ORGANIC LETTERS
2012
Vol. 14, No. 6
1652–1655

Copper-Catalyzed Coupling of 1,1-Dibromo-1-alkenes with Phenols: A General, Modular, and Efficient Synthesis of Ynol Ethers, Bromo Enol Ethers, and Ketene Acetals

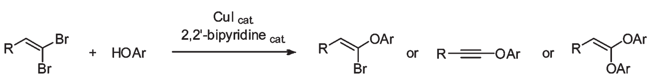
Kévin Jouvin,[†] Alexandre Bayle,[†] Frédéric Legrand,[†] and Gwilherm Evano*,[†,‡]

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint-Quentin en Yvelines, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France, and Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université Libre de Bruxelles, Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium

gevano@ulb.ac.be

Received February 29, 2012

ABSTRACT



An efficient and general copper-catalyzed method is reported for the synthesis of phenol-derived 1-bromoenol ethers, ynol ethers, and ketene acetals by chemodivergent copper-catalyzed cross-coupling between readily available 1,1-dibromo-1-alkenes and phenols.

Heteroatom-substituted alkenes and alkynes are functional groups that display enormous potential in organic chemistry and high versatility. Significant advances have been made recently in the synthesis of ynamides,[1] enamides,[2] phosphorus-substituted acetylenes,[3] and olefins,[4] which considerably expanded their synthetic utility, as exemplified with the renaissance of the chemistry of nitrogen-substituted alkynes due to the development of efficient methods for their preparation. Alkynyl[5,6] and alkenyl[2,7] ethers, while possessing many of the reactivity features of their nitrogen-substituted counterparts, have been far less investigated because of the relatively few methods available for their synthesis, except in the case of simple enol ethers. Here we report an efficient, general, and chemodivergent method for the synthesis of stable, phenol-derived 1-bromoenol ethers **3**, ynol ethers **4**, and ketene acetals **5** by copper-catalyzed cross-coupling between readily available 1,1-dibromo-1-alkenes **1** and phenols **2** (Scheme 1).

While the use of *gem*-dibromoalkenes **1** in palladium catalysis has been extensively studied,[8] their use in combination with copper-based catalytic systems, which might

[†] Université de Versailles Saint-Quentin en Yvelines.
[‡] Université Libre de Bruxelles.

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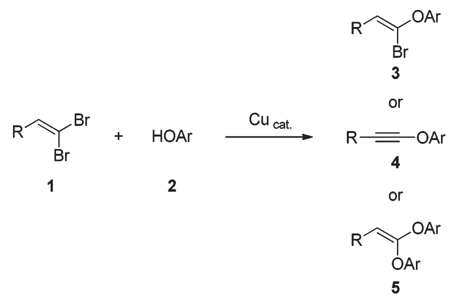
10.1021/ol300491d
Published on Web 03/07/2012

be especially useful for the introduction of various heteroatoms, has been far less developed. We have recently shown that they are indeed versatile partners that can be readily coupled with nitrogen or phosphorus nucleophiles, yielding ynamides, ketene *N*,*N*-acetals, or vinylphosphonates with remarkable efficiency.[9] Based on these results, we felt that their reaction with phenols in combination with a suitable copper catalyst[10,11] might provide an efficient and modular entry to 1-bromo-enol ethers **3**,[12] ynol ethers **4**, and ketene acetals **5**, especially useful building blocks with limited availability, provided that both the cross-coupling mode (regioselective monocoupling, double coupling, or alkynylative coupling) and the easy dimerization of **1** could be controlled.

Scheme 1. Chemodivergent Synthesis of 1-Bromoenol Ethers, Ynol Ethers, and Ketene Acetals from Vinyl Dibromides



To test this hypothesis, we initiated our studies by examining the reaction of *m*-cresol **2a** with 1.5 equiv of 1,1-dibromooct-1-ene **1a**, in order to promote the selective formation of the monocoupled product **3a**, in the presence of excess potassium phosphate, catalytic amounts of copper(I) iodide, and various bidentate ligands susceptible to promote the cross-coupling (Figure 1). Best results were obtained with 3,4,7,8-tetramethyl-1,10-phenanthroline **F** and 2,2′-bipyridine **G**, the latter affording bromoenol ether **3a** in 81% yield with a slightly better diastereoselectivity (*Z*/*E*: 91/9). Finally, toluene and potassium phosphate were found to be the most suitable solvent and base, respectively, to minimize the dimerization of **1a**.

To evaluate the scope of this site-selective cross coupling, we examined the reactivity of a series of 1,1-dibromo-1-

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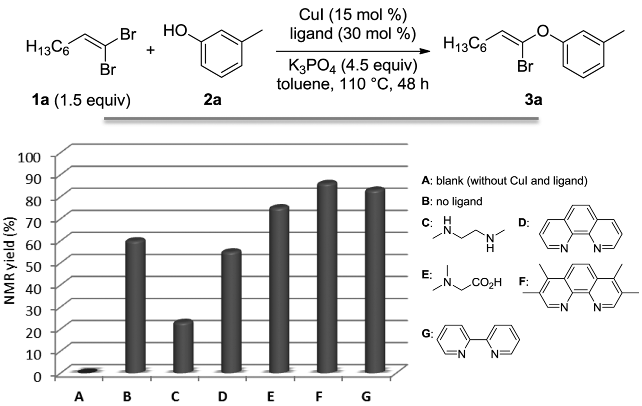

Figure 1. Ligand influence on the cross-coupling.

alkenes **1** and phenols **2** under the optimized conditions (Figure 2). *Para*-, *meta*-, and *ortho*-substituted phenols were all readily transformed to the corresponding bromoenol ethers **3**, although the cross-coupling was slowed down in the last case. The presence of electron-withdrawing or -donating groups had virtually no effect on the outcome of the reaction and even the challenging 4-bromophenol could be smoothly transformed to the corresponding enol ether **3g**, without competing reaction involving the aromatic bromide. The reaction was found to be equally efficient for the synthesis of alkyl- (**3a-s**), alkenyl- (**3t**) and aryl- (**3u**, **3v**) substituted bromoenol ethers and allowed the synthesis of more complex bromoenol ethers such as the ones derived from citronellal, **3w**, or *β*-estradiol, **3x**.[13] Trifluoroethanol could also be used as a cross-coupling partner in place of phenols, yielding stable bromoenol ethers **3′** in moderate yields. In all cases, a site selective cross-coupling involving the least hindered C–Br bond occurred, favoring the formation of the *Z*-isomers,[14] compound that cannot be obtained using other methods, with synthetically useful levels of stereoselectivity (*Z*/*E*: 74/26 to 96/4).[15] In an attempt to further extend the scope of this cross-coupling, the use of aliphatic alcohols was also evaluated but, as anticipated, mostly resulted in homodimerization of the starting dibromoalkene. Interestingly, the reaction is not limited to the small scale used for the coupling reactions described above (i.e., 0.7 mmol) as illustrated by the gram scale synthesis of bromoenol ethers **3a** and **3c**.

We next turned our attention to the selective formation of ynol ethers **4** starting from the same reaction partners **1** and **2** and found that exposure of the crude reaction mixtures to potassium *tert*-butoxide after dilution with dioxane triggered a rapid *β*-elimination of the intermediate bromoenol ethers (Figure 3).[16] Using this slight modification,

(13) The lower yields observed with some substrates can be attributed to catalyst deactivation or dimerization of the dibromoalkene.

(14) The stereochemistry of bromoenol ethers **3a′** and **3c′** was assigned on the basis of NOE experiments. See the Supporting Information for details.

(15) *Z*/*E* ratio from crude reaction mixtures.

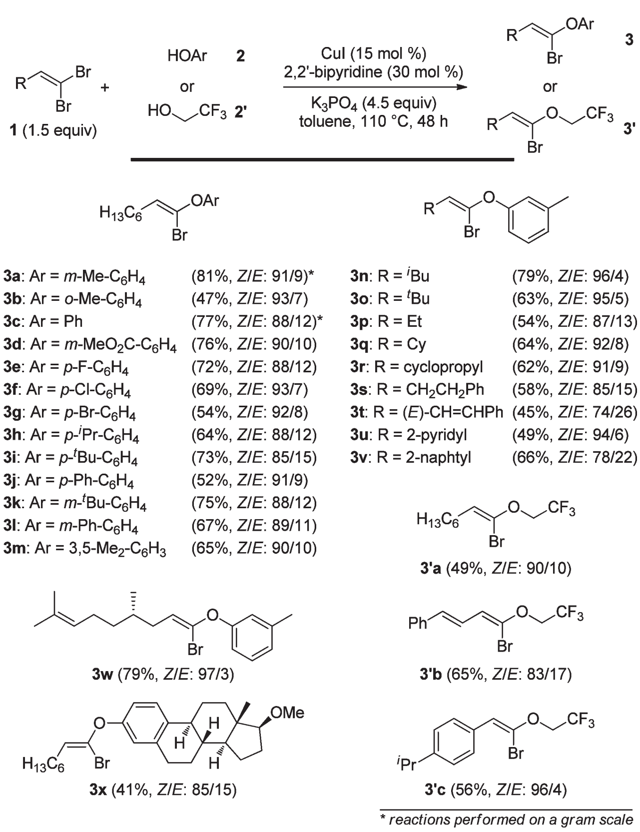

Figure 2. Site-selective cross-coupling to 1-bromoenol ethers.

ynol ethers **4** with representative substitution patterns could be obtained with high efficiency, which nicely complements their classical synthesis involving reaction with trichloroethylene followed by a Fritsch–Buttenberg–Wiechel rearrangement.[6]

We finally envisioned a modification of our procedure that would allow for a clean and selective double cross-coupling, which would provide a straightforward entry to phenol-derived ketene acetals **5**, compounds for which there is no general preparation to date. The optimization of this coupling turned out to be a lot more complicated due to problems associated to the high sensitivity of these building blocks toward hydrolysis or during their purification. Ketene acetals **5** could however be obtained in virtually pure form by performing the reaction with excess phenol in dioxane at 110 °C followed by simple removal of the catalyst and base by filtration, concentration of the crude mixture and elimination of excess phenol by extraction of the apolar product with pentane. Using this optimized procedure, phenol- and trifluoroethanol-derived ketene acetals **5** and **5′** could be obtained with high efficiency, regardless of the substitution pattern or electronic properties of the starting materials (Figure 4).[13]

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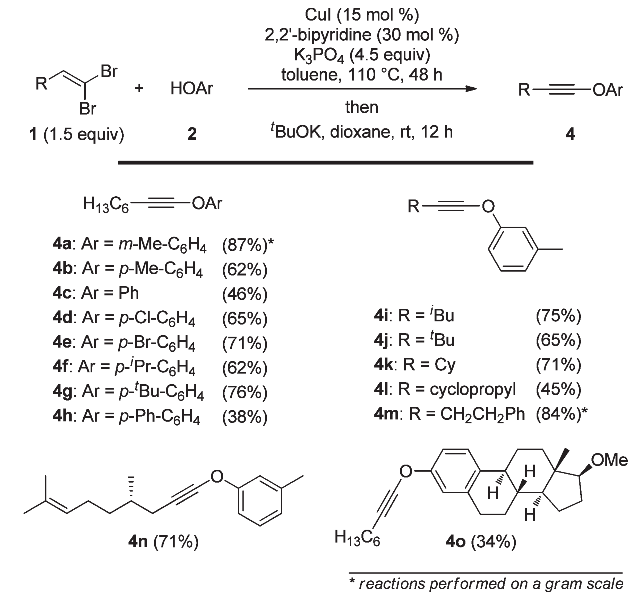


Figure 3. Synthesis of ynol ethers by site-selective coupling/elimination.

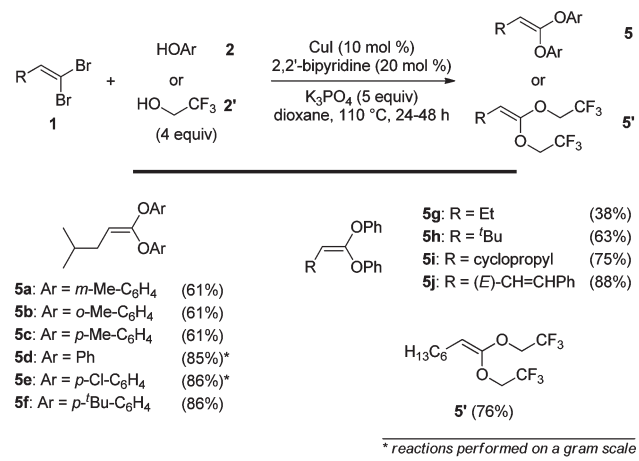
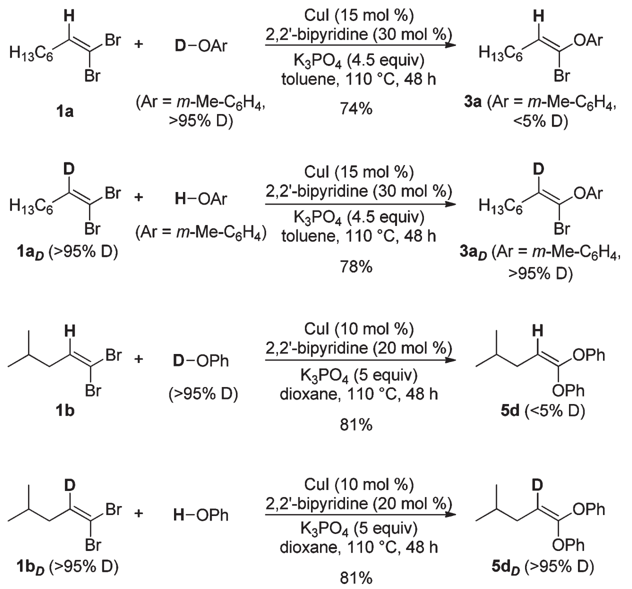


Figure 4. Synthesis of ketene acetals by double cross-coupling.

From a mechanistic point of view, both bromo enol ethers **3** and ketene acetals **5** could be respectively formed by either site-selective/double cross coupling from the corresponding dibromoalkenes or by hydrobromination/hydroalkoxylation of intermediate ynol ethers. To probe the operative mechanism, deuterated (**1a**$_D$ and **1b**$_D$) and nondeuterated (**1a** and **1b**) dibromoalkenes were respectively reacted with deuterated and nondeuterated phenols under our coupling conditions optimized for the synthesis of bromoenol ethers **3** and ketene acetals **5** (Scheme 2). Results from these experiments unambiguously demonstrate that the vinylic hydrogen atom of the starting dibromides is fully retained during the reaction, clearly

Scheme 2. Cross-Coupling with Deuterated Substrates



indicating that β-elimination followed by hydrobromination or hydroalkoxylation is not a competitive pathway.

This result is also in agreement with the stereoselectivity observed for the formation of **3**. Bromoenol ethers **3** would therefore arise from a regioselective cross coupling governed by the known higher reactivity of the *trans* C–Br bond of dibromides **1** toward oxidative addition,[8,17] while a double cross-coupling would account for the formation of ketene acetals **5**.[18]

In conclusion, we have developed an efficient and general copper-catalyzed method for the synthesis of phenol-derived 1-bromo-enol ethers, ynol ethers, and ketene acetals from readily available 1,1-dibromo-1-alkenes. The outcome and chemoselectivity of the reaction are controlled by simple modification of the reaction conditions. We envision great acceptance and applicability for these simple and practical procedures which provide straightforward entries to highly valuable building blocks. Further studies are underway in our laboratory to further extend their use in organic synthesis.

Acknowledgment. We thank the CNRS, the University of Versailles, and the ANR (Project Nos. ProteInh ANR-07-JCJC-0025-01 and DYNAMITE ANR-2010-BLAN-704) for financial support. K.J. acknowledges the Ministère de la Recherche for a graduate fellowship.

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

The authors declare no competing financial interest.

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(18) This mechanism is also supported by the formation of ketene acetals from the corresponding bromoenol ethers when the latter were reacted under the reaction conditions shown in Figure 4 and by the presence of bromoenol ethers before completion of the reaction yielding to ketene acetals.