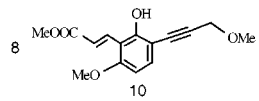
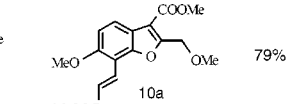
1			84%
2			81%
3			85%
4			80%
5			78%
6			84%
7			80%
8			79%

[a]pure product after flash chromatography.

proved to be as effective as in solution phase, and a combinatorial synthesis of a benzo[*b*]furan library is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and ^1H and C^{13} NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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