Communication

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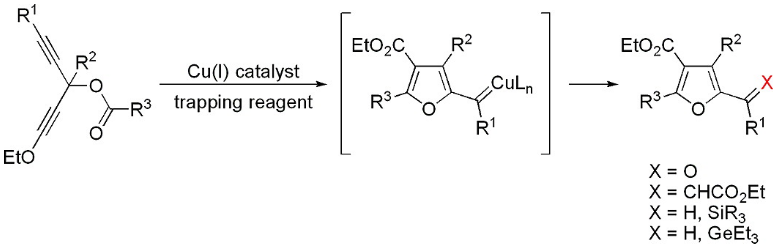

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Cu(I)-Catalyzed Regioselective Synthesis of Polysubstituted Furans from Propargylic Esters via Postulated (2-Furyl)carbene Complexes

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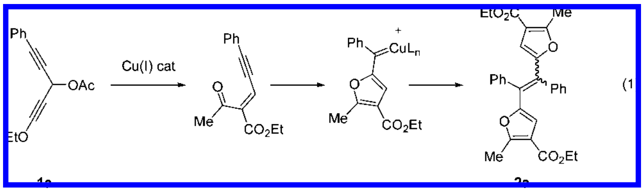
The transition metal-catalyzed transformations of propargyl esters have become in recent years a powerful key process which has led to the development of a variety of cycloisomerization as well as atom-economy cascade reactions.[1] Although the reaction course has not been well-established yet, it is 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.[2] Recent studies from our laboratory[3] 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[4] 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[5] as well as preliminary studies on the reactivity of the proposed copper(I) 2-furylcarbene complex.[6,7]

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^1 = Ph) in CH_2Cl_2 (25 °C, 4 h) with $[Cu(CH_3CN)_4][BF_4]$ (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).[8] Next, we examined the suitability of an alkyl-substituted substrate like **1b** (R^1 = *n*pent) and found that, under the same reaction conditions, the furan **4b** was produced in 68% yield.[9] Interestingly, the reaction can be successfully extended to alkyl substrates since the presumed Cu(I)-carbene species undergoes Si−H insertion in preference over *β*-hydride elimination.[10]

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).

Scheme 1. Cu(I)-Catalyzed Reaction of Diynes **1a** and **1b** and Triethylsilane **3a**

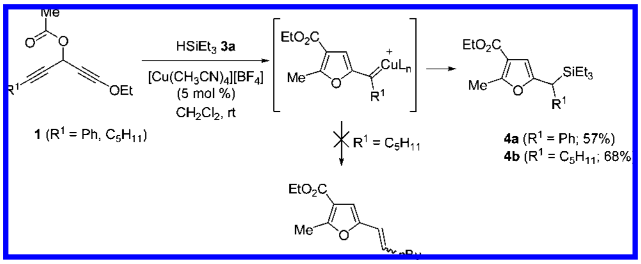
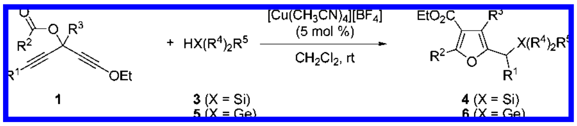
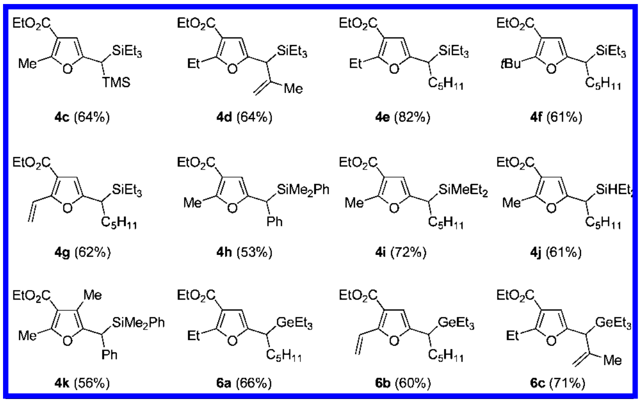


Table 1. Cu(I)-Catalyzed Synthesis of Tri- and Tetrasubstituted Furan Derivatives **4** and **6** from Propargyl Esters **1** and Silanes **3** and Germane **5**[a]





[a] Yields of isolated product after column chromatography.

Thus, the reaction was found to tolerate a broad substitution range for the alkyne terminus R^1, including aryl, alkyl, trimethylsilyl, and alkenyl groups (compounds **4a−d**). Different 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** (R^3 = Me) 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

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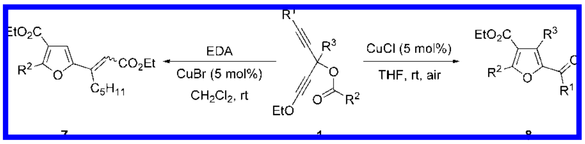
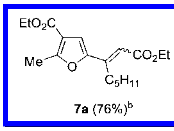
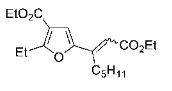
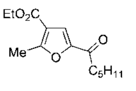
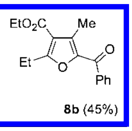
Table 2. Cu(I)-Catalyzed Synthesis of Furan Derivatives **7** and **8** from Propargylic Esters **1**[a]




7a (76%)[b]


7b (82%)[c]


8a (47%)


8b (45%)

[a] Yield of isolated product after column chromatography. [b] A 80:20 mixture of *Z*/*E* isomers was obtained. [c] 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**).[11,12]

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.[13,14] 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.[15] 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.[16] 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.[17] This unprecendented approach to copper(I) 2-furylcarbene complexes[18] 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.

Acknowledgment. Financial support for this work is acknowledged (Grants CTQ2004-08077, CTQ2007-61048, and IB 05-136). L.R. thanks the Ministerio de Educación y Ciencia for a predoctoral fellowship.

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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(6) For a review on the synthetic applications of copper(I) carbene complexes resulting from copper(I)-catalyzed decomposition of diazoesters, see: Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088.

(7) The generation of a Cu(I) isoindazolylcarbene by CuCl-catalyzed azo-enyne cyclization and the cyclopropanation to tetramethylethene has been reported: (a) Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 1572. (b) Shirtcliff, L. D.; Haley, M. H.; Herges, R. *J. Org. Chem.* **2007**, *72*, 2411.

(8) The copper-catalyzed Si−H insertion into diazoesters and ketones has been reported: Bagheri, V.; Doyle, M. P.; Taunton, J.; Claxton, E. E. *J. Org. Chem.* **1988**, *53*, 6158.

(9) The reaction of the alkyl substituted diyne **1b** with [Cu(CH$_3$CN)$_4$][BF$_4$] (5 mol%, CH$_2$Cl$_2$, room temp) in the absence of triethylsilane **3a** afforded the corresponding dimer **2b** in 85% yield.

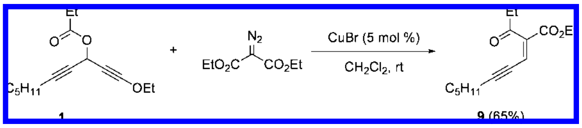
(10) The extremely ease with which most transition metal alkyl carbenes suffer *β*-hydride elimination is well documented, see for example: (a) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908 In some cases the use of low reaction temperatures and sterically demanding carboxylates proved to be useful in order to avoid *β*-hydride elimination. For recent successful Rh(I)-catalyzed reactions of α-alkyl-α-diazoesters with alkynes and alkenes, see: (b) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987.

(11) In all the cases examined, the dimer resulting from the competing carbene ligand dimerization was detected in less than 10% yield.

(12) Unfortunately, all attempts to perform the reaction with Bu$_3$SnH resulted only in extensive decomposition and no furane derivative was ever isolated.

(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$_3$CN)$_4$][BF$_4$], 5 mol %, CH$_2$Cl$_2$, room temp) or EDA (CuBr, 5 mol %, CH$_2$Cl$_2$, room temp) afforded the furan derivatives **4e** (92%) and **7b** (89%), respectively.



(15) The oxidation of the gold(I) carbene intermediate formed by 1,2-pivaloyloxy rearrangement of propargylic esters has been achieved using sulfoxides as the stoichiometric oxidants: Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.

(16) The metal-catalyzed reactions of bis-propargylic esters are extremely rare. For an isolated example involving (1,1-diethynylmetyl) acetates, see: Kato, K.; Teraguchi, R.; Kusakabe, T.; Motodate, S.; Yamamura, S.; Mochida, T.; Akita, H. *Synlett* **2007**, 63.

(17) Nonmetal 2-furfurylidenes from diazocompounds cannot be trapped due to rapid ring-opening rearrangement; see: (a) Sun, Y.; Wong, M. W. *J. Org. Chem.* **1999**, *64*, 9170 For successful trapping of 2-furyl carbenes derived from photocyclization of 1,2-diketones conjugated with eneyne, see: (b) Nakatani, K.; Adachi, K.; Tanabe, K.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8221.

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