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Copper(I) 1,2,3-Triazol-5-ylidene Complexes as Efficient Catalysts for Click Reactions of Azides with Alkynes

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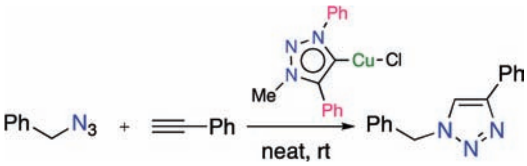
ABSTRACT



Complexes of copper with 1,4-diphenyl, 1,4-dimesityl, and 1-(2,6-diisopropylphenyl)-4-(3,5-xylyl)-1,2,3-triazol-5-ylidene (abnormal NHC = N-heterocyclic carbene) were prepared by consecutive treatment of the corresponding azolium salts with silver oxide and copper chloride. The new CuCl(aNHC) complexes efficiently catalyzed click reactions of azides with alkynes to give 1,4-substituted 1,2,3-triazoles in excellent yields at room temperature with short reaction times. CuCl(TPh) was particularly effective for the reaction between sterically hindered azides and alkynes.

Since the successful isolation of *N*-heterocyclic carbenes (NHCs) by Arduengo and co-workers in 1991,[1,2] *N*-heterocyclic carbene (NHC) ligands have been widely used as ancillary ligands not only for transition metal complexes but also for main group elements. Although the majority of NHC ligands are imidazol-2-ylidenes or 1,2,4-triazol-5-ylidenes (normal NHC), some alternative NHC ligands (abnormal NHC) have also been reported,[3] including 1,2,3-triazol-5-ylidene, which is easily prepared by copper-catalyzed azide−alkyne cycloaddition (click reaction). The preparation of this class of compounds and their application as ligands for transition metals have been reported by various research groups.[4] Although these series of abnormal NHC (aNHC) ligands and their complexes have been researched, the catalytic merit of these ligands has yet to be developed in detail. The synthesis of 1,2,3-triazolylidene NHC complexes and its application to transition metal catalytic reactions have scarcely been studied.

We recently reported the synthesis of a palladium complex bearing a 1,4-dimesityl-1,2,3-triazol-5-ylidene ligand (TMes) and its application in Suzuki−Miyaura coupling reactions using aryl chlorides.[5] It was found that the 1,2,3-triazol-5-ylidene palladium complex had greater catalytic activity than the corresponding palladium complex

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[1] Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

[2] Recent reviews of *N*-heterocyclic carbenes, see: (a) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776. (b) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (c) Cavell, K. *Dalton Trans.* **2008**, 6676. (d) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445. (e) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (f) John, A.; Ghosh, P. *Dalton Trans.* **2010**, 7183. (g) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8810. (h) Kirmse, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8798. (i) *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Cazin, C. S. J., Ed.; Springer: Dordrecht, 2010.

[3] (a) Aldeco-Perez, E.; Rosenthal, A. J.; Donnadieu, B.; Parameswaran, P.; Frenking, G.; Bertrand, G. *Science* **2009**, *326*, 556. (b) Lavallo, V.; Dyker, C. A.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5411. For reviews of aNHCs, see:(c) Arnold, P. L.; Pearson, S. *Coord. Chem. Rev.* **2007**, 596. (d) Albrecht, M. *Chem. Commun.* **2008**, 3601.

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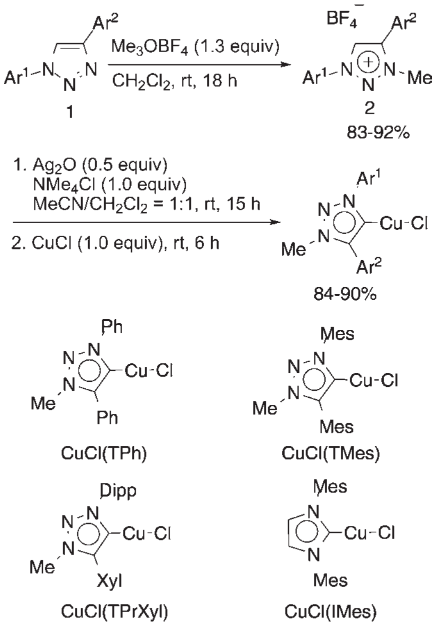
bearing an imidazol-2-ylidene ligand. In order to establish the utility of the 1,2,3-triazol-5-ylidene ligand, we decided to extend its chemistry to include the synthesis of complexes with other transition metals and their application in catalytic transformation reactions. Herein, we describe the first synthesis of a copper complex bearing a 1,2,3-triazole carbene ligand and its application in azide−alkyne cycloaddition reactions (Scheme 1).[6,7]

Scheme 1. Preparation of Copper−aNHC Complexes[a]



[a] Mes = 2,4,6-trimethylphenyl, Dipp = 2,6-diisopropylphenyl, Xyl = 3,5-dimethylphenyl, IMes = 1,3-dimesityl-imidazol-2-ylidene.

The triazolium salts **2** were obtained as stable solids in quantitative yield by treatment of 1,2,3-triazoles **1** with Me_3OBF_4, according to Crowley's method.[4d] Consecutive treatment of **2** with Ag_2O/ammonium chloride and then CuCl at room temperature successfully afforded the air-stable 1,2,3-triazol-5-ylidene−copper(I) complexes CuCl(TPh), CuCl(TPrXyl), and CuCl(TMes), which were characterized by ^1H, ^{13}C NMR, and HRMS analysis. A signal attributable to a metal-bonded carbon was observed around 160 ppm in the ^{13}C NMR spectrum, demonstrating the formation of a copper carbene complex. A single crystal of CuCl(TPrXyl) suitable for X-ray analysis was obtained by recrystallization in dichloromethane/diethyl ether. An ORTEP drawing of CuCl(TPrXyl) is shown in Figure 1. Bond distances and angles in this complex were similar to those in the previously reported copper imidazole carbene complex CuCl(IPr).[8] The bond lengths between the carbene carbon and copper and chlorine and copper were 1.879(5) Å and 2.115 (15) Å, respectively, compared with lengths of 1.881(7) Å and 2.106(2) Å, respectively, in the corresponding complex CuCl(IPr). The carbene C−Cu−Cl bond angle was 177.8 (15)°—almost linear.

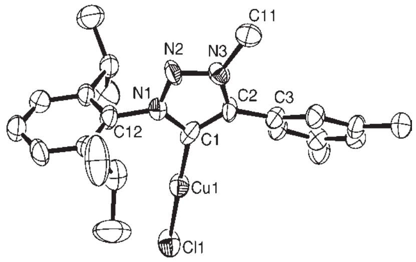


Figure 1. ORTEP drawing of CuCl(TPrXyl) with thermal ellipsoids at the 50% probability level. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Cu(1)−C(1) = 1.879(5), Cu(1)−Cl(1) = 2.115(15). Selected bond angles (deg): C(1)−Cu(1)−Cl(1) = 177.8(15), C(1)−N(1)−C(12) = 125.5(4), C(1)−C(2)−C(3) = 127.7(4).

Nolan and Diéz-Gonzaléz reported that (NHC)Cu complexes were excellent and highly efficient catalysts in click reactions of azides and alkynes (CuAAC reaction). It was expected that the copper-1,2,3-triazol-5-ylidene complexes would also be good catalysts for such reactions because the triazolylidene NHC ligand has been revealed to have good donor capabilities in the palladium complex $[PdCl_2(TMes)_2]$, which was used to catalyze a Suzuki−Miyaura coupling reaction.[5]

We first evaluated the activity of CuCl(TPh), CuCl(TMes), and CuCl(TPrXyl) in the benchmark click reaction of benzyl azide with phenylacetylene. The imidazol-2-ylidene−copper complex CuCl(IMes) was also tested for comparison. The products were the expected 1,4-substituted 1,2,3-triazoles, and the results of the reactions are summarized in Table 1. Conversion vs time graphs for CuCl(TPh), CuCl(TMes), and CuCl(IMes) are shown in Figure 2. The reaction was carried out at room temperature for 1 h under air in the absence of solvent with a catalyst loading of 1.0 mol %. The percentage conversion was determined by ^1H NMR integration of the two benzyl protons of the starting benzyl azide (4.31 ppm) and the product 1,2,3-triazole (5.55 ppm). No decomposition of the catalysts or precipitation of metallic copper was observed during these reactions. The product was isolated as a solid simply by washing with pentane after an aqueous workup. As can be seen from the graph, the fastest reaction was achieved using CuCl(TPh), with a conversion of 100% after 30 min. When CuCl(TMes) was used as a catalyst, the

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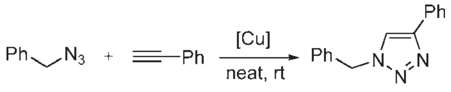
Table 1. Results of the Benchmark Reaction of Benzyl Azide with Phenylacetylene Using Copper(I)−aNHC Complexes as Catalysts[a]



3a

entry	catalyst	[Cu] (mol %)	time (min)	yield (%)[b]
1	CuCl(TPh)	1	30	97
2	CuCl(TPh)	3	20	95
3	CuCl(TPh)	0.5	90	87
4[c]	CuCl(TPh)	3	1440	62
5[d]	CuCl(TPh)	3	40	80
6	CuCl(TMes)	1	60	35
7	CuCl(IMes)	1	60	25
8	CuCl(TPrXyl)	1	60	95
9	CuCl(TPrXyl)	1	30	11
10	CuCl	1	60	trace

[a] Benzyl azide (0.50 mmol), phenylacetylene (0.55 mmol). [b] Isolated yield. [c] The reaction was carried out in 1:1 *tert*-BuOH/H_2O. [d] The reaction was carried out in H_2O.

product yield was 35% after 60 min, with a conversion of 100% after 90 min. The use of CuCl(IMes) resulted in a 25% yield after 60 min, and even after 180 min a conversion of 100% was not achieved; 300 min were required to achieve 100% conversion. Based on these results, the 1,2,3-triazol-5-ylidene ligand was concluded to be superior to the imidazol-2-ylidene ligand in catalyzing the reaction. Although the initial reaction rates were nearly identical, the reaction rate was considerably accelerated with CuCl(TPh). However, the acceleration effect was not observed by the addition of a slight amount of **3a** (1 mol %), suggesting that autocatalysis may be ruled out.[9] CuCl(TPrXyl) also seemed to be an effective catalyst, giving a good yield (95%) after 60 min; however, the yield was considerably smaller after a shorter (30 min) reaction time. The use of CuCl(TPh) gave a high product yield even when the reaction was stopped after 30 min (entry 1). Moreover, the reaction was nearly completed in an even shorter time (20 min) with a catalyst loading of 3 mol % (entry 2). With a reduced catalyst loading of 0.5 mol %, a longer reaction time (100 min) was required to complete the reaction (entry 3). The finding that CuCl(TPh) was the most efficient catalyst suggested that sterically hindered ligands are not suitable for the reaction; the steric factor of the ligand is more critical than the electronic factor. The reaction with ligand-free CuCl (catalyst loading 1 mol %) under neat conditions for 60 min gave a trace of **3a** (entry 10), which showed that 1,2,3-triazole-5-ylidene acted as a good σ-donor ligand in activating the Cu(I) center. It was concluded that Cu(I)−aNHC complexes are highly efficient catalysts for click reactions.

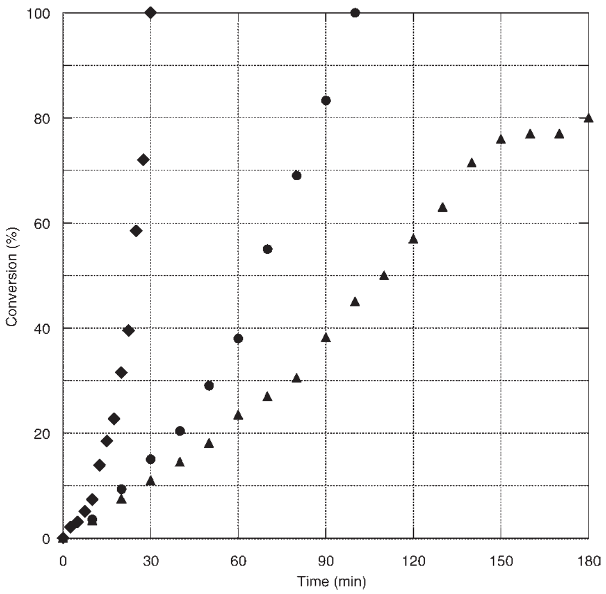


Figure 2. Time vs conversion plot for the Cu(I)−aNHC-catalyzed reaction of benzyl azide with phenylacetylene. (◆) CuCl(TPh), (●) CuCl(TMes), (▲) CuCl(IMes).

Since the click reaction is exothermic, carrying out such reactions under neat conditions has some drawbacks even with short reaction times. In order to address this problem, we examined the catalytic activity of CuCl(TPh) (3 mol %) in a 1:1 mixture of *tert*-BuOH/water and in water only at room temperature. The reaction was very slow in *tert*-BuOH/water (entry 4), with a conversion of only 62% after 24 h of stirring. The reaction in water gave a conversion of 80% after 40 min, showing the efficiency of the catalyst even in water (entry 5).

Next, we investigated the scope of the reaction with respect to alkynes by carrying out reactions of benzyl azide with a variety of alkynes using 3 mol % CuCl(TPh) as a catalyst under neat conditions. The results are summarized in Table 2. Cycloaddition with electron-poor (*p*-CF_3, *o*-F) phenylacetylenes proceeded smoothly to give the corresponding 1,2,3-triazoles in almost quantitative yield in 20 min (entries 4−5). The reaction tended to be slow for electron-rich alkynes such as 3,5-dimethylphenylacetylene, alkyl alkynes, and trimethylsilylacetylene (entries 3, 10−12). The exception to this was *p*-methylphenylacetylene, for which the reaction was completed in 10 min (entry 2). Functional groups such as alcohol, amine, ester, and pyridine were tolerated (entries 9, 13−15), while primary amine was not; the reaction of propargyl amine (entry 15) produced a complex mixture. For sterically hindered alkynes such as *o*-substituted (*o*-Me, *o*-MeO, *o*-AcNH) phenylacetylenes, the reaction time was longer, but it still took less than 60 min to complete the reaction (entries 6−8). In summary, aromatic, electron-rich, electron-poor, sterically hindered, and functionalized alkynes were tolerated, and the reactions were fast (from 20 min to 2.5 h).

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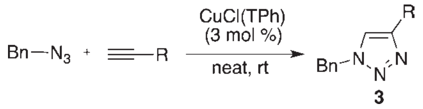
(9) Since the heat of the reaction could accelerate the reaction though its participation may be small, the curves might lack accuracy. However, we may figure out the tendency of the activity of catalyst from the plots.

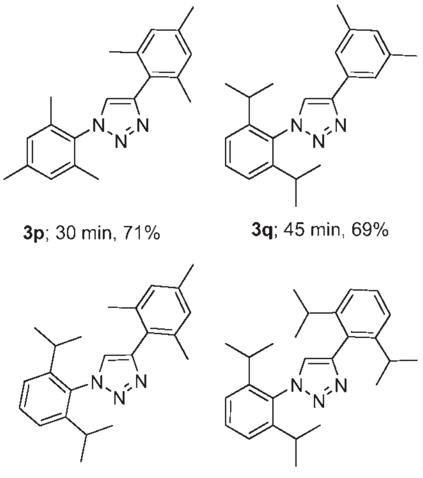
Table 2. Scope of the Reaction Using Alkynes[a]



entry	R	prod.	time (min)	yield (%)[b]
1	C_6H_5	**3a**	20	95
2	*p*-MeC$_6$H$_4$	**3b**	10	99
3	3,5-xylyl	**3c**	40	92
4	*p*-CF$_3$C$_6$H$_4$	**3d**	15	95
5	*o*-FC$_6$H$_4$	**3e**	10	95
6	*o*-MeC$_6$H$_4$	**3f**	45	90
7	*o*-MeOC$_6$H$_4$	**3g**	45	96
8	*o*-AcNHC$_6$H$_4$	**3h**	60	93
9	2-pyridyl	**3i**	15	99
10	*c*-C$_6$H$_{11}$	**3j**	40	80
11	*n*-C$_6$H$_{13}$	**3k**	40	90
12[c]	Me$_3$Si	**3l**	80	82
13	CH$_2$OH	**3m**	25	91
14	CO$_2$Me	**3n**	150	90
15	CH$_2$NH$_2$	**3o**	60	–

[a] Benzyl azide (0.5 mmol), alkyne (0.55 mmol). [b] Isolated yield. [c] Desilylated products were included.

Encouraged by these results, we attempted reactions of more sterically hindered alkynes with sterically hindered azides. The results are shown in Figure 3. We usually employ Sharpless conditions[10] to prepare the precursor triazole of TMes (**3p**) by the reaction of mesitylacetylene with mesitylazide, with reaction conditions as follows: rt, 36 h, *tert*-BuOH/water, and 100 mol % CuSO$_4$/sodium ascorbate. However, the reaction using 3 mol % CuCl(TPh) for 30 min at 100 °C under neat conditions gave **3p** in 71% yield, contaminated with a slight amount ($<4\%$) of 1,5-substituted 1,2,3-triazole. The 1,5-isomer was concluded to result from a thermal Huisgen reaction. Catalyst-free conditions gave a mixture of 1,4- and 1,5-isomers in a ratio of 1:3 with 16% conversion after 60 min. This result suggests that an uncatalyzed reaction might be involved but is of negligible effect in the catalyzed reaction. The use of CuCl(TPh) gave **3q**, the precursor of TPrXyl, and the more sterically hindered **3r** in good yield from the reaction of 2,6-diisopropylphenylazide with 3,5-dimethylphenylacetylene and mesitylacetylene, respectively, under the same conditions. So far, we have not been able to obtain 1,4-bis(2,6-diisopropylphenyl)-1,2,3-triazole (**3s**), a precursor of the TPr ligand, using Sharpless or even Meldal's conditions (CuI/DIPEA).[11]



3p; 30 min, 71% **3q**; 45 min, 69%

3r; 5.5 h, 65% **3s**; 18 h, 63%

Figure 3. CuAAC reactions of sterically hindered azides with sterically hindered alkynes.

We succeeded in preparing the triazole **3s** in 63% yield by the reaction of 2,6-diisopropylphenylazide with 2,6-diisopropylphenylacetylene using CuCl(TPh).

We then investigated the possibility of recycling the catalyst. The activity of the catalyst was found to decrease in the second cycle, with a slightly longer reaction time (30 min) required to obtain a high yield (86%). In the third and fourth cycle, the catalyst was still active but required even longer reaction times (60 min, 80%; 120 min, 86%) (see Supporting Information).

In conclusion, 1,2,3-triazol-5-ylidene was found to be a good alternative NHC ligand for copper complexes, and Cu(I)−aNHC complexes efficiently catalyzed many click reactions of azides and alkynes. Furthermore, for the first time, CuCl(TPh) successfully catalyzed the reaction between sterically hindered azides and sterically hindered alkynes.

Acknowledgment. We thank Dr. Yoshiaki Tanabe (Tokyo University) for X-ray diffraction analysis. This study was financially supported by a Grant-in-Aid, No. 22550044, for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available. Full experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF) for new compounds; crystallographic data for CuCl(TPrXyl) in a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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