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Four-component coupling reactions of silylacetylenes, allyl carbonates, and trimethylsilyl azide catalyzed by a Pd(0)–Cu(I) bimetallic catalyst. Fully substituted triazole synthesis from seemingly internal alkynes

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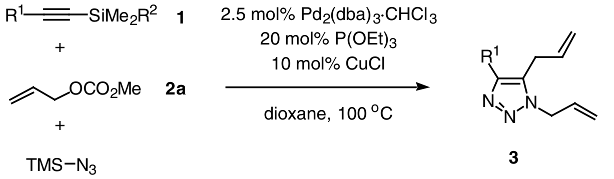
Abstract—Fully substituted triazoles were synthesized via the four-component coupling reaction of unactivated silylacetylenes, two equivalents of allyl carbonates, and trimethylsilyl azide in the presence of a Pd(0)–Cu(I) bimetallic catalyst. Various trisubstituted 1,2,3-triazoles were obtained in good yields. The reaction most probably proceeds through the [3+2] cycloaddition reaction between the alkynylcopper species and azide followed by the cross-coupling reaction between the vinylcopper intermediate and π-allylpalladium complex.

In recent years, triazole forming reactions[1] have received much attention and new conditions were developed for the 1,3-dipolar cycloaddition reaction[2] between alkynes and azides. The thermal cycloaddition is a traditional procedure for this purpose, but there exist several drawbacks inherent in this protocol.[1] The major problem arises due to the low reactivity of the substrates, therefore the installation of an electron withdrawing group is usually required to activate the alkynes. The recent investigations on the copper-catalyzed cycloaddition made it possible to use unactivated terminal alkynes as a starting material.[3] Terminal alkynes are activated by forming a copper-acetylide species. However, a problem still remains since the copper-catalyzed method is applicable only to terminal alkynes. We herein report the synthesis of triazoles[4] from seemingly internal alkynes through a four-component coupling (FCC) reaction. The reaction of the silylacetylenes **1**, allyl carbonates **2**, and trimethylsilyl azide in the presence of a bimetallic catalyst, Pd(0)–Cu(I), gave the 1,4,5-trisubstituted triazoles **3**, the formal [3+2] cycloaddition products between allyl azide and internal alkynes, $R^1C{\equiv}C$(allyl), in good yields (Eq. 1).



(1)

The results are summarized in Table 1. When a mixture of 1-phenyl-2-(trimethylsilyl)acetylene **1a**, allyl methyl carbonate **2a**, and $TMSN_3$ in 1,4-dioxane was stirred at 100 °C for 8 h in the presence of 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol% $P(OEt)_3$, and 10 mol% CuCl, 1,5-diallyl-4-phenyl-1,2,3-triazole **3a** was formed in 77% yield (Table 1, entry 1). The choice of the bimetallic catalyst, $Pd_2(dba)_3{\cdot}CHCl_3$–CuCl, and phosphine ligand, $P(OEt)_3$, is essential in order to obtain the desired triazole **3a**, and formation of the triazole was not observed in the absence of any of these components in the catalytic system. We investigated the reactivity of the arylacetylenes **1b–f**. The alkynes bearing electron donating groups **1b** and **1c** at the *para*-position of the phenyl ring gave the

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Keywords: Triazole; Four-component coupling; Palladium catalyst; Copper catalyst; Bimetallic catalyst; π-Allylpalladium complex; TMS-azide.

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Table 1. Four-component coupling reaction between **1**, **2a**, and $TMSN_3$[a]

Entry	R^1	**1**	Time, h	Triazole **3**	Yield, %[b]
1	Ph	**1a**	8	**3a**	77
2	4-MeO–C_6H_4	**1b**	5	**3b**	67
3	4-Me_2N–C_6H_4	**1c**	5	**3c**	75
4	4-MeO_2C–C_6H_4	**1d**	13	**3d**	66
5	4-Cl–C_6H_4	**1e**	10	**3e**	71
6	4-NC–C_6H_4	**1f**	15	**3f**	57
7	Isopropenyl	**1g**	5	**3g**	69
8	*t*-Bu	**1h**	24	**3h**	51
9	$CH_3(CH_2)_5$	**1i**	24	**3i**	27[c]

[a] The reaction of the alkyne (R^2 = Me) **1** (0.5 mmol), allyl methyl carbonate **2a** (1.2 mmol), and $TMSN_3$ (0.6 mmol) was conducted in the presence of $Pd_2(dba)_3·CHCl_3$ (12.5 μmol), $P(OEt)_3$ (100 μmol), and CuCl (50 μmol) in 1,4-dioxane (1 mL) at 100 °C for the time indicated in this table.

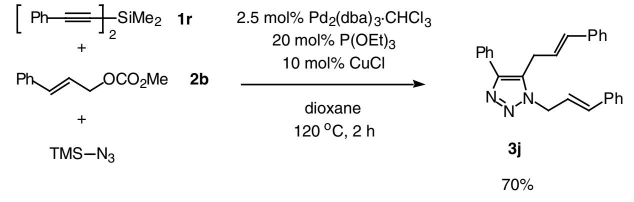
[b] Isolated yield.

[c] NMR yield.

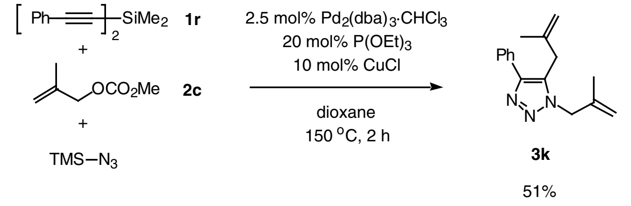
corresponding triazoles **3b** and **3c** in good yields, respectively (Table 1, entries 2 and 3). The alkynes **1d–f** having electron withdrawing groups also produced the corresponding triazoles **3d–f** in good to moderate yields (Table 1, entries 4–6). The conjugated enyne **1g** afforded the desired triazole **3g** in 69% yield (Table 1, entry 7). Bulky 1-(*tert*-butyl)-2-(trimethylsilyl)acetylene **1h** gave the corresponding product **3h** in 51% yield, though a longer reaction time was required (Table 1, entry 8). In contrast, the reaction of a simple alkylacetylene such as 1-(trimethylsilyl)-1-octyne **1i** was sluggish and gave the desired triazole **3i** only in a low yield (Table 1, entry 9).

It occurred to us that modification of the silyl group might increase the reactivity of the alkylacetylenes.[5] The FCC reaction of the alkynes **1j–q** having a variety of substituents on the Si atom was carried out under the usual conditions (Table 2). The fluorosilane **1j** showed a slight increase of the yield (Table 2, entry 1). To our surprise, the introduction of the methoxy group in **1k** increased the reactivity and **3i** was produced in 51% yield (Table 2, entry 2). On the other hand, the silanol **1l** resulted in formation of a mixture of unidentified products (Table 2, entry 3). The disilane **1m** produced **3i** in 44% yield (Table 2, entry 4). The installation of two alkynyl groups on the Si atom **1n** dramatically increased the reactivity and **3i** was obtained in 63% isolated yield in 4 h (Table 2, entry 5). This means that the two alkynyl groups of the dialkynylsilyl molecule **1n** can be utilized in the FCC reaction. The tetra(alkynyl)silane **1o** was not as reactive as **1n** (Table 2, entry 6). The introduction of allyl **1p** and phenyl **1q** groups was less effective (Table 2, entries 7 and 8).

We further conducted the reaction of the substituted allyl carbonates **2b–d** with $TMSN_3$ and di(phenylethynyl)dimethylsilane **1r**. The mono-substituted allyl carbonates, such as cinnamyl **2b** and methallyl carbonate **2c**, furnished the corresponding triazoles **3j** and **3k** in 70% and 51% yields, respectively (Eqs. 2 and 3). The prenyl carbonate **2d** afforded the desired triazole **3l** in a lower yield (Eq. 4). It should be noted that no γ-addition products were detected in the reactions of **2b** and **2d**.



(2)



(3)

Table 2. Effect of the silyl group on the triazole formation[a]

Entry	$[CH_3(CH_2)_5–C{\equiv}C]SiMeR^2$	**1**	Time, h	Triazole **3**	Yield, %[b]
1	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2F$	**1j**	24	**3i**	39
2	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2OMe$	**1k**	3	**3i**	51
3	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2OH$	**1l**	3	**3i**	Mixture
4	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2–SiMe_3$	**1m**	14	**3i**	44
5[c]	$[CH_3(CH_2)_5–C{\equiv}C]_2SiMe_2$	**1n**	4	**3i**	63[d]
6[e]	$[CH_3(CH_2)_5–C{\equiv}C]_4Si$	**1o**	3	**3i**	36
7	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2(CH_2CH_2{=}CH_2)$	**1p**	24	**3i**	46
8	$[CH_3(CH_2)_5–C{\equiv}C]SiMe_2Ph$	**1q**	24	**3i**	20[f]

[a] Unless otherwise noted, the reaction of the alkyne **1** (0.5 mmol), **2a** (1.2 mmol), and $TMSN_3$ (0.6 mmol) was conducted in the presence of $Pd_2(dba)_3·CHCl_3$ (12.5 μmol), $P(OEt)_3$ (100 μmol), and CuCl (50 μmol) in 1,4-dioxane (1 mL) at 100 °C for the time indicated in this table.

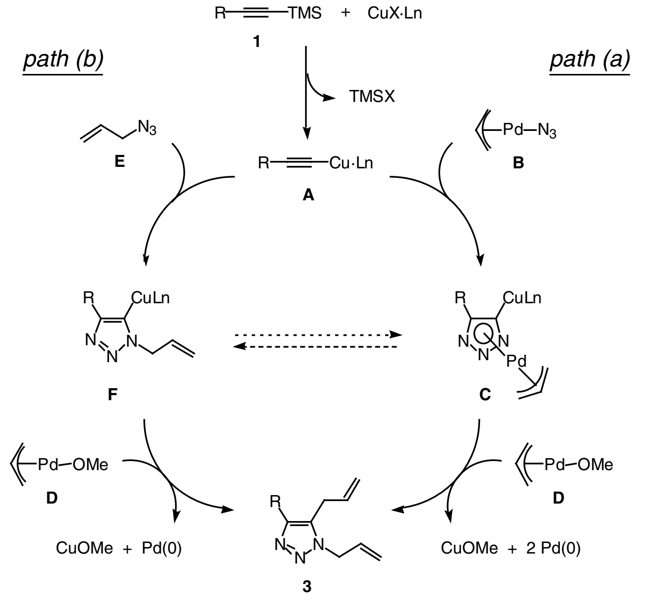
[b] NMR using *p*-xylene as an internal standard except when otherwise indicated.

[c] The di(alkynyl)silane **1n** (0.25 mmol) was used as the starting material.

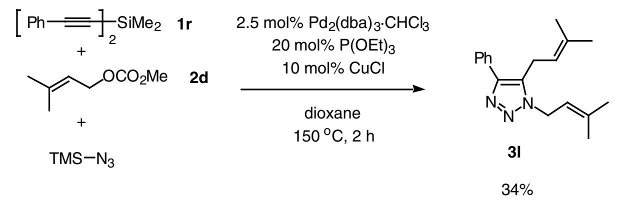
[d] Isolated yield.

[e] The tetra(alkynyl)silane **1o** (0.125 mmol) was used as the starting material.

[f] The alkyne **1q** was recovered in 32% yield.



Scheme 1. Proposed mechanism for the formation of triazoles **3**.



(4)

A proposed mechanism for the FCC reaction is illustrated in Scheme 1. The copper-acetylide species **A** would be formed from alkynes **1** and CuCl with extrusion of TMSCl at the initial stage of the catalytic cycle.[6] At this point, two pathways are conceivable to reach the final products **3**. In the path (a), [3+2] cycloaddition[4] between the copper-acetylide **A** and the π-allylpalladium azide complex **B**,[7] which is generated in situ from Pd(0), allyl carbonate **2a**, and $TMSN_3$, would give the intermediate **C**. The cross-coupling reaction[8] between the vinylcopper derivative **C** and the π-allylpalladium methoxide **D**[9] would form the triazole **3** with regeneration of the Pd(0)–Cu(I) bimetallic catalyst. Alternatively in the path (b), [3+2] cycloaddition would take place between **A** and allyl azide **E**,[3] which is formed by reductive elimination of **B**, to give the intermediate **F**. The successive cross-coupling reaction between **F** and **D** would afford the triazole **3**. There might be an equilibrium between **C** and **F**. Needless to say, a more detailed investigation is needed to clarify the mechanism of the FCC reaction.

Irrespective of the precise mechanism, we are now in a position to synthesize a wide variety of triazoles **3** through the FCC reaction, which are formal [3+2] cycloaddition products of seemingly internal alkynes, not easily available in a single step via the previously known procedures. In addition, we have disclosed that the introduction of two alkynyl groups on the Si atom increased the reactivity of the starting alkyne. Further studies on the synthetic application of this novel reaction and the mechanistic detail are underway in our laboratory.

Acknowledgements

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