

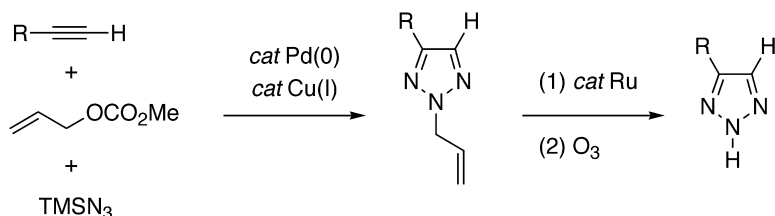
Communication

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Shin Kamijo, Tienan Jin, Zhibao Huo, and Yoshinori Yamamoto

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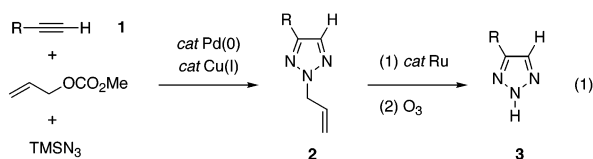
Shin Kamijo,[†] Tienan Jin,[‡] Zhibao Huo,[‡] and Yoshinori Yamamoto^{*,†}

Research Center for Sustainable Materials Engineering, Institute of Multidisciplinary Research for Advanced Materials, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received January 16, 2003; E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

1,2,3-Triazoles have found broad use in agrochemicals and industrial applications such as dyes and corrosion inhibitors and have also been regarded as an interesting unit in terms of biological activity.¹ Because of their potent usefulness, several synthetic methods have been developed recently.² The [3 + 2] cycloaddition reaction between alkynes and azides is well investigated for the construction of the triazole framework (Scheme 1): (1) the reaction of alkynes having EWG (an electron-withdrawing group) with simple azides,³ and (2) the reaction of simple alkynes with azides having EWG.⁴ Accordingly, for the efficient [3 + 2] cycloaddition, EWG is needed as a substituent either at the alkyne or at the azide part.⁵ We now report that the synthesis of triazoles **3** from a simple alkyne and a simple azide is accomplished through the Pd(0)–Cu(I) catalyzed three-component coupling (TCC) reaction between alkynes **1**, allyl methyl carbonate, and TMSN₃, followed by the deallylation of the resulting allyltriazoles **2** (eq 1). Here, the use of the bimetallic catalyst, Pd(0)–Cu(I),⁶ is a key for promoting the [3 + 2] cycloaddition (Scheme 2, *vide post*).

In the TCC reaction of phenylacetylene **1a** using Pd₂(dba)₃·CHCl₃ catalyst, we surveyed the effect of Cu additives (Table 1). The reaction without a copper additive gave a complex mixture of products (entry 1). Among the Cu(I) additives we tested, CuCl(PPh₃)₃ gave the highest yield of **2a** (entry 2). The addition of CuCl and CuI gave lower yields (entries 3 and 4). Copper(I) phenylacetylide also showed a high catalytic activity for the formation of **2a** (entry 5). Other copper catalysts such as CuCl₂ and Cu powder were not effective (entries 6 and 7). Further optimization revealed that the use of Pd₂(dba)₃·CHCl₃–P(OPh)₃ catalyst combined with CuCl(PPh₃)₃ increased the yield of the allyltriazole **2a**, as mentioned below.



Scheme 1. The Synthesis of Triazoles via the [3 + 2] Cycloaddition Reaction Using Activated Substrates

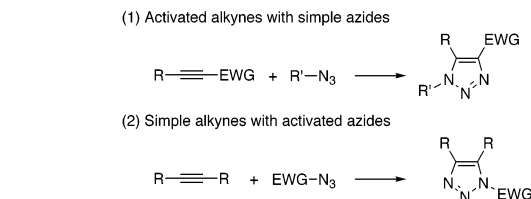


Table 1. Effect of Cu Additives on the Formation of the Triazole **2a**^a

entry	additive	reaction time, h	GC yield (isolated), % ^b
1	none	24	complex mixture
2	CuCl(PPh ₃) ₃	12	73 (66)
3	CuCl	12	15
4	CuI	12	12
5	Ph–C≡C–Cu	12	78 ^c
6	CuCl ₂	12	0 ^d
7	Cu powder	12	trace

^a The reaction of phenylacetylene **1a** with allyl methyl carbonate (1.2 equiv) and TMSN₃ (1.2 equiv) was carried out in the presence of Pd₂(dba)₃·CHCl₃ (2.5 mol %), dppp (10 mol %), and an additive (20 mol %) in AcOEt (0.5 M) at 100 °C for the time indicated in Table 1. ^b GC yield using tetradecane as an internal standard. Isolated yield is shown in parentheses. ^c ¹H NMR yield using *p*-xylene as an internal standard. ^d The starting alkyne **1a** was recovered.

Table 2. Synthesis of the Triazoles **2** under the Pd(0)–Cu(I) Bimetallic Catalyst^a

entry	R	1	reaction time, h	2	yield, % ^b
1	Ph	1a	10	2a	83
2	<i>p</i> -Cl–C ₆ H ₄	1b	6	2b	78
3	<i>p</i> -MeO ₂ C–C ₆ H ₄	1c	5	2c	72
4	<i>p</i> -MeO–C ₆ H ₄	1d	18	2d	63
5	<i>p</i> -Me ₂ N–C ₆ H ₄	1e	17	2e	66
6	1-naphthyl	1f	6	2f	77
7	CH ₃ (CH ₂) ₅	1g	24	2g	63
8	<i>t</i> -Bu	1h	24	2h	58
9	PhSO ₂ N(Me)CH ₂	1i	6	2i	75
10	BnOCH ₂	1j	6	2j	56
11	1-cyclohexenyl	1k	15	2k	54
12	isopropenyl	1l	24	2l	50
13	CH ₃ (CH ₂) ₅ –C≡C	1m	4	2m	59

^a The reaction of the terminal alkynes **1** with allyl methyl carbonate (1.2 equiv) and TMSN₃ (1.2 equiv) was carried out in the presence of Pd₂(dba)₃·CHCl₃ (2.5 mol %), P(OPh)₃ (20 mol %), and CuCl(PPh₃)₃ (10 mol %) in AcOEt (0.5 M) at 100 °C for the time indicated in Table 2. ^b Isolated yield.

1i and **1j** having a heteroatom substituent at the propargyl-position gave the corresponding triazoles **2i** and **2j** in 75% and 56% yields, respectively (entries 9 and 10). We then examined the reactions of the conjugated enynes **1k** and **1l** (entries 11 and 12). The reaction took place chemoselectively at the alkyne moiety to produce the corresponding allyltriazoles **2k** and **2l** in moderate yields. The

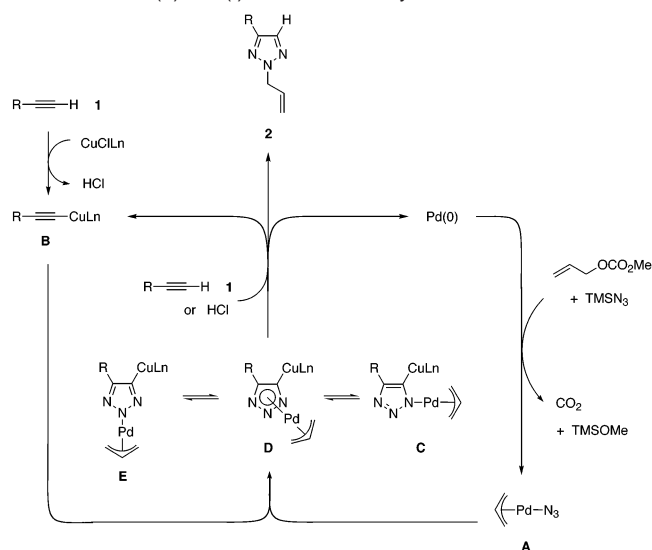
[†] Institute of Multidisciplinary Research for Advanced Materials.

[‡] Department of Chemistry.

reaction of the conjugated diyne **1m** proceeded at the terminal alkyne moiety to give the triazole **2m** in 59% yield (entry 13). The structure of the 2-allylthiazole **2e** was confirmed by X-ray crystallographic analysis.⁷ It is clear that the allyl group is attached to the central nitrogen in the triazole framework.

A plausible mechanism for the 2-allylthiazole forming reaction under the Pd(0)–Cu(I) bimetallic catalyst is illustrated in Scheme 2. At the initial stage of the catalytic cycle, the π -allylpalladium azide complex **A**⁸ is formed with the extrusion of CO₂ and TMSOMe via the reaction of Pd(0), allyl methyl carbonate, and TMSN₃. At the same time, the copper-acetylide **B** would be formed along with the generation of HCl via the reaction of the terminal alkynes **1** and CuClLn. Next, [3 + 2] cycloaddition between the azide moiety of the complex **A** and the C–C triple bond of the copper-acetylide **B** takes place to form the intermediate **C**. Cu would activate the C–C triple bond by forming a copper-acetylide species, which makes the [3 + 2] cycloaddition feasible.^{2a–b,9} The intermediate **C** would be in equilibrium with the intermediate **E** through intervention of the (η^3 -allyl)(η^5 -triazoyl)palladium complex **D**.¹⁰ Reductive elimination of Pd(0) from the intermediate **E** and the protonolysis of the C–Cu bond by the terminal alkynes **1** or HCl afford the 2-allylthiazoles **2**.

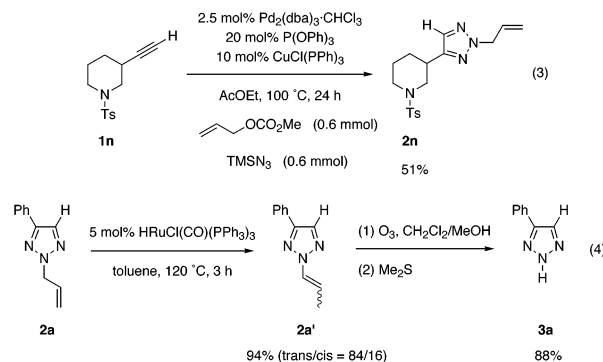
Scheme 2. A Plausible Mechanism for the Formation of Triazoles **2** under the Pd(0)–Cu(I) Bimetallic Catalyst



Taking account of the observations that internal alkynes such as 4-octyne and chloro phenyl acetylene did not afford the corresponding triazoles and that copper(I) phenylacetylide exhibited a high catalytic activity for the formation of the triazole, as indicated in Table 1, we found it is reasonable to propose the involvement of the copper-acetylide **B** as a partner of the [3 + 2] cycloaddition.

We utilized the newly developed protocol using bimetallic catalyst for the selective synthesis of the piperidine derivative **2n**, a precursor of biological active muscarinic agonist (eq 3).¹¹ The reaction of the alkyne **1n** afforded the expected allylthiazole **2n** as the sole product in 51% yield under the same conditions as indicated in Table 2. The deprotection of allyl group from **2** is quite easy

and efficient. For example, **2a** was converted to **3a** via the two-step procedure (eq 4). The Ru-catalyzed isomerization provided the propenylthiazole **2a'**, and ozonolysis furnished the triazole **3a**.



We are now in a position to synthesize various triazoles from nonactivated terminal alkynes, which are not easily available from the previously known methodologies. A key for this new transformation is to use the Pd(0)–Cu(I) bimetallic catalyst. The scope and limitation of bimetallic catalyzed [3 + 2] cycloadditions and extension of the TCC method to tetrazole synthesis are under investigation.

Supporting Information Available: Experimental procedures, compound characterization data of **2a–n**, **2a'**, and **3a**, and X-ray crystallographic data of **2e** (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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