

## Cu(I)-Catalyzed Regioselective Synthesis of Polysubstituted Furans from Propargylic Esters via Postulated (2-Furyl)carbene Complexes

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The transition metal-catalyzed transformations of propargyl esters have become in recent years a powerful key process which has led to the development of a variety of cycloisomerization as well as atom-economy cascade reactions.<sup>1</sup> Although the reaction course has not been well-established yet, it is assumed that the process initiates by either 1,2- or 1,3-acyloxy migration giving rise to metal vinyl carbenes and metal-coordinate allenes, respectively, as reactive intermediates.<sup>2</sup> Recent studies from our laboratory<sup>3</sup> revealed that (i) the use of an alkoxy group as the alkyne substituent controls perfectly the regiochemistry (1,3- in preference to 1,2-acyloxy migration) leading to the Knoevenagel adducts and (ii) Pt(II) and Cu(I) catalysts are stereochemically complementary leading to the (Z)- and (E)-adducts, respectively. It was also noted that the unsymmetrical bis-propargylic ester **1a** undergoes a Cu(I)-catalyzed process yielding the furyl dimer **2a** (eq. 1).



This finding features a Cu(I)-chemoselective catalyzed reaction cascade with a manifold interest: (i) the relevant furan ring<sup>4</sup> is easily available by a novel Cu(I)-catalyzed carbonyl-alkyne cyclization; (ii) a new type of Cu(I)-carbene complex is likely to operate whose reactivity could be exploited and, therefore, the cascade process extended.

On the basis of these assessments we report an efficient synthesis of tri- and tetrasubstituted furans<sup>5</sup> as well as preliminary studies on the reactivity of the proposed copper(I) 2-furylcarbene complex.<sup>6,7</sup>

When the Cu(I)-catalyzed cycloisomerization of **1a** was conducted in the presence of activated and unactivated alkenes no cyclopropanation by the metal carbene occurred but dimerization was found to be faster. On the contrary, we were pleased to find that stirring **1a** (R<sup>1</sup> = Ph) in CH<sub>2</sub>Cl<sub>2</sub> (25 °C, 4 h) with [Cu(CH<sub>3</sub>CN)<sub>4</sub>][BF<sub>4</sub>] (5 mol%) in the presence of triethyl silane **3a** (3 equiv) resulted in the formation of the furan derivative **4a** in 57% yield after chromatographic purification (Scheme 1).<sup>8</sup> Next, we examined the suitability of an alkyl-substituted substrate like **1b** (R<sup>1</sup> = *n*pent) and found that, under the same reaction conditions, the furan **4b** was produced in 68% yield.<sup>9</sup> Interestingly, the reaction can be successfully extended to alkyl substrates since the presumed Cu(I)-carbene species undergoes Si-H insertion in preference over  $\beta$ -hydride elimination.<sup>10</sup>

The scope of this Cu(I)-catalyzed tandem reaction was next investigated using substrates with substituents of varied nature and various silicon and germanium hydrides (Table 1).  $\textit{Scheme 1. Cu(I)-Catalyzed Reaction of Diynes 1a and 1b and Triethylsilane <math display="inline">3a$ 







<sup>a</sup> Yields of isolated product after column chromatography.

Thus, the reaction was found to tolerate a broad substitution range for the alkyne terminus  $\mathbb{R}^1$ , including aryl, alkyl, trimethylsilyl, and alkenyl groups (compounds **4a**-**d**). Different  $\mathbb{R}^2$ -substituted esters, including acetate, propanoate, pivalate, and acrylate, proved also amenable to cyclization (compounds **4a**-**g**). On the other hand, the reaction proceeds efficiently with various silanes **3**, for example, tertiary silanes (trialkylsilanes and mixed dialkylarylsilanes) and diethylsilane (compounds **4 g**-**j**). The goal of synthesizing tetrasubstituted furans was exemplified by starting from **1** ( $\mathbb{R}^3 = \mathbb{M}e$ ) which produces furan **4k** in acceptable yield (yield slightly higher than that of the trisubstituted analogue **4h**). We also found that the proposed Cu(I) carbene intermediate derived from representative *Table 2.* Cu(I)-Catalyzed Synthesis of Furan Derivatives 7 and 8 from Propargylic Esters  $1^a$ 



<sup>*a*</sup> Yield of isolated product after column chromatography. <sup>*b*</sup> A 80:20 mixture of Z/E isomers was obtained. <sup>*c*</sup> A 85:15 mixture of Z/E isomers was obtained.

propargylic substrates is smoothly intercepted by triethylgermanium **5** to provide (furan-2-ylmethyl)germane derivatives (compounds 6a-c).<sup>11,12</sup>

Furthermore, the heterocoupling reaction to create a carbon–carbon double-bond was investigated by running the Cu(I)-catalyzed cycloisomerization of **1** in the presence of 2.5 equiv of ethyl diazoacetate (EDA) (Table 2). Gratifyingly, the heterocoupling event occurred cleanly in the presence of CuBr (5 mol%) to furnish ethyl 3-(furan-2-yl)prop-2-enoates **7a,b** (*Z/E* mixtures) along with variable amounts of maleate and fumarate esters.<sup>13,14</sup> This new heterocoupling reaction proceeds in high yields (76–82%) and moderate steroselectivity allowing the preparation of furan derivatives bearing a vinyl moiety at C-2.

Finally, the sequence cycloisomerization/carbene oxidation would allow the preparation of 2-acylfurans.<sup>15</sup> This goal was achieved directly by stirring at room temperature the bis-propargylic system 1 in the presence of CuCl (5 mol %) under air, as it is illustrated in Table 2 for the tri- and tetrasubstituted 2-pentanoyl and 2-benzoylfurans **8a,b**.

In conclusion, we have developed a regioselective Cu(I)catalyzed synthesis of highly substituted furans from readily available bis-propargylic esters.<sup>16</sup> The multistep process is consistent with the intermediacy of a 2-furyl copper(I) carbene complex which allows for further variable functionalization or coupling at C-2.<sup>17</sup> This unprecendented approach to copper(I) 2-furylcarbene complexes<sup>18</sup> has made possible the exploration of its capability for C–X (X = Si, Ge) and C=Y (Y = C, O) bond formation. Hopefully this work will open the way to study the potential of these copper carbene species.

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**Supporting Information Available:** Experimental procedures and spectral and analytical data for compounds **1**, **4**, and **6**–**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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- (13) In this coupling process CuBr proved to be superior to the cationic complex in terms of chemical yield.
- (14) During the study of the optimization and scope of this process we found that the treatment of diyne 1d with diethyl diazomalonate in the presence of CuBr (5 mol %) did not produce the heterocoupling product. In this case the diazo derivative acts just as a modulating ligand giving rise to the Knoevenagel adduct 9 in 65% yield. Furthermore, the treatment of compound 9 with triethylsilane 3a ([Cu(CH<sub>3</sub>CN)<sub>4</sub>]]BF<sub>4</sub>], 5 mol %, CH<sub>2</sub>Cl<sub>2</sub>, room temp) or EDA (CuBr, 5 mol %, CH<sub>2</sub>Cl<sub>2</sub>, room temp) afforded the furan derivatives 4e (92%) and 7b (89%), respectively.



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