JOC Article

A One-Pot Procedure for the Regiocontrolled Synthesis of Allyltriazoles via the Pd−Cu Bimetallic Catalyzed Three-Component Coupling Reaction of Nonactivated Terminal Alkynes, Allyl Carbonate, and Trimethylsilyl Azide

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A one-pot procedure for the regiocontrolled synthesis of both 2-allyl- and 1-allyl-1,2,3-triazoles via the three-component coupling (TCC) reaction between nonactivated terminal alkynes, allyl carbonate, and trimethylsilyl azide ($TMSN_3$) under a palladium and copper bimetallic catalyst has been developed. To accomplish the regioselective synthesis of the allyltriazoles, proper choice of two different catalyst systems is needed. The combination of $Pd_2(dba)_3{\cdot}CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$ catalyzes the formation of 2-allyl-1,2,3-triazoles, while the combination of $Pd(OAc)_2$−$CuBr_2$−PPh_3 promotes the formation of 1-allyl-1,2,3-triazoles. The cooperative activity of palladium and copper catalysts plays an important role in the present transformations. Most probably, the palladium catalyst works as a catalyst for generating reactive azide species, π-allylpalladium azide complex and allyl azide. The copper catalyst probably behaves as an activator of the C−C triple bond of the starting terminal alkynes by forming a copper−acetylide intermediate and thereby promotes the [3 + 2]-cycloaddition reaction between the reactive azide species and the copper−acetylide to form the triazole framework.

Introduction

1,2,3-Triazoles are an important class of compounds because of their wide utilities.[1] They have been considered as an interesting component from the viewpoint of biological activity and are seen in many drugs.[2] Triazole heterocycles have also found broad use in industrial applications such as dyes and brighteners for fibers; corrosion inhibitors for many metals and alloys; light stabilizers for organic materials and polymers; and agrochemicals as herbicides, fungicides, and antibacterial agents.[1b] More recently, triazoles have been utilized as a backbone of a bidentate phosphine ligand, and several new compounds have been synthesized.[3] Because of their potent usefulness, several synthetic methods have been developed for the construction of triazole frameworks. Among them, 1,3-dipolar cycloaddition reactions are a powerful tool for the formation of a wide variety of cyclic compounds.[4] 1,2,3-Triazoles are in general prepared through the coupling reaction between alkynes and azides.[1,4] In the standard procedure for the synthesis of triazoles, it is usually required that starting alkynes and/or azides are substituted with an activating electron-withdrawing functional group, and the reaction is often conducted at high temperatures for a prolonged time. The thermal cycloaddition reaction between terminal alkynes and azides causes another problem with regard to the regioselectivity of the derived triazoles: a mixture of 1,4-substituted- and 1,5-substituted-1,2,3-triazoles is produced in most cases. The recent advances in triazole synthesis using a catalytic amount of copper salt have settled the above issues to some extent.[5] Thus, it occurred to us that the employment of a transition-metal catalyst may overcome the above-mentioned problems: both the acceleration of the coupling reaction between alkynes and

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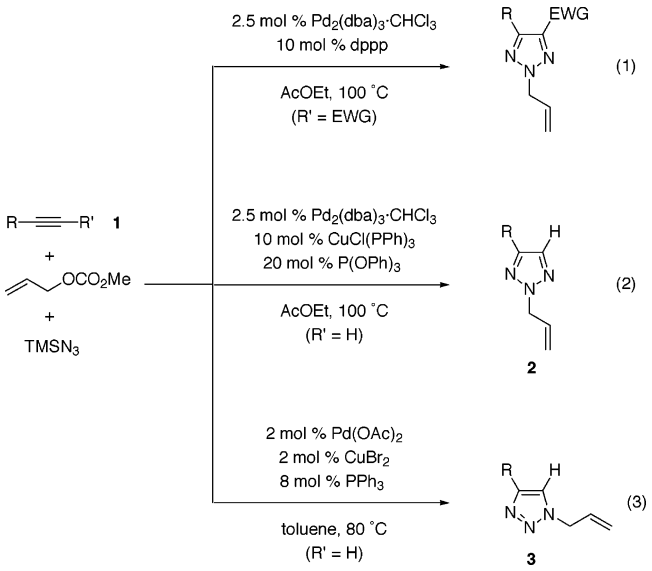
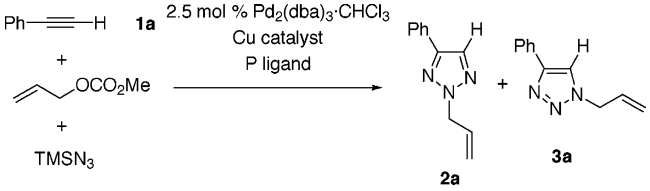
SCHEME 1. Regiocontrolled Synthesis of Allyltriazoles via the Three-Component Coupling Reaction



azide compounds and the selective formation of the substituted triazoles might be observed under a transition-metal catalyst.

Previously, we reported the regioselective formation of 2-allyltriazoles via the three-component coupling (TCC) reaction between *activated alkynes* conjugated with an electron-withdrawing group (EWG), allyl methyl carbonate, and $TMSN_3$ in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ and 1,3-bis(diphenylphosphino)propane (dppp), as shown in eq 1 (Scheme 1).[6] A wide range of activated alkynes can be used as a substrate in this protocol; however, nonactivated alkynes did not afford any desired allyltriazoles. The limitation of the starting alkynes is apparently the major drawback in this allyltriazole synthesis via the palladium-catalyzed TCC reaction strategy. A dramatic change occurred when a catalytic amount of a Cu salt was introduced to the reaction mixture.[7] In the TCC reaction of phenylacetylene **1a**, *a nonactivated terminal alkyne*, under the combination of $Pd_2(dba)_3{\cdot}CHCl_3{-}CuCl(PPh_3)_3{-}P(OPh)_3$ catalyst, gave 2-allyl-4-phenyl-1,2,3-triazole **2a** in a high yield; the Pd−Cu bimetallic catalyst efficiently promoted the 2-allyltriazole-forming reaction from a nonactivated terminal alkyne (eq 2, Scheme 1).[8] Later on, it was found that 1-allyltriazoles were regioselectively synthesized by the proper choice of Pd, Cu, and phosphine ligand. We herein report a detailed investigation of the regiocontrolled synthesis of 2-allyl-1,2,3-triazoles (eq 2, Scheme 1) and 1-allyl-1,2,3-triazoles (eq 3, Scheme 1) via the Pd−Cu bimetallic catalyzed TCC reaction between nonactivated terminal alkynes, allyl carbonate, and $TMSN_3$.

TABLE 1. Effects of Cu Catalyst and P Ligand on the Formation of the 2-Allyltriazole 2a[a]



			yield, %[b]	
entry	Cu catalyst	P ligand	**2a**	**3a**
1	CuCl (20 mol %)	dppp (10 mol %)	15	49
2	CuBr (20 mol %)	dppp (10 mol %)	31	61
3	CuI (20 mol %)	dppp (10 mol %)	12	39
4	$CuCl(PPh_3)_3$ (20 mol %)	dppp (10 mol %)	73 (66)	0
5	Ph−C≡C−Cu (20 mol %)	dppp (10 mol %)	78	0
6	$CuBr_2$ (20 mol %)	dppp (10 mol %)	0	51
7	none	dppp (10 mol %)	complex mixture	
8	$CuCl(PPh_3)_3$ (10 mol %)	dppp (10 mol %)	75 (68)	0
9	$CuCl(PPh_3)_3$ (5 mol %)	dppp (10 mol %)	34	13
10	$CuCl(PPh_3)_3$ (5 mol %)	dppp (10 mol %)	48	21
11	$CuCl(PPh_3)_3$ (10 mol %)	dppb (10 mol %)	44	0
12	$CuCl(PPh_3)_3$ (10 mol %)	dppe (10 mol %)	52	21
13	$CuCl(PPh_3)_3$ (10 mol %)	$(p\text{-MeO-}C_6H_4)_3P$ (20 mol %)	45	20
14	$CuCl(PPh_3)_3$ (10 mol %)	$(p\text{-}CF_3\text{-}C_6H_4)_3P$ (20 mol %)	15	49
15	$CuCl(PPh_3)_3$ (10 mol %)	Bu_3P (20 mol %)	45	22
16	$CuCl(PPh_3)_3$ (10 mol %)	$(2\text{-furyl})_3P$ (20 mol %)	63	0
17	$CuCl(PPh_3)_3$ (10 mol %)	$P(OPh)_3$ (20 mol %)	83 (83)	0
18	$CuCl(PPh_3)_3$ (10 mol %)	none	30	22

[a] The reaction of phenylacetylene **1a** with allyl methyl carbonate (1.2 equiv) and $TMSN_3$ (1.2 equiv) was carried out in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P ligand, and Cu catalyst in AcOEt (0.5 M) at 100 °C for 12 h. [b] The yield was calculated by ^{1}HNMR or GC analysis. The isolated yield is shown in parentheses.

Results and Discussion

Synthesis of 2-Allyl-1,2,3-triazoles via the TCC Reaction under $Pd_2(dba)_3{\cdot}CHCl_3{-}CuCl(PPh_3)_3{-}P(OPh)_3$ Bimetallic Catalyst. After the discovery of the unique effect of Cu salt on the indole synthesis,[7] we investigated the effect of Cu salts and ligands on the regioselective formation of either isomer of the two allyltriazoles. First, the effect of Cu catalysts on the TCC reaction of phenylacetylene **1a**, allyl methyl carbonate, and $TMSN_3$ was surveyed under the standard conditions, $Pd_2(dba)_3{\cdot}CHCl_3{-}$dppp catalyst. The representative results of the TCC reaction performed with various Cu additives are summarized in Table 1. The Cu(I) salts such as CuCl, CuBr, and CuI gave a mixture of the corresponding 2-allyltriazole **2a** and 1-allyltriazole **3a** (entries 1−3). $CuCl(PPh_3)_3$ promoted the TCC reaction efficiently and produced the 2-allyltriazole **2a** selectively in a high yield (entry 4). Copper(I) phenylacetylide also showed comparable reactivity to $CuCl(PPh_3)_3$ (entry 5). In contrast, $CuBr_2$ did not afford the 2-allyltriazole **2a** at all, and the 1-allyltriazole **3a** was produced as a single product (entry 6). The reaction without Cu salt resulted

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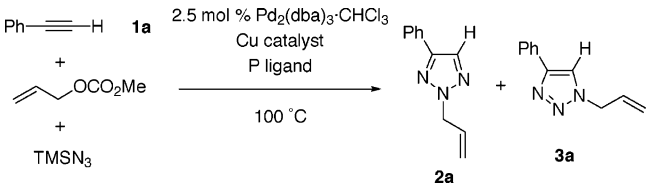
TABLE 2. Effect of P Ligand and Cu Catalyst on the Formation of the 1-Allyltriazole 3a[a]

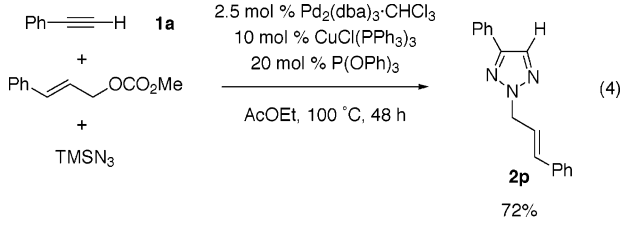


			yield, %[b]	
entry	P ligand	Cu catalyst	2a	3a
1[c]	dppp (10 mol %)	$CuBr_2$ (20 mol %)	0	51
2[c]	$P(OPh)_3$ (20 mol %)	$CuBr_2$ (20 mol %)	5	47
3[c]	$(2\text{-furyl})_3P$ (20 mol %)	$CuBr_2$ (20 mol %)	10	50
4[c]	PPh_3 (20 mol %)	$CuBr_2$ (20 mol %)	0	72
5[c]	none	$CuBr_2$ (20 mol %)	no reaction	
6[d]	PPh_3 (20 mol %)	$CuBr_2$ (5 mol %)	0	85 (88)
7[d]	PPh_3 (20 mol %)	$CuCl_2$ (5 mol %)	8	60
8[d]	PPh_3 (20 mol %)	$Cu(OMe)_2$ (5 mol %)	18	54
9[d]	PPh_3 (20 mol %)	CuBr (5 mol %)	15	60
10[d]	PPh_3 (20 mol %)	Ph−C≡C−Cu	(5)	(38)
11[d]	PPh_3 (20 mol %)	Cu powder (5 mol %)	0	32
12[d]	PPh_3 (20 mol %)	none	complex mixture	

[a] The reaction of phenylacetylene **1a** with allyl methyl carbonate (1.2 equiv) and $TMSN_3$ (1.2 equiv) was carried out in the presence of $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), P ligand, and Cu additive at 100 °C. [b] The yield was calculated by ^{1}HNMR or GC analysis. The isolated yield is shown in parentheses. [c] The reaction was conducted in AcOEt (0.5 M) for 10 h. [d] The reaction was conducted in toluene (0.5 M) for 5 h.

in formation of a complex mixture of unidentified products, probably due to rapid oligomerization of the terminal alkyne **1a** under the palladium catalyst (entry 7). At this stage, we focused on the selective synthesis of 2-allyltriazole **2a**, and $CuCl(PPh_3)_3$ was chosen for further investigations. The amount of $CuCl(PPh_3)_3$ exerted a great influence on regioselectivity of the allyltriazoles. The Cu additive could be reduced from 20 to 10 mol % without loss of the regioselectivity (entry 8), but a mixture of **2a** and **3a** was formed when the amount of the Cu catalyst was further decreased to 5 mol % (entry 9). We next examined the effect of phosphine ligand on the regioselectivity. The TCC reaction proceeded smoothly with the addition of 10 mol % dppp and gave **2a** selectively in a high yield, as shown in entry 8. However, decrease of the amount of the phosphine ligand caused low regioselectivity. When the amount of dppp was reduced from 10 to 5 mol %, a mixture of **2a** and **3a** was formed (entry 10). Among other bidentate phosphine ligands we tested, 1,4-bis(diphenylphosphino)butane (dppb) furnished **2a** as a sole product (entry 11), whereas 1,2-bis(diphenylphosphino)ethane (dppe) did not improve the ratio of **2a** and **3a** (entry 12). Monodentate phosphine ligands such as $(p\text{-MeO-}C_6H_4)_3P$, $(p\text{-}CF_3\text{-}C_6H_4)_3P$, and Bu_3P resulted in formation of a mixture of **2a** and **3a** (entries 13−15). The intensive investigation revealed that the use of tri(2-furyl)phosphine efficiently promoted the TCC reaction and afforded the desired 2-allyltriazole **2a** as a sole product (entry 16). Among the phosphine ligands we examined, triphenyl phosphite exhibited the highest catalytic activity and the 2-allyltriazole **2a** was isolated in 83% yield (entry 17). Without addition of the phosphine ligand, no regioselectivity was observed, which clearly proves the effect of $P(OPh)_3$ ligand in the present regioselective transformation (entry 18). Other reaction parameters, such as palladium sources and solvents, were also studied. As for the palladium sources, we examined $Pd_2(dba)_3$·$CHCl_3$, $Pd(OAc)_2$, and π-allylpalladium chloride dimer. Among them, $Pd_2(dba)_3$·$CHCl_3$ afforded the highest yield of the desired product **2a**. AcOEt was the solvent of choice; nonpolar solvents such as toluene and octane decreased the yield of **2a**, and polar solvents such as THF, 1,2-dichloroethane, CH_3CN, and DMF gave a mixture of **2a** and **3a**. The best result for the synthesis of 2-allyltriazole **2a** was obtained by carrying out the TCC reaction under $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %)−$CuCl(PPh_3)_3$ (10 mol %)−$P(OPh)_3$ (20 mol %) catalyst in AcOEt at 100 °C, as indicated in eq 2.

The TCC reactions using various simple terminal alkynes **1** substituted with aryl, alkyl, alkenyl, and alkynyl groups gave the corresponding 2-allyltriazoles **2** in the range of 50−83% yields. The bulkiness of the starting alkyne did not exert a significant influence on the reaction progress, and the reaction took place chemoselectively at the terminal alkyne moiety to afford the corresponding products when conjugated enynes and diyne were utilized as a starting material. The reaction of (triisopropylsilyl)acetylene **1m** also furnished the corresponding 2-allyltriazole **2m** in 31% yield. A substituted allylic carbonate could be used in the 2-allyltriazole forming reaction; the TCC reaction of **1a**, cinnamyl methyl carbonate, and $TMSN_3$ under the usual reaction conditions gave the corresponding 2-allyltriazole **2p** in 72% yield (eq 4). It should be noted that no γ-addition



(4)

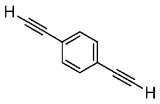
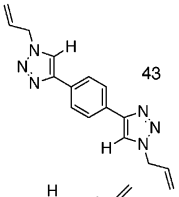
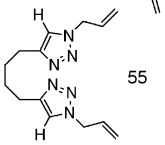
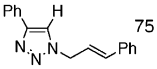
product was detected in this case. The structure of the product, 2-allyl-4-(*p*-dimethylamino)phenyl-1,2,3-triazole, was confirmed unambiguously by the X-ray crystallographic analysis (see Supporting Information for details).

Synthesis of 1-Allyl-1,2,3-triazoles via the TCC Reaction under $Pd(OAc)_2$−$CuBr_2$−PPh_3 Bimetallic Catalyst. We next turned our attention to the regiocontrolled preparation of 1-allyltriazoles **3a** and started to optimize the reaction conditions. We have already found that the addition of $CuBr_2$ afforded 1-allyltriazole **3a** as a single product; thus, we examined the effect of a variety of phosphine ligands under the $Pd_2(dba)_3$·$CHCl_3$−$CuBr_2$ bimetallic catalyst in the first place. The results are summarized in Table 2. As mentioned in the previous section, the addition of dppp afforded the 1-allyltriazole **3a** in a moderate yield (entry 1). The monodentate phosphine ligands such as $P(OPh)_3$ and $(2\text{-furyl})_3P$ furnished a mixture of **2a** and **3a** (entries 2 and 3). Among them, PPh_3 promoted the TCC reaction most efficiently and gave the desired product **3a** as a single product with a high chemical yield (entry 4). The reaction without addition of phosphine ligand resulted in recovery of the starting alkyne **1a** and allyl methyl carbonate (entry 5).

We then performed the TCC reaction using the $Pd_2(dba)_3$·$CHCl_3$−PPh_3 catalyst with addition of some Cu salts to reconfirm their catalytic activity. The amount of the $CuBr_2$ could be reduced from 20 to 5 mol % without loss of the regioselectivity and the yield of **3a** (entry 6). The other Cu(II) catalysts, such as $CuCl_2$ and $Cu(OMe)_2$, produced a mixture of **2a** and **3a** (entries 7 and 8). The Cu(I) catalysts, such as CuBr and Cu(I) phenylacetylide, did not improve the ratio of the products (entries 9 and 10). Cu powder afforded **3a** as a sole product, though the yield of **3a** was low (entry 11). Of course, without addition of Cu catalyst, the reaction gave only a complex mixture of unidentified products due to oligomerization of the terminal alkyne **1a** (entry 12). Other reaction parameters, such as palladium sources, solvents, and reaction temperature, were also studied. As for the palladium sources, $Pd_2(dba)_3$·$CHCl_3$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, and π-allylpalladium chloride dimer were examined, and all the palladium catalysts showed a comparable reactivity. Among them, $Pd(OAc)_2$ was chosen because of the convenience for the product purification. As for the solvents, toluene, THF, 1,2-dichloroethane, AcOEt, and CH_3CN, were examined. Again, all the solvents gave similar chemical yields of the desired product **3a**. Among them, toluene was chosen because it seemed that only **3a** was obtained and almost no side products were produced by the use of this solvent judging from the crude reaction mixture. The reaction temperature could be lowered for the formation of the 1-allyltriazole **3a**, and the reaction proceeded smoothly even at 80 °C. Furthermore, we found that the total amount of the catalysts could be reduced. The best result for the synthesis of the 1-allyltriazole **3a** was obtained by running the TCC reaction under $Pd(OAc)_2$ (2 mol %)−$CuBr_2$ (2 mol %)−PPh_3 (8 mol %) catalyst in toluene at 80 °C, as depicted in eq 3.

Since the optimum reaction conditions for the regioselective synthesis of 1-allyltriazoles **3** were in hand, we conducted the TCC reaction by employing various nonactivated terminal alkynes **1**. The results are summarized in Table 3. The TCC reaction of phenylacetylene **1a** with allyl methyl carbonate and $TMSN_3$ was completed in 3 h and the corresponding 1-allyltriazole **3a** was isolated in 88% yield (entry 1). The arylacetylenes bearing an electron-withdrawing methoxycarbonyl group **1b**, **1c**, and **1d** on the aromatic ring gave the corresponding 1-allyltriazoles **3b**, **3c**, and **3d** in good to high yields (entries 2−4). The substituent position on the aromatic ring did not exert a significant influence on the reaction progress. The reaction of *p*-cyanophenylacetylene **1e** did not reach completion, and the corresponding 1-allyltriazole **3e** was obtained in 41% yield along with the recovery of the starting alkyne **1e** (entry 5). On the other hand, the reaction of the arylacetylene **1f** having an electron-donating methoxy group at the para-position on the aromatic ring proceeded smoothly to give the 1-allyltriazole **3f** in a high yield (entry 6). The reaction of alkylacetylenes such as 1-octyne **1g** and *tert*-butylacetylene **1h** furnished the desired products **3g** and **3h** in good yields, although prolonged reaction times were required (entries 7 and 8). The reaction of 4-pentyn-1-ol **1i**, containing a hydroxy functional group, produced the corresponding 1-allyltriazole **3i** in 75% yield (entry 9).

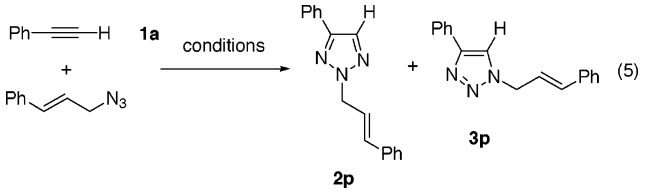
TABLE 3. Synthesis of the 1-Allyltriazoles 3 via the Pd−Cu Bimetallic Catalyzed TCC Reaction[a]

entry	R	1	time, h	3	yield, %[b]
1	Ph	**1a**	3	**3a**	88
2	4-MeO_2C–C_6H_4	**1b**	6	**3b**	83
3	3-MeO_2C–C_6H_4	**1c**	4	**3c**	72
4	2-MeO_2C–C_6H_4	**1d**	3.5	**3d**	81
5	4-NC–C_6H_4	**1e**	24	**3e**	41[c]
6	4-MeO–C_6H_4	**1f**	2	**3f**	82
7	$CH_3(CH_2)_5$	**1g**	24	**3g**	75
8	*t*-Bu	**1h**	24	**3h**	77
9	$HO(CH_2)_3$	**1i**	48	**3i**	75[d]
10	$Cl(CH_2)_4$	**1j**	48	**3j**	38[e]
11	1-cyclohexenyl	**1k**	20	**3k**	71
12	$CH_3(CH_2)_5$–C≡C	**1l**	48	**3l**	35
13	*i*-Pr_3Si	**1m**	48	**3m**	85
14[f]		**1n**	24	**3n**	 43
15[f]		**1o**	24	**3o**	 55
16[g]	Ph	**1a**	20	**3p**	 75

[a] The reaction of the terminal alkynes **1** (R′ = H in eq 3), allyl methyl carbonate (1.2 equiv), and $TMSN_3$ (1.2 equiv) was conducted in toluene (0.5 M) under a catalytic amount of $Pd(OAc)_2$ (2 mol %), PPh_3 (8 mol %), and $CuBr_2$ (2 mol %) at 80 °C for the time shown in Table 3. [b] Isolated yield. [c] The starting material **1e** was recovered in 17% yield. [d] After the reaction was completed, the crude mixture was treated with AcOH. [e] The starting material **1j** was recovered in 22% yield. [f] The reaction was conducted under $Pd(OAc)_2$ (4 mol %)−PPh_3 (16 mol %)−$CuBr_2$ (4 mol %) catalyst. [g] Cinnamyl methyl carbonate was used instead of allyl methyl carbonate.

In this case, the treatment of the crude mixture with an acid was necessary prior to the isolation to cleave the silyl ether formed during the reaction. The reaction of 6-chloro-1-hexyne **1j**, containing halide moiety, did not reach completion and the desired 1-allyltriazole **3j** was formed in 38% yield together with the recovery of the staring alkyne **1j** (entry 10). The reaction of 1-ethynylcyclohexene **1k** proceeded chemoselectively at the terminal alkyne moiety and the desired 1-allyltriazole **3k** was formed in 71% yield (entry 11). The reaction of the conjugated diyne **1l** also took place at the terminal alkyne moiety to give the 1-allyltriazole **3l** (entry 12). Even a bulky silylacetylene **1m** reacted to give the expected product **3m** in 85% yield (entry 13). The 1-allyltriazole-forming reaction was applicable for the substrates having two reactive sites in one molecule, such as 1,4-diethynylbenzene **1n** and 1,7-octadiyne **1o**, and the corresponding products **3n** and **3o** were obtained in moderate yields, respectively (entries 14 and 15). A substituted allylic carbonate could be used in the 1-allyltriazole-forming reaction instead of allyl methyl carbonate; the TCC

TABLE 4. Coupling Reaction of 1a with Cinnamyl Azide under Various Conditions[a]



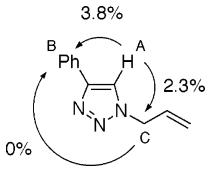
	conditions			NMR yield, %	
entry	Pd catalyst	Cu catalyst	P ligand	**2p**	**3p**
1[b]	$Pd(OAc)_2$ (2 mol %)	$CuBr_2$ (2 mol %)	PPh_3 (8 mol %)	0	88
2[b]		$CuBr_2$ (2 mol %)		0	53
3[b]		$CuBr_2$ (2 mol %)	PPh_3 (8 mol %)	0	99
4[b]	$Pd(OAc)_2$ (2 mol %)		PPh_3 (8 mol %)	0	4
5[c]	$Pd_2(dba)_3$·$CH Cl_3$ (2.5 mol %)	$CuCl(PPh_3)_3$ (10 mol %)	$P(OPh)_3$ (20 mol %)	51	0
6[c]		$CuCl(PPh_3)_3$ (10 mol %)		0	79
7[c]		$CuCl(PPh_3)_3$ (10 mol %)	$P(OPh)_3$ (20 mol %)	0	77
8[c]	$Pd_2(dba)_3$·$CH Cl_3$ (2.5 mol %)		$P(OPh)_3$ (20 mol %)	11	16

[a] The reaction of **1a** and cinnamyl azide (1.2 equiv) was carried out under the conditions indicated in Table 4. [b] The reaction was conducted in toluene at 80 °C for 20 h. [c] The reaction was conducted in AcOEt at 100 °C for 48 h.

reaction of **1a**, cinnamyl methyl carbonate, and $TMSN_3$ under the standard reaction conditions afforded the corresponding 1-allyltriazole **3p** in 75% yield (entry 16). It should be noted that only α-addition product was detected in this case. The structures of the 1-allyltriazoles **3** were determined by the analysis of their spectroscopic data. The position of the allyl group of **3a** was confirmed by performing NOE experiments[9] and the comparison with the NMR spectra of its regioisomer, 2-allyltriazole **2a**.

Mechanistic Considerations: The Roles of Pd and Cu Catalysts and Phosphine Ligand. To elucidate the roles of palladium and copper complexes and phosphine ligand in the catalyst systems for the preparation of 1-allyltriazoles and 2-allyltriazoles, the coupling reaction between phenylacetylene **1a** and cinnamyl azide was investigated under several conditions (eq 5, Table 4). The coupling reaction under the standard catalytic conditions for the 1-allyltriazole synthesis, $Pd(OAc)_2-CuBr_2-PPh_3$, gave the expected 1-allyltriazole **3p** in 88% yield as the sole product (entry 1). This result corresponds well with the outcome of the TCC reaction of **1a**, cinnamyl methyl carbonate, and $TMSN_3$, as reported in entry 16 of Table 3, where **3p** was obtained in 75% isolated yield. On the contrary, the reaction between phenylacetylene **1a** and trimethylsilyl azide did not proceed under $Pd(OAc)_2-CuBr_2-PPh_3$ catalyst conditions and recovery of the starting acetylene **1a** was observed. The coupling reaction under $CuBr_2$ catalyst alone resulted in formation of **3p** in a moderate yield (entry 2), whereas the combination of $CuBr_2$ and PPh_3 afforded **3p** quantitatively (entry 3). It is clear that Cu catalyst promotes the [3 + 2]-cycloaddition reaction between the terminal alkyne and allyl azide to form the triazole skeleton. It is known that the PPh_3 reduces Cu(II) to generate Cu(I),[10] and that Cu(I) is the active catalyst in the Cu-catalyzed triazole-forming reaction reported recently by other research groups.[5] These observations account well for the fact that $CuBr_2-PPh_3$ catalyst gave a higher yield of **3p** than $CuBr_2$ alone.[11] However, we cannot exclude the possibility of the [3 + 2]-cycloaddition reaction between an alkyne and a π-allylpalladium azide intermediate under the copper catalyst, since the reaction also proceeded smoothly under $Pd(OAc)_2-CuBr_2-PPh_3$ catalyst. At least we can point out that both allyl azide and a π-allylpalladium azide intermediate did not react efficiently with an alkyne in the absence of the copper catalyst (entry 4). The role of the palladium catalyst would be to generate active azide species, allyl azide and a π-allylpalladium azide intermediate, judging from a blank test of the TCC reaction; the recovery of the starting alkyne and allyl methyl carbonate was observed when the TCC reaction was conducted under $CuBr_2-PPh_3$ catalyst without the addition of $Pd(OAc)_2$. We then examined the coupling reaction of **1a** with cinnamyl azide under the standard catalytic conditions for the synthesis of 2-allyltriazoles, $Pd_2(dba)_3$·$CHCl_3-CuCl(PPh_3)_3-P(OPh)_3$. The reaction gave the expected 2-allyltriazole **2p** in 51% yield (entry 5). The same product **2p** has been obtained via the TCC reaction of **1a**, cinnamyl methyl carbonate, and $TMSN_3$, as shown in eq 4. The reaction between phenylacetylene **1a** and trimethylsilyl azide did not proceed under $Pd_2(dba)_3$·$CHCl_3-CuCl(PPh_3)_3-P(OPh)_3$ catalyst conditions and the starting acetylene **1a** was recovered. In the case of the coupling reactions of **1a** with cinnamyl azide under the copper catalyst, both $CuCl(PPh_3)_3$ and $CuCl(PPh_3)_3-P(OPh)_3$ promoted the formation of the 1-allyltriazole **3p** in good yields without affording the 2-allyltriazole **2p** (entries 6 and 7). The coupling reaction under $Pd_2(dba)_3$·$CHCl_3-P(OPh)_3$ cata-

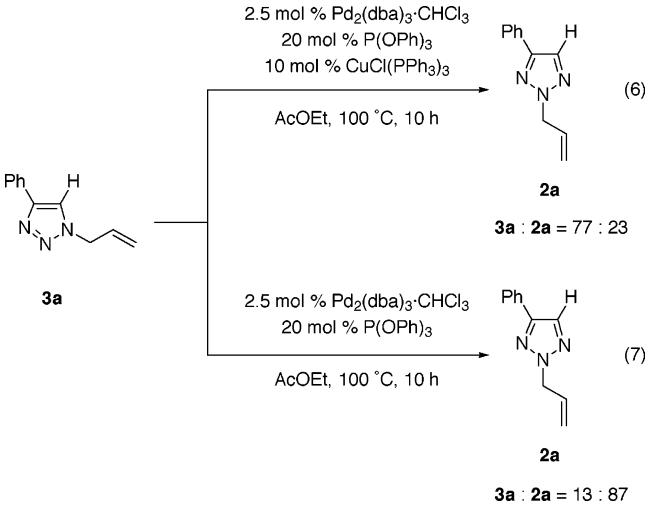
(9) The geometry of 1-allyl-4-phenyl-1,2,3-triazole **3a** was established by NOE experiments. Irradiation of the H_A proton on the triazole ring gave the enhancement of both H_B and H_C protons. The enhancement between H_B and H_C protons was not observed.



(10) (a) Jardine, F. H.; Rule, L.; Vohra, A. G. *J. Chem. Soc. (A)* **1970**, 238−239. (b) Reichle, W. T. *Inorg. Chim. Acta* **1971**, *5*, 325−332.

(11) It is reported that a terminal alkyne reduces Cu(II) to generate Cu(I); see: Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658−659.

SCHEME 2. Isomerization between the 2-Allyltriazole 2a and 1-Allyltriazole 3a



lyst resulted in formation of a mixture of **2p** and **3p** in low yields (entry 8). Of course, the recovery of the starting alkyne and allyl methyl carbonate was observed when the TCC reaction was conducted under $CuCl(PPh_3)_3$−$P(OPh)_3$ catalyst without the addition of $Pd_2(dba)_3$·$CHCl_3$. Here again, the palladium catalyst would work as a generator of reactive azide species, allyl azide and a π-allylpalladium azide intermediate. The copper catalyst would behave as a promoter of the [3 + 2]-cycloaddition reaction between a terminal alkyne and active azide species to form the triazole framework, but it does not control the regiochemistry of the allyl group. The phosphine ligand, $P(OPh)_3$, most probably plays a key role in controlling the position of allyl group on the triazole ring.

We further investigated the possibility of isomerization between the 2-allyltriazole **2a** and 1-allyltriazole **3a** (Scheme 2). Neither **2a** nor **3a** was isomerized under $Pd(OAc)_2$−$CuBr_2$−PPh_3 catalyst at 80 °C for 3 h and the starting material was recovered in both cases. On the other hand, isomerization from the 1-allyltriazole **3a** to the 2-allyltriazole **2a** occurred under $Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$ catalyst and the ratio of **3a** to **2a** reached to 77:23 after heating at 100 °C for 10 h (eq 6); the ratio was determined by GC. The isomerization took place also in the presence of $Pd_2(dba)_3$·$CHCl_3$−$P(OPh)_3$ catalyst and the ratio of **3a** to **2a** reached to 13:87 (eq 7). These results clearly indicate that the isomerization from 1-allyltriazoles to 2-allyltriazoles proceeds under the standard sets of the catalyst for the 2-allyltriazole forming reaction, $Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$, and the nature of the phosphine ligand plays an important role for the determination of the position of the allyl group on the triazole ring. The perfect isomerization (**3a**:**2a** = ∼0:100) did not take place within 10 h, the reaction time observed in the TCC reaction of phenylacetylene **1a**, allyl methyl carbonate, and $TMSN_3$ in the presence of $Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$ catalyst, which produces **2a** exclusively. This difference suggests intervention of other pathways to furnish 2-allyltriazoles **2**. One possibility is the direct formation of 2-allyltriazoles through the coupling reaction between the alkyne and the π-allylpalladium azide complex under the Cu catalyst.

Taken together, a proposed mechanism for the regiocontrolled formation of allyltriazoles via the TCC reaction is illustrated in Scheme 3. The copper−acetylide species **A** would be formed from the simple terminal alkynes **1** and Cu(I)X complex (X = Cl or Br) with generation of HX at the initial stage of the catalytic cycle.[5,12] As a coupling partner for **A**, two reactive azide species can be conceivable, π-allylpalladium azide complex **B**[13] and allyl azide **C**.[14] The π-allylpalladium azide complex **B** is formed via the reaction of Pd(0), allyl methyl carbonate, and $TMSN_3$ with the extrusion of CO_2 and TMSOMe. Reductive elimination of Pd(0) from **B** furnishes allyl azide **C**. According to the formation of two reactive azide species, two reaction pathways could be proposed to reach the final products, 1-allyltriazoles **3** and 2-allyltriazoles **2**, respectively. The formation of 1-allyltriazoles **3** is rationalized as follows. In path a, [3 + 2]-cycloaddition would take place between the copper−acetylide **A** and allyl azide **C** to afford the copper-containing intermediate **D**.[5,15] The protonolysis of the C−Cu bond of **D** by terminal alkynes **1** or HX produces the 1-allyltriazoles **3** and regenerates **A** or Cu(I)X catalyst. Alternatively, in path b, [3 + 2]-cycloaddition between the copper−acetylide **A** and the π-allylpalladium azide complex **B** would produce the palladium and copper-containing intermediate **E**.[16] The protonolysis of the C−Cu bond of **E** and reductive elimination of Pd(0) produce the corresponding 1-allyltriazoles **3**. The formation of 2-allyltriazoles **2** is explained as follows. One plausible pathway is isomerization of the 1-allyltriazoles **3**, formed during the TCC reaction, under the conditions for the 2-allyltriazole synthesis [$Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$] through the π-allylpalladium intermediates **E′**, **F′**, and **G′**. Oxidative addition of the Pd(0)−$P(OPh)_3$ complex would form **E′**, which would be in equilibrium with **G′** through intervention of the (η^3-allyl)(η^5-triazoyl)palladium complex **F′**.[17] Reductive elimination of Pd(0)−$P(OPh)_3$ from the intermediate **G′** furnishes the 2-allyltriazoles **2** as the final product. To confirm the involvement of π-allylpalladium intermediates **E′**−**G′**, we conducted the reaction between 1-trimethylsilyl-4-phenyl-1,2,3-tri-

(12) For generation of a copper−acetylide species under similar conditions, see: (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535−2538. (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797−2811. (c) Wei, C.; Li, C.-J.; *J. Am. Chem. Soc.* **2002**, *124*, 5638−5638. (d) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731−5733. (e) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054−6055.

(13) (a) Busetto, L.; Palazzi, A.; *Inorg. Chim. Acta* **1975**, *13*, 233−238. (b) Shaw, B. L.; Shaw, G. *J. Chem. Soc. (A)* **1971**, 3533−3535.

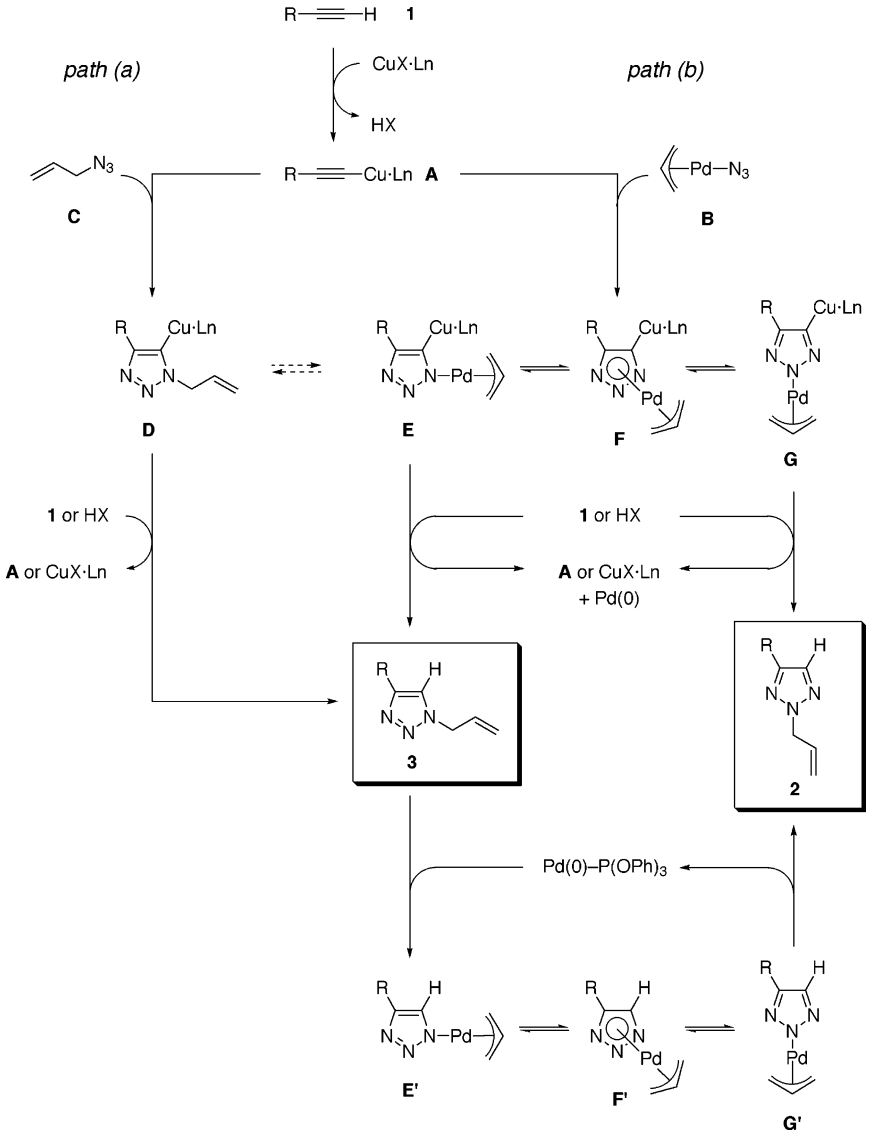
(14) Tornøe and co-workers have reported in ref 5b that the coupling reaction between the terminal alkyne and trimethylsilyl azide did not occur in the presence of CuI catalyst. We also confirmed that the reaction between phenylacetylene and trimethylsilyl azide did not take place at all under the two bimetallic catalyst conditions, $Pd(OAc)_2$−$CuBr_2$−PPh_3 and $Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$.

(15) For copper−acetylide in cycloaddition reactions, see: (a) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466−467. (b) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999−5004. (c) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572−4573. (d) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778−10779.

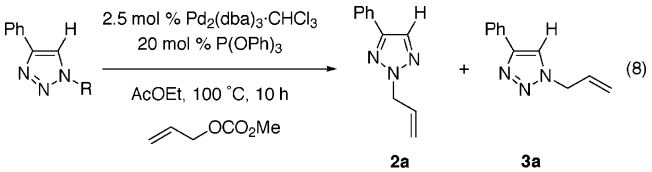
(16) For reactions involving a π-allylpalladium azide complex, see: (a) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9453−9454. (b) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940−11945. (c) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 7413−7417. (d) Reference 6. (e) Reference 8.

(17) Analogous complexes, (η^3-allyl)(η^5-cyclopentadienyl)palladium complex, have been synthesized; see: Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1979**, *19*, 221−223.

SCHEME 3. Mechanism for the Regiocontrolled Formation of 2-Allyltriazoles 2 and 1-Allyltriazoles 3



azole **4** and allyl methyl carbonate in the presence of a catalytic amount of $Pd_2(dba)_3$·$CHCl_3$ and $P(OPh)_3$ at 100 °C for 10 h (eq 8). The corresponding 2-allyltriazole **2a**



4:	R = TMS	75% (NMR yield)	15% (NMR yield)
4':	R = H	71% (NMR yield)	14% (NMR yield)

was obtained as a major product along with formation of the 1-allyltriazole **3a**. The reaction of unprotected phenyltriazole **4′** under the same conditions also showed almost the same result. The other possible pathway is the direct formation of 2-allyltriazoles **2** through the palladium and copper-containing intermediates **E**, **F**, and **G** formed by the coupling of the copper−acetylide **A** and the π-allylpalladium azide complex **B**. The intermediate **E** would be in equilibrium with the intermediate **G** through intervention of the (η^3-allyl)(η^5-triazoyl)palladium complex **F** under the reaction conditions [$Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$] for the formation of 2-allyltriazoles. The protonolysis of the C−Cu bond of **G** and reductive elimination of Pd(0) afford the 2-allyltriazoles **2** directly as the final product. There might be an equilibrium between the intermediates **D** and **E** in the presence of the Pd(0)−$P(OPh)_3$ complex.

Conclusions

We developed a novel one-pot procedure for the regiocontrolled synthesis of allyltriazoles via the Pd−Cu bimetallic catalyzed TCC reaction of nonactivated terminal alkynes **1**, allyl carbonate, and $TMSN_3$. The selective formation of 2-allyltriazoles **2** is attained by conducting the reaction under $Pd_2(dba)_3$·$CHCl_3$−$CuCl(PPh_3)_3$−$P(OPh)_3$ catalyst. The selective synthesis of 1-allyltriazoles **3** are accomplished by running the reaction under $Pd(OAc)_2$−$CuBr_2$−PPh_3 catalyst. The cooperative activity of Pd and Cu catalysts plays an important role for the construction of the triazole framework, and the nature of phosphine ligand controls the position of allyl group on the triazole ring. We are now

in a position to synthesize regioselectively either 1-allyl- or 2-allyl-1,2,3-triazoles just by choosing the proper catalyst system.

Experimental Section

Representative Procedure for the Synthesis of 2-Allyltriazoles (2) via the TCC Reaction. To an AcOEt solution (1 mL) of $Pd_2(dba)_3{\cdot}CHCl_3$ (13.0 mg, 0.0125 mmol) and $CuCl(PPh_3)_3$ (44.3 mg, 0.05 mmol) were added $P(OPh)_3$ (26 μL, 0.1 mmol), phenylacetylene **1a** (55 μL, 0.5 mmol), allyl methyl carbonate (68 μL, 0.6 mmol), and $TMSN_3$ (80 μL, 0.6 mmol) under an Ar atmosphere. The reaction mixture was stirred at 100 °C for 10 h in a tightly capped 5-mL microvial. After consumption of **1a**, the mixture was cooled to room temperature and filtered through a short Florisil pad with Et_2O (∼100 mL) and concentrated. The residue was purified by a silica gel column chromatography (*n*-hexane/AcOEt = 50:1 to 20:1) to afford 2-allyl-4-phenyl-1,2,3-triazole **2a** in 83% yield (77.0 mg).

Representative Procedure for the Synthesis of 1-Allyltriazoles (3) via the TCC Reaction. To a toluene solution (1 mL) of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), PPh_3 (10.5 mg, 0.04 mmol), and $CuBr_2$ (2.2 mg, 0.01 mmol) were added phenylacetylene **1a** (55 μL, 0.5 mmol), allyl methyl carbonate (68 μL, 0.6 mmol), and $TMSN_3$ (80 μL, 0.6 mmol) under an Ar atmosphere. The reaction mixture was stirred at 80 °C for 3 h in a tightly capped 5-mL microvial. After consumption of **1a**, the mixture was cooled to room temperature and filtered through a short Florisil pad with Et_2O (∼100 mL) and concentrated. The residue was purified with a silica gel column chromatography (*n*-hexane/AcOEt = 20:1 to 2:1) to afford 1-allyl-4-phenyl-1,2,3-triazole **3a** in 88% yield (81.3 mg).

Acknowledgment. We thank the members in the Instrumental Analysis Center at Tohoku University for the measurements of mass spectra, elemental analyses, NMR spectra, and X-ray crystallography.

Supporting Information Available: Characterization data and NMR spectra of the 2-allyltriazoles **2a**, **2m**, and **2p** and the 1-allyltriazoles **3a**−**p** and crystallographic data of 2-allyl-4-(*p*-dimethylaminophenyl)-1,2,3-triazole. This material is available free of charge via the Internet at http://pub.acs.org.

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