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Palladium(II)-Mediated Cascade Carbonylative Annulation of *o*-Alkynyl-phenols on Silyl Linker-Based Macrobeads: A Combinatorial Synthesis of a 2,3-Disubstituted Benzo[*b*]furan Library

Yun Liao,*,†,‡ Michael Reitman,† Yan Zhang,† Reza Fathi,*,†,‡ and Zhen Yang*,†,‡

Harvard Institute of Chemistry and Cell Biology, Harvard Medical School,
250 Longwood Avenue, SGM 604, Boston, Massachusetts 02115-5731, and
VivoQuest, Inc., 711 Executive Blvd., Valley Cottage, New York, 10989

r.fathi@vivoquest.com

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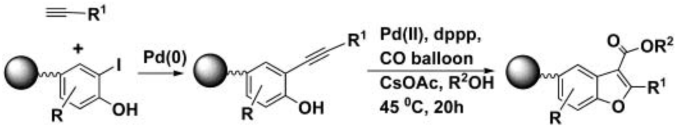
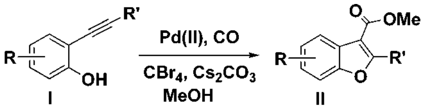
ABSTRACT



A palladium(II)-mediated cascade carbonylative annulation of *o*-alkynylphenols was achieved successfully on silyl linker-based macrobeads, which led to an efficient combinatorial synthesis of a 2,3-disubstituted benzo[*b*]furan library.

The prominence of 2-disubstituted-benzo[*b*]furan-3-carboxylates as a basic scaffold in natural products and biologically active molecules has promoted considerable efforts toward their synthesis.[1] Our interest in constructing natural product-based combinatorial libraries had led us to develop an efficient method for the synthesis of diversified benzofuran molecules (Scheme 1).[2] Given the ability of our method to generate diverse and complex benzo[*b*]furan molecules in solution, we sought to apply it to solid-phase synthesis as well. Herein we describe our efforts aimed at achieving the palladium(II)-mediated carbonylative annulations of *o*-alkynylphenols on silyl linker-based high-loading polystyrene macrobeads.[3] Although combinatorial syntheses employing the palladium-catalyzed Stille, Heck, and Suzuki coupling reactions are well documented,[4] to the best of our knowledge, the palladium(II)-mediated domino reaction to generate complex natural product-like compounds on a solid support has not been reported yet.

Scheme 1



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* E-mail: Z.Yang@vivoquest.com (Z.Y.); Y.Liao@vivoquest.com (Y.L.).

† Harvard Medical School.

‡ VivoQuest, Inc.

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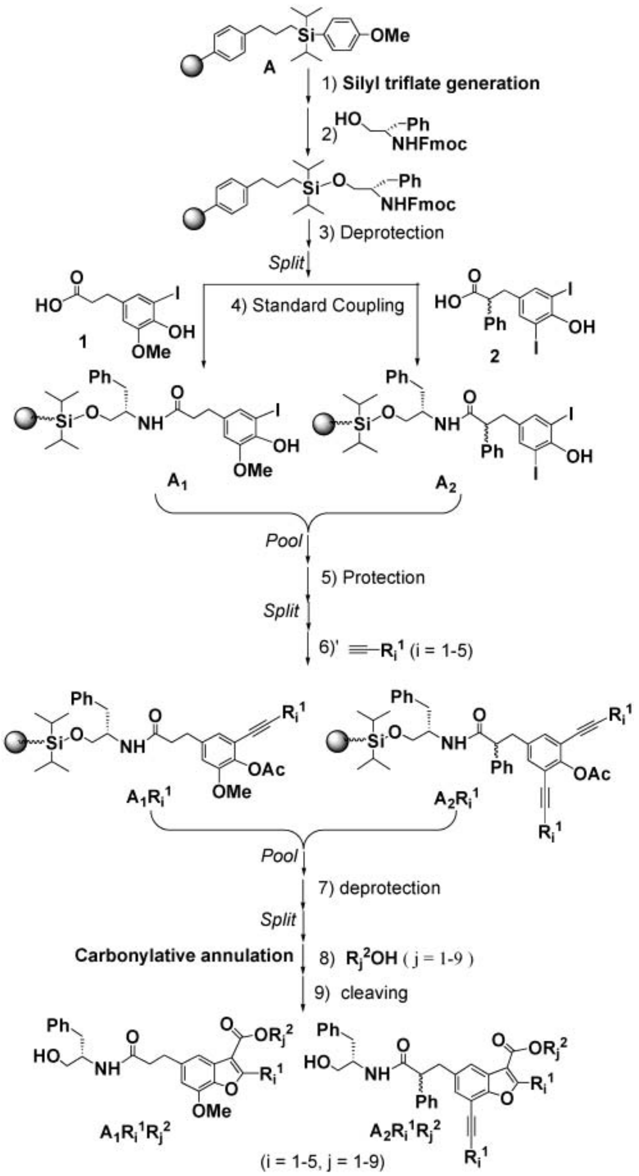
In accordance with our objective, we had previously optimized the Sonogashira reaction for the synthesis of diversified *o*-alkynylphenols[5] as an indispensable requirement for developing en masse synthesis of benzofuran molecules.

However, application of carbonylative annulation reaction from the solution phase[2] to the silyl linker-based macrobeads was hampered by a number of difficulties. In addition to a lack of precedence for such a reaction under a balloon pressure of carbon monoxide on a solid support, there were a number of shortcomings that were not desirable for solid-phase synthesis of the desired products, such as sensitivity of the silyl linker to Lewis acid, clogging of the solid-phase pores by precipitation of palladium catalyst, direct cyclization of the precursor to form 2-substituted benzo[*b*]furan without incorporation of carbon monoxide specifically when Cs_2CO_3 was used as a base, and finally the slow rate of reaction from 30 min in solution to more than 4 days on solid support.

To overcome these difficulties, we initiated systematic studies where all the essential elements of synthesis were considered individually as well as holistically, and the results are described below. (a) To avoid Cs_2CO_3-induced direct cyclization of *o*-alkynylphenols, other types of bases (organic and inorganic) had been screened, and CsOAc eventually proved to be ideal for both its basicity and its solubility in DMF. (b) Pd^0 precipitation was minimized by using bidentate ligand (dppp), and anhydrous solvents had to be used since, in the presence of water, carbon monoxide can be oxidized into formic acid, inducing therefore palladium bleeding.[6] (c) To prevent the consumption of Pd^{II}, some easily oxidized alcohols had to be avoided, such as methanol due to its easy oxidative tendency to form formaldehyde or methyl formate.[7] (d) The significant cleavage of the silyl linker-attached *o*-alkynylphenols from the solid supports was caused by CBr_4 acting as a bromide salt, and such an observation was not noticed during the solution-phase synthesis, since most of the carbonylative annulations were completed in less than 1 h rather than the 4 days needed for the solid-phase synthesis. Although other oxidative agents (such as inorganic copper (II) and phenyl halides) were tested for turnover of Pd^0 to Pd^{II}, they all failed to give desired results. Eventually, a stoichiometric amount of $PdCl_2(PPh_3)_2$−dppp (1:1) proved to effectively promote the carbonylative annulation on the macrobeads, and the reaction was completed overnight rather than in 4 days.

On the basis of the aforementioned study, a 90-membered benzo[*b*]furan library was designed (Scheme 2). The primary loading of an Fmoc-protected chiral amino alcohol was achieved by coupling it with the on-bead silyl triflate. After deprotection of the Fmoc group, coupling of two iodophenol-based acids (**1** and **2**) mediated by Py-BOP afforded two different on-bead iodophenols (**A_1** and **A_2**), which were then put into the IRORI Micro-Kan with radio frequency tags.[8]

Scheme 2. Split-Pool Synthesis of a Benzofuran Library[a]



[a] Conditions: (1) Me_3SiCl, imidazole, CH_2Cl_2, rt, 2 h; T_fOH, CH_2Cl_2, rt, 1.5 h. (2) 2,6-Lutidine, CH_2Cl_2, rt, 4 h. (3) piperidine, DMF, rt, 1 h. (4) Py-BOP, NMM, 1/2 DMF/THF, rt, 12 h. (5) LiCl, Ac_2O, Py, CH_2Cl_2, rt, 10 h. (6) $Pd(PPh_3)_2Cl_2$ (0.3 equiv), CuI, DIPEA, CH_3CN, rt, 24 h. (7) NH_2NH_2/THF (0.1 M). (8) CO, R^2OH, $Pd(PPh_3)_2Cl_2$−dppp (1.2 equiv), CsOAc, DMF, 45 °C, 48 h. (9) HF/Py 5% in THF, rt, 1 h; TMSOMe, 0.5 h.

The pooled **A_1** and **A_2** were first protected as their acetates, split into 5 pools, and finally coupled with 5 acetylenes (see Table 1) to give 10 phenylacetylenes (**$A_1R_i^1$** and **$A_2R_i^1$**), although **$A_2R_i^1$** exist as a pair of diastereomers. All these coupling products were subsequently pooled, and the acetate protecting group was removed; the products were then divided into nine pools to undergo the final palladium^{II}-mediated carbonylative annulations with nine alcohols (see Table 1) to generate a library represented as two groups of structures (**$A_1R_i1R_j^2$** and **$A_2R_i1R_j^2$** as shown in Scheme 2) after cleavage from the beads.

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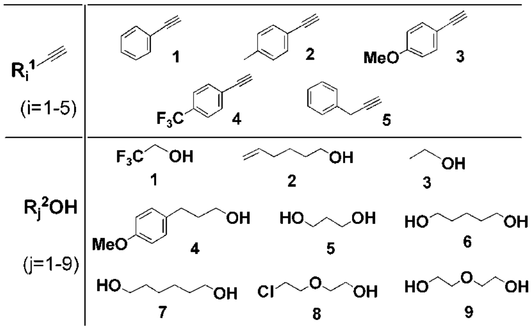
Table 1. Building Blocks for the 90-Membered Library



All the intermediates and the final 2,3-disubstituted-benzo[*b*]furan compounds, corresponding to 45 optically active compounds $\mathbf{A_1R_i^1R_j^2}$ and another 45 pairs of diastereomers ($\mathbf{A_2R_i1R_j^2}$), were fully identified by both LCMS and ^{1}H NMR. All the selected substituted *o*-alkynylphenols smoothly underwent the palladium-mediated carbonylative annulations to give 2-substituted-benzo[*b*]furan-3-carboxylates. Examinations of all the identified products confirmed that 70 of them gave the desired products in over 90% purities; 15 of them were in the purity range 80−90%, and 5 were between 50 and 80% purities. The major side products for all these samples were the 2-substituted benzo[*b*]furans, emanating from direct cyclization of *o*-alkynylphenols without CO insertion. A trace amount of dimers corresponding to the 2-substituted-benzo[*b*]furan-3-carboxylates was also observed when terminal diols were used in the carbonylative annulations (See Table 1, alcohols 5−7, 9).

It is noteworthy that the single-bead MAS-^{1}H NMR follow-up study showed that the loading levels of all the final on-bead products were maintained during the entire process. Figure 1 illustrates a selected compound's NMR spectra generated from a single bead.

In summary, here we have described a novel and practical method for the combinatorial synthesis of 2,3-disubstituted-benzo[*b*]furan from substituted *o*-alkynyl-phenols. The following are the salient features of this chemistry: (1) a large number of complex and diverse 2,3-disubstituted-benzo[*b*]-furans were effectively generated via the palladium^{II}-mediated cascade carbonylative annulation from readily available starting materials in few steps, and the formation of all library members were confirmed by both LC-MS (based on single bead) and ^{1}H NMR (based on 10 beads), which provides a high degree of confidence that complex natural product-like molecules can be synthesized in a combinatorial format; (2) high-loading silyl linker-based macrobeads are compatible with our studied palladium chemistries; (3) high yields and conversion will allow the cleaved compounds to be utilized directly in various biological assays without further purifications, which demonstrates the capability of combinatorial chemistry as a unique format for chemical genetic studies.[9]

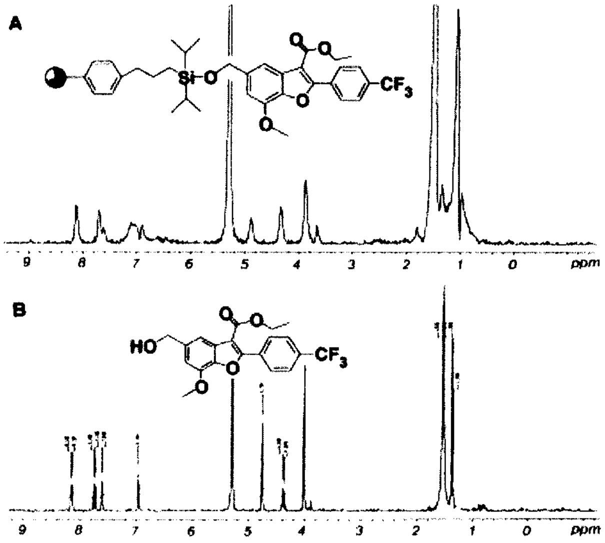


Figure 1. (**A**) Single-bead spin−echo MAS-^{1}H NMR (500 MHz, in nanoprobe, solvent = CD_2Cl_2 (δ 5.3 ppm); (**B**) cleaved from one macrobead.

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Supporting Information Available: Experimental procedures and NMR and LC-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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