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Copper-Catalyzed Silylation Reactions of Propargyl Epoxides: Easy Access to 2,3-Allenols and Stereodefined Alkenes

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Xi-Hao Chang,^a Zheng-Li Liu,^a Yun-Cheng Luo,^a Chao Yang,^a Xiao-Wei Liu,^a Bing-Chao Da,^a Jie-Jun Li,^a Tanveer Ahmad,^a Teck-Peng Loh^{*a,b,c} and Yun-He Xu^{*a}

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Efficient silylation reactions of propargyl epoxides catalyzed by copper catalyst have been developed. Under mild reaction conditions, the tri- and tetrasubstituted functionalized allenols and alkenes could be selectively obtained in moderate to high yields via tuning the bases and solvents used in the reactions. This work provides straightforward and efficient approaches to the synthesis of multifunctionalized 2,3-allenols and stereodefined alkenes from the same starting material of propargyl epoxides.

Multifunctionalized alkenes are fundamental building blocks for the construction of complex molecules.^[1,2,] Although numerous methods have been developed for the preparation of these compounds, the need to control the stereoselectivity as well as to access structural diversity is still a challenging task.^[3] Therefore, methods such as carbometallation of alkynes and direct functionalization of diverse allenes have been developed.^[4,5] However, the difficulty in controlling the stereochemistry as well as limited substrate scope encourage us to develop versatile methods to access a wide variety of polyfunctionalized alkenyl compounds via formation of 2.3-allenols as precursors. In conjunction with our continuous interests in the preparation of multifunctionalized alkenes^[6] and allenes,^[7] herein we report copper-catalyzed silylation reactions of propargyl epoxides for the synthesis of silyl-substituted 2,3-allenols and alkenes. The product distributions can be precisely predicted and controlled by tuning the solvents and bases used in the reactions (Scheme 1). Moreover, boryl and silyl functionalized alkenes can be easily accessed via the transformation of 2,3-allenol products.

As a class of versatile building blocks,^[8] the 2,3-allenols have been widely applied in the synthesis of complex organic molecules and natural products such as (+)-varitriol^[9] and Liatrin^[10]. Among the reliable procedures for the preparation of multisubstituted allenols, the S_N2' -type reactions between alkynyl oxiranes and

organometallic reagents have attracted much attention.^[11] Nevertheless, the use of expensive transition-metal catalysts or/and sensitive organometallic reagents limited their wide application.



Scheme 1. Copper-Catalyzed Synthesis of Multi-substituted Fuanctional 2,3-Allenols and Alkenes Using Propargyl Epoxides.

Therefore, we attempted to use copper salts as the catalysts to test the silylation reaction of propargyl epoxides.^[12] Firstly, the propagyl epoxide 1a and silylboronate 2 were chosen for the model reaction to optimize the reaction conditions. To our delight, the desired product 2,3-allenol 3a could be obtained in 45% isolated yield in the presence of 3 mol % CuCN as the catalyst and 10 mol % diisopropylethylamine as the additive in isopropanol solution at 28 °C (Table 1, entry 1). Next, different solvents were screened, and methanol was found to be the optimal solvent to provide the highest product yield (entries 2-4). It was found that other bases such as triethylamine and sodium methoxide could be used to give the desired product with comparable efficiency (entries 5 and 6). In addition, other copper salts such as CuCl, CuBr or CuI were less efficient to catalyze this reaction (entries 7-9). Finally, increasing the use of silviboronate 2 up to 1.5 equivalents would greatly improve the product yield to 92% (Partial silvlboronate would decompose and form unreactive hexamethyldisilane under the catalytic conditions which could be observed by crude ¹H NMR spectrum analysis, entry 10). The control experiments showed that both the copper catalyst and base are crucial to make the desired 2,3-allenol product 3a (entries 11 and 12).

^a Department of Chemistry, University of Science and Technology of China, Hefei, Anhui, China, 230026. E-mail: xyh0709@ustc.edu.cn, teckpeng@ustc.edu.cn

^{b.} Institute of Advanced Synthesis, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing, Jiangsu, China, 210009.

^c Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637616. †Electronic Supplementary Information (ESI) available: Experimental details ofsynthesis and NMR and NOE spectra. See DOI: 10.1039/x0xx00000x

 Table 1. Optimization of Reaction Conditions of Copper-catalyzed Silylation

 Reaction of Propargyl Epoxide 1a with PhMe₂Si-Bpin.^[a]



| entry | Catalyst (mol %) | Base | solvent | temp (°C) | yield (%) ^[b] |
|-------------------|---------------------|-------------------|-----------------|--------------|-----------------------------|
| 1 | CuCN (3) | DIPEA | isopropanol | 28 | 45 |
| 2 | CuCN (3) | DIPEA | ethylene glycol | 28 | 13 |
| 3 | CuCN (3) | DIPEA | THF | 28 | 14 ^[c] |
| 4 | CuCN (3) | DIPEA | MeOH | 28 | 78 |
| 5 | CuCN (3) | Et ₃ N | MeOH | 28 | 69 |
| 6 | CuCN (3) | MeONa | MeOH | 28 | 74 |
| 7 | Cul (3) | DIPEA | MeOH | 28 | 16 |
| 8 | CuBr (3) | DIPEA | MeOH | 28 | 43 |
| 9 | CuCl (3) | DIPEA | MeOH | 28 | 25 |
| 10 ^[d] | CuCN (3) | DIPEA | MeOH | 28 | 92 |
| 11 | CuCN (3) | | MeOH | 28 | 9 ^c |
| 12 | | DIPEA | MeOH | 28 | e |

[a] Unless noted otherwise, the reaction was conducted with **1a** (0.2 mmol), **2** (0.21 mmol, 1.05 equiv), copper catalyst (0.006 mmol, 3 mol %) and base (0.02 mmol, 10 mol %) in solvent (1.2 mL) for 8 h at 28 °C under nitrogen atmosphere. [b] Isolated yield. [c] ¹H NMR yield. [d] The silylboronate **2** was used as 1.5 equivalents. [e] No reaction.

Chart 1. Synthesis of 2,3-Allenols Using Propargyl Epoxide Substrates and $\mathsf{PhMe}_2\mathsf{Si-Bpin.}^{[a,b]}$



[a] Unless noted otherwise, the reaction condition was performed under the following reaction conditions: 0.2 mmol epoxide 1, 0.3 mmol 2 (1.5 equiv), 3 mol % CuCN and 10

mol % DIPEA in 1.2 mL MeOH at 28 $^{\circ}\text{C}$ under nitrogen atmosphere for 8 hours. [b] Isolated yield.



Scheme 2. Determination of Relative Configuration of Compound 3p.

With the optimized reaction conditions in hand, a range of propargyl epoxides substrates were subjected to this copper(I) cyanide catalysed silylation reaction. Different aryl-substituted propargyl epoxides proceeded well to afford the corresponding 2,3-allenols in moderate to high yields. Various functional groups such as halides, cyano and acetal in the substrates were well tolerated. Furthermore, when aliphatic substituted propargyl epoxide compounds were employed, the corresponding products were also obtained in high yields. It is noteworthy that the tetrasubstituted allenols with *anti*-configuration could be afforded in high yields and with excellent stereoselectivities. The stereochemical assignment of the 2,3-allenol **3p** was determined by NOE measurement of its dihydrofuran derivative obtained *via* treatment **3p** with AgNO₃ (Scheme 2, please see the details in SI).^[13] Other tetrasubstituted allenols were assigned by the analogy of their ¹H NMR spectrum.

Chart 2. Copper-catalyzed Disilylation of Propargyl Epoxides for the Synthesis of Tetrasubstituted Alkenes with PhMe_2Si-Bpin. $^{\rm [a,c]}$



[a] Reaction was run under the following reaction conditions: 0.2 mmol epoxide 1, 0.6 mmol 2 (3.0 equiv), 10 mol % CuCN and 10 mol % K_2CO_3 in 1.2 mL dry DMF at 0 °C under nitrogen atmosphere for 14 h. [b] The reaction time was 20 h. [c] Isolated yield.

During screening the reaction conditions for the synthesis of 2,3allenol **3a**, minor disilylation product **4a** was detected in some cases. Given the unique performances of the disilylated alkenes in the synthesis of organic materials and biologically active molecules,^[14] we intended to develop a practical strategy to prepare these molecules in a highly stereodefined manner. After further careful optimization of the reaction conditions, it was found that the tetrasubstituted alkene product **4a** with *trans*-configuration could be obtained in 77% isolated yield in the presence of 10 mol % CuCN

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as the catalyst and 10 mol % K_2CO_3 in DMF solution. Next, various aryl-substituted propargyl epoxides were tested as substrates for this reaction. All the desired products could be obtained in good yields and with excellent stereoselectivities. However, only 35% isolated yield of **4I** was isolated when the aliphatic substituted substrate was subjected to this reaction.

Inspired by the observed results, we proposed that the tetrasubstituted alkene **4** should be generated from the 2,3-allenol *via* selective silylcupration of the allenic double bond and β -hydroxyl elimination processes. Therefore, we hypothesized whether it was possible to get another silyl-substituted alkene product **5** *via* tuning the silylcupration to the other allenic double bond (Scheme 3). We proposed that rapid protonation step could favor the formation of the desired product. After careful screening the reaction conditions, the desired product **5a** was obtained in 83% yield as the major stereoisomer by using 1-pentanol as the solvent (chart 3). Moreover, other aryl groups substituted propargyl epoxides could afford the corresponding products in moderate to high yields and with good stereoselectivities. Unfortunately, no desired product could be accessible when the aliphatic substituted substrate was tested in this reaction.



Scheme 3. Design of Regio- and Stereoselective Silylcupration of 2,3-Allenol.

Chart 3. Copper-catalyzed Disilylation of Propargyl Epoxides for the Synthesis of Trisubstituted Alkenes with $\mathsf{PhMe}_2\mathsf{Si-Bpin}.^{[a,b]}$



[a] Reaction was run under the following reaction conditions: 0.2 mmol epoxide 1, 0.6 mmol 2 (3.0 equiv), 5 mol % CuCN and 10 mol % K₂CO₃ in 1.2 mL 1-pentanol at 60 $^{\circ}$ C under nitrogen atmosphere for 11 h. [b] Isolated yield.

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Control experiments were carried out to disclose the possible mechanistic pathway of the silylation reactions. The results showed that the disilyl-substituted alkene products **4a** and **5a** could be generated in high yields and with excellent stereoselectivities from the 2,3-allenol **3a** under the optimized reaction conditions respectively (Scheme 4, eq 1-2).

Finally, we briefly studied the copper-catalyzed silylation reaction of propargyl aziridine. Under the optimized reaction conditions for the synthesis of 2,3-allenols, the allenylsilane product **3s** was obtained in 98% yield (Scheme 5, eq 3). Furthermore, the borylsilyl-substituted alkenes **6a** and **6b** could be obtained in high yields and with moderate stereoselectivities by using B_2pin_2 under the optimized reaction conditions for the synthesis of olefin product **4** (Scheme 5, eqs 4 and 5).



Scheme 4. Control Experiments to Explore the Possible Reaction Pathways.



Scheme 5. Copper-Catalyzed Silylation or Boronation of Propargyl Aziridine and 2.3-Allenols.



Scheme 6. Proposed Plausible Mechanism for the Copper-Catalyzed Hydrosilylation of Propargyl Epoxides.

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A plausible mechanistic pathway of CuCN catalyzed hydrosilylation reaction of propargyl epoxides was depicted as in Scheme 6.^[15] First, a [Cu]-Si species I was generated from silylboronate 2 in the presence of CuCN as catalyst and base as additive, followed by coordinating with the triple bond of propargyl epoxide 1 to generate the intermediate II. After addition, an alkoxycopper species III generated in situ would be protonated by MeOH to give the desired 2,3-allenol product 3. The released CuOMe as catalyst (IV) would be involved into next catalytic cycle.

In conclusion, a copper-catalyzed silylation reaction of propargyl epoxides was developed. In this work, the multifunctionalized 2,3allenols and stereodefined tri- and tetrasubstituted alkenes could be selectively obtained in good yields under mild reaction conditions. Moreover, the useful boryl- and silyl-substituted alkenes could also be achieved *via* the derivation of 2,3-allenols obtained in this approach. Therefore, current work provides a simple and practical method to prepare multifunctionalized 2,3-allenols and stereodefined alkenes.

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