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**Authors:** Masahiro Sai and Seijiro Matsubara



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# Copper-Catalyzed Direct and Stereoselective Synthesis of Conjugated Enynes from α-Allenols

Masahiro Sai[a,*] and Seijiro Matsubara[b]

[a] Research Foundation ITSUU Laboratory, C1232 Kanagawa Science Park R & D Building, 3-2-1 Sakado, Takatsu-ku, Kawasaki, Kanagawa 213-0012, Japan
Phone: (+81)-44-819-4044; fax: (+81)-44-819-4483; e-mail: msai@itsuu.or.jp

[b] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan
Phone: (+81)-75-383-7130; fax: (+81)-75-383-2438; e-mail: matsubara.seijiro.2e@kyoto-u.ac.jp

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**Abstract.** A novel strategy for the stereoselective synthesis of conjugated enynes directly from α-allenols has been developed. The reaction proceeds with perfect *E*-selectivity and exhibits high functional group compatibility. This catalytic system can also be applied to the stereoselective synthesis of conjugated dienynes and enediynes.

**Keywords:** α-allenols; copper; enynes; dienynes; enediynes

Conjugated enynes are important structures that serve as key components of a wide range of biologically active compounds, natural products, pharmaceuticals, and functional materials.[1] The Sonogashira cross-coupling of alkenyl halides with terminal alkynes is the most widely employed method for the construction of enyne scaffolds.[2,3] However, despite its usefulness, stereocontrolled synthesis of conjugated enynes by this method remains challenging, largely because the transformation proceeds in a stereospecific manner, necessitating the preparation of stereochemically pure alkenyl halides as starting materials. In addition, these reagents often lose their stereospecificity during the coupling reaction, resulting in a mixture of *E* and *Z* isomers. Therefore, the development of a new strategy for stereocontrolled enyne synthesis from simple starting materials with high functional group tolerance is highly desirable.

α-Allenols react through the activation of their two functional groups: the allene moiety and the hydroxy group. Over recent decades, oxycyclization of α-allenols to 2,5-dihydrofurans via activation of the allene moiety has been intensively studied (Scheme 1, path a).[4] Furthermore, Ma et al. and Cho et al. have independently reported the $S_N2'$ reaction of α-allenols with metal halides to give 2-halo-1,3-butadienes (Scheme 1, path b).[5] Moreover, in 2009, Malacria, Lacôte, and Gandon reported the first catalytic Nazarov-type cyclization[6] of α-allenols to benzofulvenes using silver triflate, triflic acid, or phosphomolybdic acid (Scheme 1, path c).[7] In our previous study, we developed a similar Nazarov-type cyclization for a broad range of substrates using $LiPF_6$ as the catalyst.[8b] In this study, enones were also obtained via the attack of in situ-generated lithium hydroxide at the allenic center of the cation intermediate (Scheme 1, path d). On the basis of this result, we envisioned that if the in situ-generated metal hydroxide could be directed to selectively abstract the terminal allenic proton instead of attacking the allenic center, a new method for the direct and stereoselective enyne synthesis would be realized (Scheme 1, path e).[9,10] To the best of our knowledge, there are only two previous reports on the preparation of enynes directly from α-allenols: in 2009, Lee et al. first reported the Lewis acid-promoted transformation of an α-allenol to an enyne.[9a] However, only one α-allenol was examined for the enyne synthesis, and considerable amounts of enone byproduct were also generated. Moreover, the reaction required stoichiometric amounts of $In(OTf)_3$ and $BF_3{\cdot}Et_2O$ or a high loading of TMSOTf (20 mol%). In 2017, Lin et al. developed a similar reaction with a broader substrate scope using $Sc(OTf)_3$ as the catalyst.[9b] However, the yields were still moderate, and the reaction also suffered from the formation of enone byproduct. Accordingly, as part of the continuation of our work on the Lewis acid-catalyzed transformation of unsaturated alcohols,[8] we herein describe a novel copper-catalyzed stereoselective enyne synthesis that proceeds directly from α-allenols.

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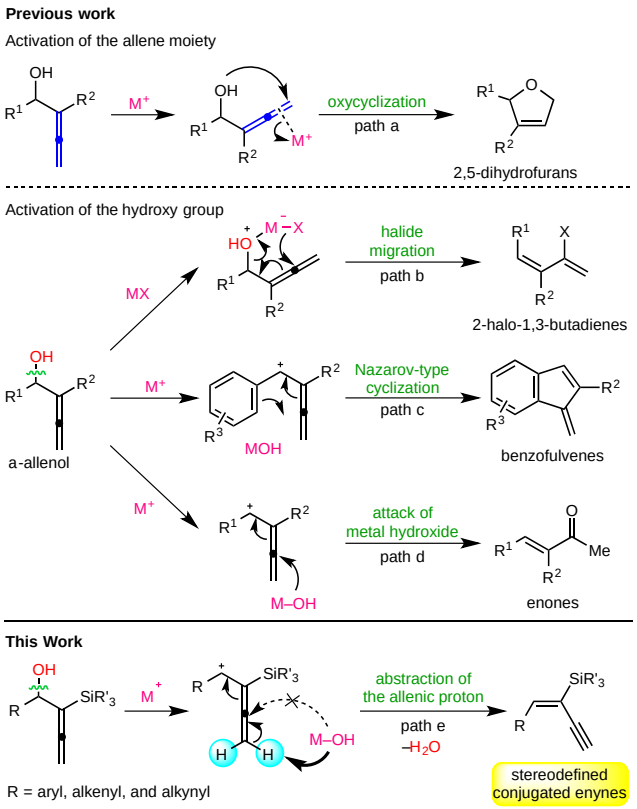
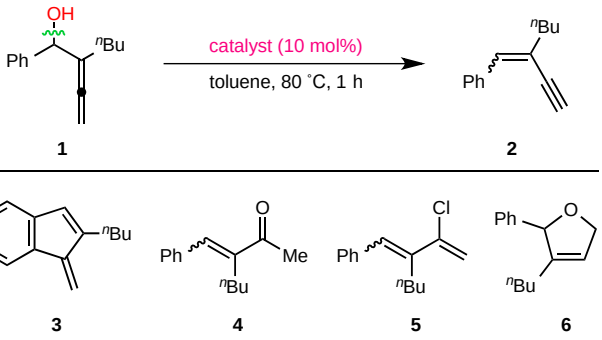



**Scheme 1.** Lewis acid-catalyzed various transformations of α-allenols.

Our initial efforts were directed toward identifying the appropriate catalyst and reaction conditions for the transformation of α-allenol **1**[11] to conjugated enyne **2** (Table 1). When $LiPF_6$, an efficient catalyst for the activation of the hydroxy group,[8b] was employed, the desired enyne **2** was obtained in only 16% yield (entry 1). Metal chlorides such as $AlCl_3$, $InCl_3$, and $FeCl_3$ mainly afforded 2-chloro-1,3-butadiene **5** via an $S_N2'$-type attack of the chloride anion on the allenic center (entries 2–4). Group 3 metal triflates such as $Sc(OTf)_3$[9b] and $Y(OTf)_3$ exhibited superior catalytic activities in this system, albeit with the generation of considerable amounts of benzofulvene **3** and enone **4** (entries 5 and 6). When AgOTf was employed, 2,5-dihydrofuran **6** was obtained as the major product with the formation of enyne **2** in only 22% yield (entry 7). However, in this case, the formation of byproducts **3** and **4** was largely suppressed. Accordingly, the catalytic activities of group 11 metal Lewis acids were further examined. As a result, we found that $Cu(OTf)_2$ was particularly effective for this enyne synthesis and that the competing side reactions were significantly inhibited (entry 8).[12]

**Table 1.** Catalyst screening.[a]

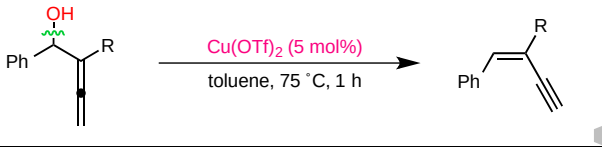



| Entry | Catalyst | Yield [%][b] | | | | | |
|---|---|---|---|---|---|---|---|
| | | **1** | **2** (dr)[b] | **3** | **4** | **5** | **6** |
| 1 | $LiPF_6$ | 0 | 16 (1.6:1) | 17 | 33 | 0 | 0 |
| 2 | $AlCl_3$ | 77 | <1 | 1 | 2 | 10 | 0 |
| 3 | $InCl_3$ | 79 | <1 | 3 | 1 | 19 | 0 |
| 4 | $FeCl_3$ | 71 | <1 | 4 | 2 | 22 | 0 |
| 5 | $Sc(OTf)_3$ | 0 | 44 (1.8:1) | 26 | 22 | 0 | 0 |
| 6 | $Y(OTf)_3$ | 0 | 41 (1:1) | 31 | 17 | 0 | 0 |
| 7 | AgOTf | 32 | 22 (1.1:1) | 1 | 5 | 0 | 35 |
| 8 | $Cu(OTf)_2$ | 0 | 83 (1.1:1) | 5 | 12 | 0 | 0 |
| 9 | CuOTf[c] | 0 | 63 (1.3:1) | 9 | 16 | 0 | 7 |

[a] Conditions: **1** (0.25 mmol) and catalyst (10 mol%) in toluene (1.5 mL) at 80 °C for 1 h. [b] Determined by $^1H$ NMR analysis of the unpurified reaction mixture. [c] CuOTf·1/2$C_6H_6$ complex was employed.

The effect of allenic substituents (R) on the stereoselectivity was subsequently evaluated (Table 2). Perfect *Z*-selectivity was observed when the *n*-butyl group was replaced by a *tert*-butyl group (**7**) (entry 1), showing that the stereoselectivity of this process is dominated by steric factors.[13] In view of the synthetic utility and the further functionalization of the product, silyl-containing substrates were examined. Notably, the use of such substrates was found to allow the exclusive formation of *E* isomers (entries 2–4). TIPS-substituted α-allenol **13a** gave the best result in terms of stereoselectivity and yield (entry 4).

**Table 2.** The effect of the allenic substituents (R) on the stereoselectivity.[a]

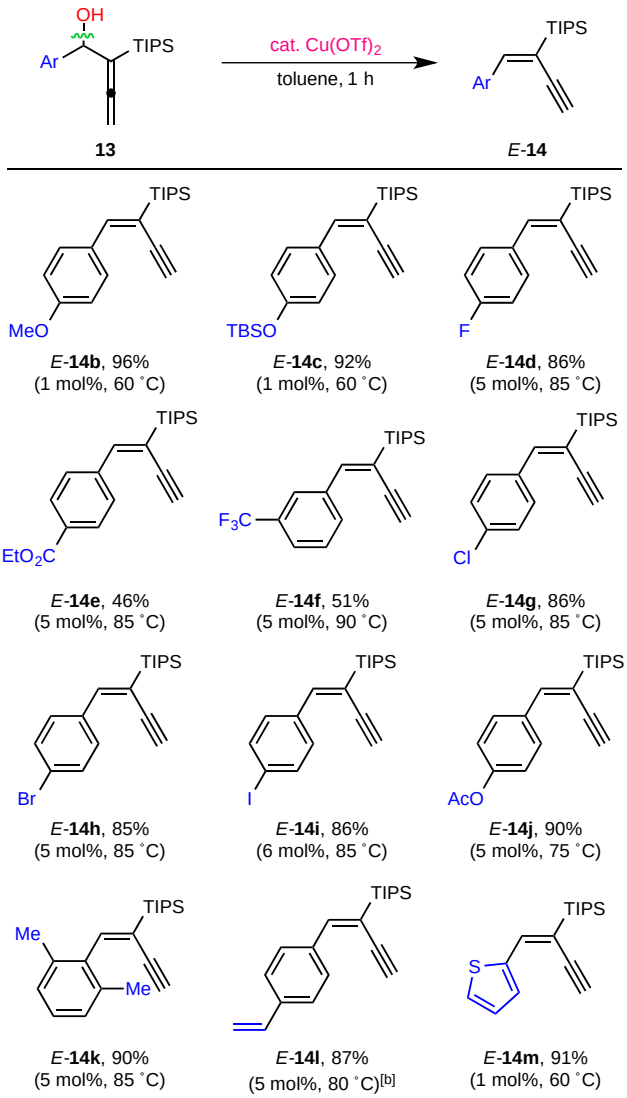



| Entry | R | Yield [%][b] | dr[b] |
|---|---|---|---|
| 1 | $^t$Bu (**7**) | 78 (**8**) | *Z* only |
| 2 | TMS (**9**) | 69 (**10**) | *E* only |
| 3 | TBS (**11**) | 64 (**12**) | *E* only |
| 4 | TIPS (**13a**) | 82[c] (**14a**) | *E* only |

[a] Conditions: α-allenol (0.25 mmol) and $Cu(OTf)_2$ (5 mol%) in toluene (1.5 mL) for 1 h. [b] Determined by $^1H$ NMR analysis of the unpurified reaction mixture. [c] Isolated yield (0.50 mmol scale).

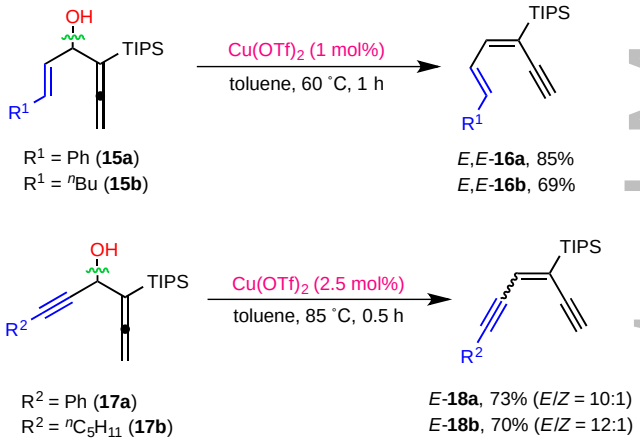
The series of TIPS-substituted secondary α-allenols **13** were converted to the corresponding conjugated enynes **14** with complete *E*-selectivity (Table 3). In all cases, none of the *Z*-isomers were detected by $^1$H NMR analysis of the crude reaction mixtures. The reaction proceeded smoothly with only 1 mol% catalyst loading when electron-rich aromatic compounds were used (**14b** and **14c**). α-Allenols containing electron-deficient aryl groups gave the corresponding enynes (**14d**–**14f**) in moderate to good yields.[14] Carbon–halogen bonds, including the C–I bond, were well tolerated under the reaction conditions employed (**14g**–**14i**), demonstrating a significant synthetic advantage of the current method over the cross-coupling method. Steric encumbrance around the hydroxy functionality has no deleterious effect on the yield (**14k**). Heteroaromatic substrates can also be employed, and enyne **14m** was isolated in 91% yield. The stereochemistry of **14k** was unambiguously determined to be *E* via X-ray crystallography,[15] and all of the enyne products were assigned by analogy.

**Table 3.** Substrate scope of the enyne synthesis.[a]




[a] Conditions: **13** (0.50 mmol) and $Cu(OTf)_2$ (5 mol%) in toluene (3 mL) for 1 h. Isolated yield is shown. [b] Run for 0.5 h.

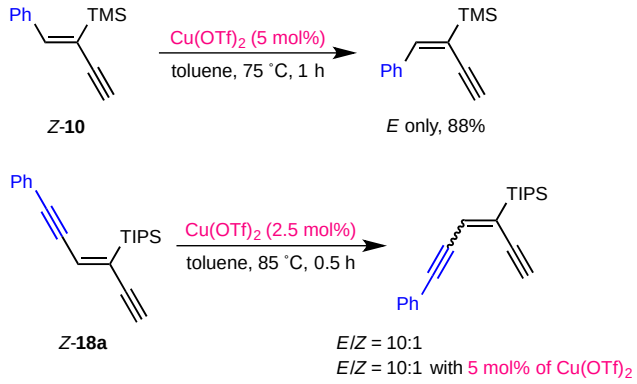
Encouraged by these results, we attempted to apply the new strategy to the stereoselective synthesis of conjugated dienynes and enediynes (Scheme 2). Conjugated dienynes are valuable precursors of polysubstituted benzene derivatives via cycloaromatization.[16] Furthermore, conjugated enediynes cleave DNA by generating reactive diradicals via the Bergman cyclization, thereby often presenting potent antitumor activity.[17] α-Allenols **15** having an aryl- or alkyl-substituted olefin were found to be suitable for the reaction, providing the corresponding *E*,*E*-dienynes as the sole products (**16a** and **16b**). The reaction of α-allenol **17a** bearing an alkyne moiety was also examined. In this case, *E*-**18a** was obtained as the major product (73% isolated yield after column chromatography), while a small amount of *Z*-**18a** was also observed (*E*/*Z* = 10:1).[18] Similarly, the reaction of **17b** showed high *E*-selectively (*E*/*Z* = 12:1), and *E*-**18b** was isolated in 70% yield. The formation of *Z*-**18** is likely due to the linear geometry of the alkyne, which decreases the steric repulsion between the alkyne moiety and the TIPS group.




**Scheme 2.** Stereoselective synthesis of conjugated dienynes and enediynes.

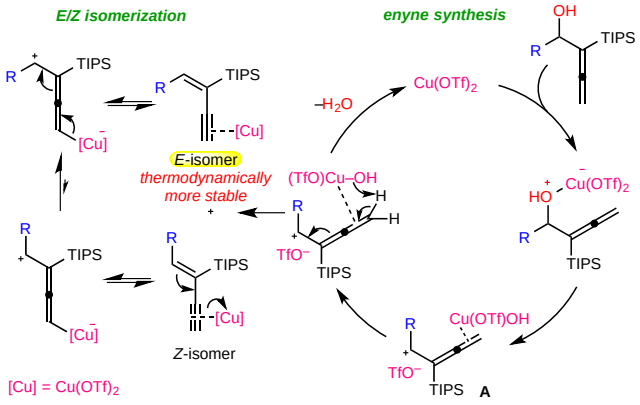
Finally, we investigated the mechanistic origin of the *E*-selectivity of the reaction (Scheme 3). We envisioned that the *E*-selectivity of this process is likely due to the *E*/*Z* isomerization during the reaction. To test this hypothesis, stereochemically pure *Z*-**10**[19] was subjected to the same reaction conditions as those presented in Table 2. As anticipated, *Z*-**10** was completely isomerized to *E*-**10**. We also performed the isomerization of *Z*-**18a** under copper catalysis, affording a 10:1 mixture of *E*- and *Z*-**18a**, which was identical to the selectivity obtained directly from **17a**. Higher catalyst loading (5 mol%) did not improve the *E*-selectivity further, again resulting in an *E*/*Z* ratio of 10:1 (see the Supporting

Information for details). These results clearly indicate that *E*/*Z*-isomers were in equilibrium and that the thermodynamically more stable *E* isomers were predominantly formed. The isomerization did not proceed in the absence of $Cu(OTf)_2$. Thus, $Cu(OTf)_2$ plays a key role in both enyne formation and *E*/*Z* isomerization.




**Scheme 3.** Investigation of the isomerization of enynes under copper catalysis.

On the basis of these results, a plausible mechanism is proposed, as shown in Scheme 4. Initially, the C–O bond of the α-allenol is cleaved by $Cu(OTf)_2$ to generate the cation intermediate **A** and copper hydroxide species. Subsequent abstraction of the terminal allenic proton by copper hydroxide affords a conjugated enyne and regenerates $Cu(OTf)_2$. As demonstrated in Scheme 3, *E*/*Z* isomers of the generated enyne are in equilibrium through the coordination of $Cu(OTf)_2$ to the alkyne moiety, and thus the *E*/*Z* ratio is determined by the thermodynamic stability of the products.




**Scheme 4.** A plausible mechanism.

In conclusion, we have developed a novel copper-catalyzed stereoselective synthesis of functionalized conjugated enyne directly from α-allenols. This method is also applicable to the stereoselective synthesis of conjugated dienynes and enediynes, which are ubiquitous substructures in bioactive compounds and functional materials.

## Experimental Section

**General procedure:** $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) was charged in an oven-dried vial equipped with a stirring bar. The vial was flushed with argon and sealed with a rubber septum. To the vial was added a solution of α-allenol (0.50 mmol) in toluene (3 mL), and the resulting mixture was stirred in a pre-heated oil bath (75 °C) for 1 h. The reaction mixture was cooled to room temperature, diluted with $Et_2O$, filtered through a short pad of activated alumina, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the corresponding enyne.

## Acknowledgements

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[12] Although it is not clear why only $Cu(OTf)_2$ exhibits high catalytic activity for the enyne formation, we assume that the coordination of copper hydroxide to the allene moiety and the basicity of copper hydroxide may play a key role for the success of the reaction.

[13] We also examined the reaction of the phenyl-substituted α-allenol, which resulted in low diastereoselectivity (d.r. = 1.2:1).

[14] In the case of α-allenols bearing strong electron-withdrawing groups, aldehydes are observed by $^1$H NMR analysis. Thus, we assume that copper-catalyzed retro-allenylation of α-allenols competitively occurs, leading to decreased yields of the enyne products. For a report on Cu-catalyzed retro-allenylation, see: M. Sai, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2011**, *50*, 3294–3298.

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[18] The *E*/*Z* isomers of **18** can be easily separated by column chromatography: $R_f$ (*E*-**18a**, hexane) = 0.37 and $R_f$ (*Z*-**18a**, hexane) = 0.56.

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**COMMUNICATION**

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