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Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes**

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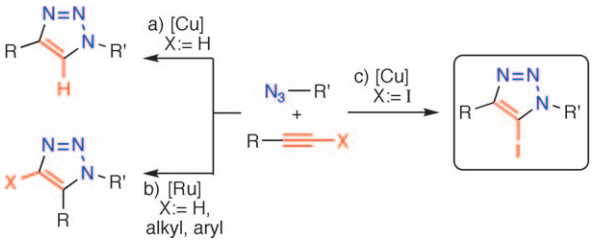
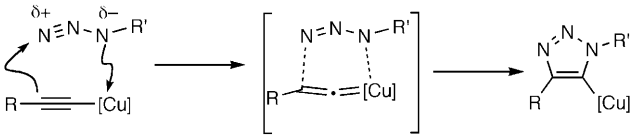
The copper-catalyzed azide–alkyne cycloaddition reaction[1] (CuAAC; Scheme 1a) is known for its high fidelity in the presence of many functional groups and under demanding



Scheme 1. Various routes to substituted 1,2,3-triazoles.

reaction conditions.[2] The experimental simplicity and high selectivity of this process have been exploited in many applications in synthetic and medicinal chemistry,[3] bioconjugations,[4] materials science,[5] and polymer chemistry.[6] The efficiency and selectivity of this transformation are a direct consequence of the reactivity of in situ generated copper(I) acetylides. Coordination of the organic azide to the copper center of the acetylide increases the nucleophilicity of the triple bond and initiates a sequence of steps which ultimately results in the formation of the new C–N bond between the nucleophilic β-carbon atom of the acetylide and the terminal, electrophilic nitrogen atom of the azide (Scheme 2). Naturally, internal alkynes are devoid of such reactivity, and therefore CuAAC is limited to terminal acetylenes, which produce only 1,4-disubstituted triazoles. Although the ruthenium-catalyzed azide–alkyne cycloaddition reaction (Scheme 1b)[7] and methods for functionalization of the triazole heterocycle itself[8] partially address these deficiencies, a general method for the regiocontrolled synthesis of



Scheme 2. Reactivity of organic azides with copper(I) acetylides.

differently substituted 1,2,3-triazoles would be a valuable addition to the family of catalytic cycloaddition reactions.

Herein, we report that 1-iodoalkynes, which are stable and readily accessible internal acetylenes, exhibit exceptional reactivity in the copper-catalyzed annulation reaction with organic azides (Scheme 1c). Indeed, their reactivity appears to surpass that of terminal alkynes. As an added benefit, the products of the reaction (5-iodo-1,2,3-triazoles) are versatile synthetic intermediates that are amenable to further functionalization. Although several syntheses of iodotriazoles are known, the reactions require stoichiometric amounts of copper catalysts and employ reactive electrophilic halogenating reagents (e.g., iodine monochloride, *N*-iodosuccinimide).[9] In addition, some procedures require extended reaction times and generate mixtures of 5-*H* and 5-iodotriazoles.[10]

Disclosed here is a general, rapid, and operationally simple method for the chemo- and regioselective synthesis of 5-iodo-1,4,5-trisubstituted-1,2,3-triazoles from organic azides and iodoalkynes. The catalysis is effected by copper(I) iodide in the presence of an amine ligand.

The initial survey of experimental conditions, which included a broad array of copper(I) and copper(II) salts, solvents, and ligands, revealed that the reaction of iodoalkyne **1** and azide **2** was catalyzed by copper(I) iodide–triethylamine (TEA) in THF, and gave 5-iodo-1,2,3-triazole **3** as the major product,[11] along with 5-proto- and 5-alkynyl triazoles **4** and **5**, respectively (Table 1, entry 2).

Inclusion of an amine ligand was crucial, as no reaction was observed when TEA was omitted (Table 1, entry 1). Furthermore, the reaction displayed a strong dependence on the quantity of TEA used (Table 1, entries 1–4). Thus, 5-iodotriazole **3** was generated as the sole product in excellent yield by simply using an excess (2 equiv) of TEA. This trend extended to other tertiary amine ligands, although the desired 5-iodotriazole was obtained in lower yield (compare Table 1, entry 4 with entries 6 and 8).

The observed rate and chemoselectivity of the reaction were strongly dependent on the nature of the amine ligand. For example, the efficiency of the reaction was markedly lowered, and as a result 5-alkynyl-triazole **5** was formed as the major product [12] when TEA was replaced with 1,2-diamines

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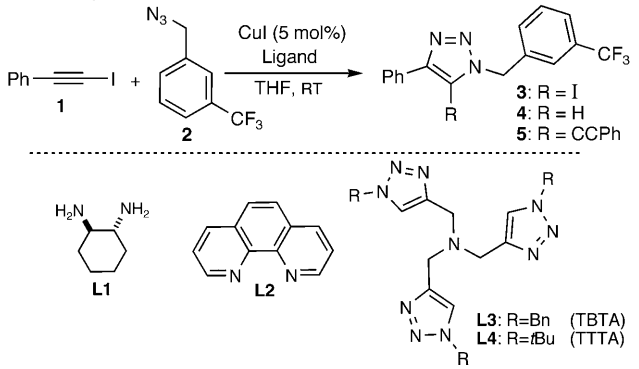
Table 1: Optimization of the reaction conditions.[a]



Entry	Additive	Equiv	**3**/**4**/**5**[b]	Yield [%][c]
1	–	–	–	n.r.
2	TEA	0.5	10:3:1	55
3	TEA	1	25:2:1	75
4	**TEA**	**2**	**1:0:0**	**90**
5	DIPEA	0.5	15:1:2	47
6	DIPEA	2	1:0:0	73
7	2,6-lutidine	0.5	30:1:0	12
8	TMEDA	0.5	20:1:0	26
9	**L1**	0.5	1:1:15	25
10	**L2**	0.5	–	n.r.
11	**L3**	0.05	1:0:0	60[d]
12	**L4**	**0.05**	**1:0:0**	**93**[d]

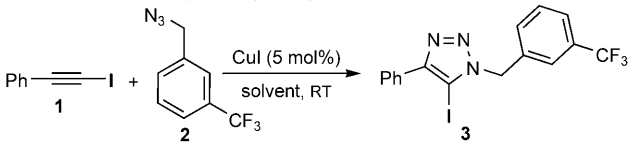
[a] General reaction conditions: CuI (0.02 mmol) and ligand in THF (2 mL), **1** (0.40 mmol) **2** (0.40 mmol), room temperature, 6 h. [b] Product ratio determined by HPLC-MS analysis. [c] Yield of isolated **3**. [d] Reaction time was 45 min. Bn = benzyl, DIPEA = *N*,*N*-diisopropylethylamine, n.r. = no reaction, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

(Table 1, entries 8 and 9). Pyridines, such as 2,6-lutidine and 1,10-phenanthroline (**L2**), were also ineffective (Table 1, entries 7 and 10). By contrast, tris((1,2,3-triazolyl)methyl)-amine ligands[13] were found to be highly efficient in promoting this cycloaddition. Both tris((1-benzyl-1*H*-1,2,3-triazolyl)-methyl)amine (TBTA) and its *tert*-butyl analogue, tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl)amine (TTTA; Table 1, entries 11 and 12) gave 5-iodotriazole **3** as the exclusive product in excellent yield. In addition, these ligands markedly accelerated the reaction, thus reducing the reaction time from 6 hours to 45 minutes.

The increased chemoselectivity of the reaction in the presence of these ligands is a consequence of the rate acceleration of the triazole-forming pathway. Both iodoalkyne **1** and 5-iodotriazole **3** slowly undergo reductive dehalogenation in the presence of various copper salts, to generate the corresponding terminal alkyne and 5-prototriazole **4**. These pathways are likely to account for the generation of the observed by-products, but are far too slow in the presence of accelerating ligands.

Based on these observations, TTTA emerged as the optimum ligand for the rapid and chemoselective construction of 5-iodo-1,2,3-triazoles. Notably, both CuI–TTTA and CuI–TEA systems were found to be compatible with a wide variety of solvents (Table 2). Although some solvents did have a large effect on the reaction rate the selectivity was not affected, even when the reaction was performed in protic solvents.

Table 2: Solvent compatibility study.[a]



	TTTA (5 mol%)		TEA (2 equiv)	
Solvent	*t* [h]	Yield [%]	*t* [h]	Yield [%]
THF	1	93	6	90
MeCN	1	94	6	85
DMF	2	91	18	86
Water	2	85	6	76
EtOH	4	78	24	69
CH_2Cl_2	4	79	24	62
toluene	5	62	24	73

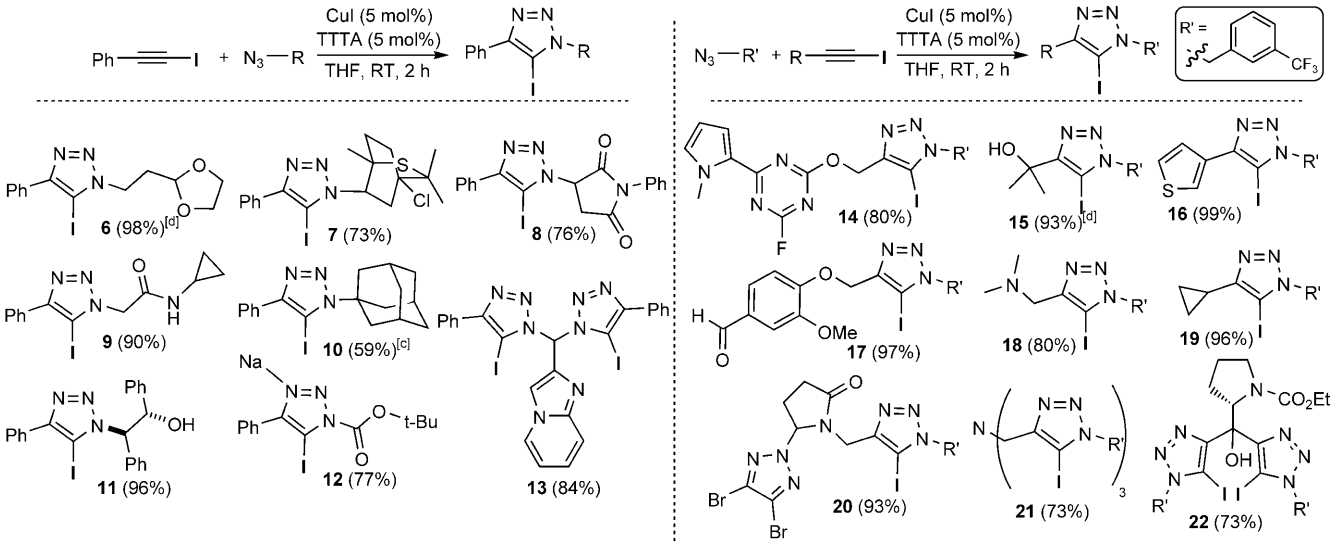
[a] General conditions: CuI (0.05 mmol) and ligand in solvent (5 mL), **1** (1.00 mmol), **2** (1.00 mmol). [b] Yield of isolated **3**.DMF = *N*,*N*-dimethylformamide.

The CuI–TTTA catalyst system was applied to a series of structurally and functionally diverse azides and 1-iodoalkynes (Scheme 3). In all cases, the 5-iodo-1,2,3-triazoles were obtained as the exclusive products. Because of the mild reaction conditions, high chemoselectivity, and low copper catalyst loading, the reaction workup was usually as simple as trituration and subsequent filtration. As a result, this method is highly amenable to scale-up, and representative 5-iodotriazoles **6** and **15** were prepared in multigram quantities. In addition, the diverse array of functional groups tolerated by this annulation stands out as a particularly exceptional feature. Both sterically demanding (e.g., **10** and **22**) as well as functionally dense (e.g., **7** and **17**) substrates could be utilized. As such, the azide–iodoalkyne cycloaddition provides a highly orthogonal means of chemical ligation, similar to the more conventional CuAAC reaction.

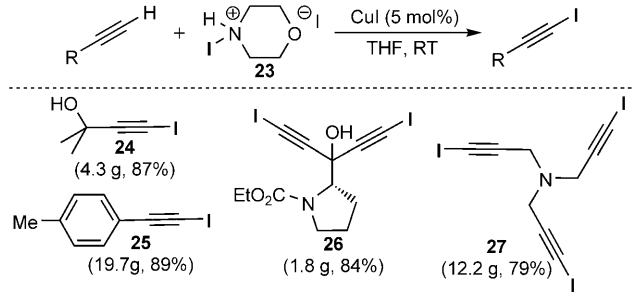
The utility of this cycloaddition was enhanced through the development of a simple and highly efficient synthesis of 1-iodoalkynes from terminal acetylenes (Scheme 4). Terminal alkynes were treated with *N*-iodomorpholine[14] (**23**), in the presence of CuI and gave the corresponding 1-iodoalkynes within 30 to 60 minutes. The products could be isolated by simply passing the reaction mixture through a pad of silica gel or alumina, which yielded the desired 1-iodoalkynes in good to excellent yield.

Given the speed and fidelity with which the 1-iodoalkynes could be synthesized, a one-pot, two-stage sequence was developed (Scheme 5). The 1-iodoalkyne was partially purified by filtration through neutral alumina prior to the introduction of the azide component.[15] This method gave 5-iodotriazoles **28**–**30** with efficiency comparable to that observed with the isolated 1-iodoalkynes.

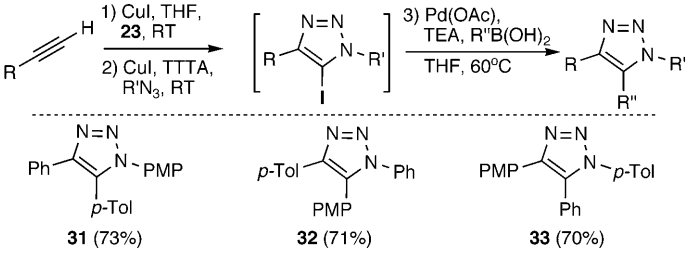
This sequence could be further extended to the synthesis of 1,4,5-triaryl-1,2,3-triazoles **31**–**33** (Scheme 6) by assembling the 5-iodotriazole and immediately employing palladium(0)-catalyzed cross-coupling with an appropriate arylboronic acid.[16] This simple step-wise construction obviates purification of any intermediates and simultaneously provides



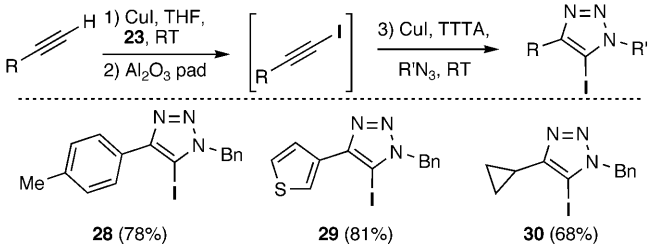
Scheme 3. Substrate scope for the copper(I)-catalyzed azide-iodoalkyne cycloaddition.[a,b] [a] General reaction conditions: azide (1.00 mmol), 1-iodoalkyne (1.00 mmol), CuI (0.05 mmol), TTTA (0.05 mmol), THF (5 mL), room temperature, 2 h. [b] Values in parentheses represent yields of isolated products. [c] Reaction time was 6 h. [d] Reaction was performed on a 10 mmol scale.



Scheme 4. Synthesis of 1-iodoalkynes using *N*-iodomorpholine·HI.



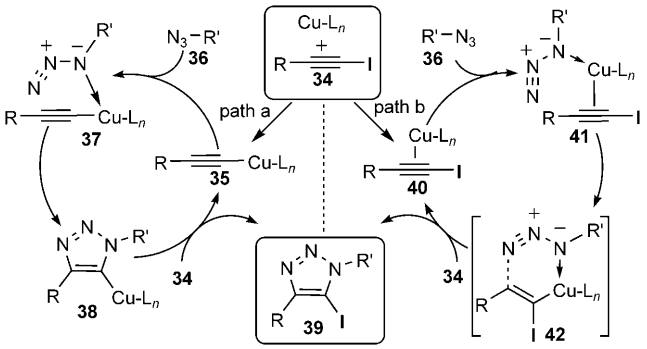
Scheme 6. One-pot, three-step synthesis of 1,4,5-triaryltriazoles. PMP = *p*-methoxyphenyl, *p*-Tol = *p*-methylphenyl.



Scheme 5. One-pot, two-step synthesis of 5-iodo-1,2,3-triazoles.

complete control over the placement of substituents around the 1,2,3-triazole core, thus allowing facile access to all regioisomeric permutations of triaryltriazoles **31**–**33**. This achievement is notable, as a similar regiocontrolled synthesis would not be possible by thermal or ruthenium-catalyzed 1,3-dipolar cycloaddition owing to the high degree of similarity between the aryl groups (phenyl, tolyl, and *p*-methoxyphenyl).

Although this newly discovered copper(I)-catalyzed cycloaddition clearly shares some similarities with the CuAAC process, the modes of activation of iodo and terminal alkynes by copper are likely to be distinctly different. Our mechanistic proposals are outlined in Scheme 7. One possible pathway is similar to that proposed for the CuAAC[1a,17] and involves the formation of the σ-acetylide complex **35** as the first key intermediate (Scheme 7a).[18] Coordination of the azide through the proximal nitrogen center and subsequent cyclization to yield the cuprated triazoles **38**. Copper exchange through σ-bond metathesis with iodoalkyne **34** completes the cycle, thus liberating iodotriazole **39** and regenerating acetylide **35**.



Scheme 7. Proposed mechanisms for the copper(I)-catalyzed azide–iodoalkyne cycloaddition.

Alternatively, copper may activate the iodoalkyne through the formation of a π-complex intermediate (Scheme 7b), which then engages the azide to produce complex **41**. Cyclization then proceeds via a vinylidene-like transition state **42** to give iodotriazole **39**. A similar transition state has been proposed to explain the involvement of dicopper intermediates in the CuAAC reaction.[19] The distinctive feature of this pathway is that the C–I bond is never severed during the catalysis.

Although a detailed examination of the mechanism has not been completed, we currently favor pathway b based on our preliminary studies and the results from the optimization experiments carried out in the reaction. The main argument in support of this hypothesis is the exclusive formation of the 5-iodotriazole: even when the reaction is performed in protic solvents (Table 2) or with the substrates containing acidic protons (Scheme 3, compounds **11**, **15**, and **22**). If pathway a was operational, the cuprated triazole intermediate **38** could be trapped with other electrophiles, including a proton, thereby producing a mixture of the 5-iodo and 5-prototriazoles. The absence of the latter products supports our proposal that pathway a is not dominant.

The new catalytic cycloaddition reaction enables rapid, controlled, and practical synthesis of 1,4,5-trisubstituted-1,2,3-triazoles. This reaction displays broad substrate scope, excellent functional group and solvent compatibility, as well as remarkably high rates which may exceed those of the more familiar CuAAC. In addition to these immediate practical benefits, the unprecedented and exquisite reactivity, as well as facile synthesis of 1-iodoactylenes disclosed here will serve as a powerful tool to probe the mechanism of other copper-catalyzed transformations of alkynes, including the CuAAC reaction.

Experimental Section

Typical procedure for the synthesis of 1-iodoalkynes—synthesis of 1-iodo-phenylacetylene (**1**): Phenylacetylene (8.17 g, 80.0 mmol) was dissolved in THF (200 mL) and treated with CuI (0.762 g, 4.00 mmol) and *N*-iodomorpholine (30.0 g, 88.0 mmol). The reaction mixture was stirred at room temperature for 45 min, after which time a fine white precipitate had formed. The suspension was poured onto a pad of activated neutral alumina (400 mL) and the filtrate was collected under vacuum. The solid phase was washed with CH_2Cl_2 (4 × 100 mL) and the combined organic fractions were concentrated by evaporation to give **1** (16.6 g, 72.8 mmol, 91%) as a yellow oil. This material was used without further purification.

Typical procedure for the synthesis of 5-iodotriazoles—synthesis of 5-iodo-4-phenyl-1-(3-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazole (**3**): CuI (9.52 mg, 0.050 mmol) and TTTA (0.021 g, 0.050 mmol) were stirred in THF (4.5 mL) at room temperature for 20 min, after which time a homogeneous solution was obtained. **1** (0.228 g, 1.00 mmol) and **2** (0.201 g, 1.00 mmol) were dissolved in THF (0.5 mL) and added in a single portion to the catalyst solution. The reaction mixture was stirred for 45 min, and then quenched by adding 1 mL of 10% NH_4OH solution. The volatile components were removed by evaporation, and the resulting residue was suspended in water and diethyl ether. A precipitate formed upon vigorous stirring and was isolated by filtration to give **3** (0.399 g, 0.930 mmol, 93%) as a fine white powder.

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[1] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.
[2] a) P. Wu, V. V. Fokin, *Aldrichimica Acta* **2007**, *40*, 7; b) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952.
[3] a) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128; b) M. Whiting, J. C. Tripp, Y. C. Lin, W. Lindstrom, A. J. Olson, J. H. Elder, K. B. Sharpless, V. V. Fokin, *J. Med. Chem.* **2006**, *49*, 7697; c) B. L. Wilkinson, L. F. Bornaghi, T. A. Houston, S.-A. Poulsen, in *Drug Design Research Perspectives* (Ed.: S. P. Kaplan), Nova, Hauppauge, **2007**, p. 57.
[4] a) A. J. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, *125*, 11164; b) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192; c) J.-F. Lutz, Z. Zarafshani, *Adv. Drug Delivery Rev.* **2008**, *60*, 958.
[5] C. J. Hawker, V. V. Fokin, M. G. Finn, K. B. Sharpless, *Aust. J. Chem.* **2007**, *60*, 381.
[6] a) R. A. Evans, *Aust. J. Chem.* **2007**, *60*, 384; b) J. A. Johnson, J. T. Koberstein, M. G. Finn, N. J. Turro, *Macromol. Rapid Commun.* **2008**, *29*, 1052.
[7] a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998; b) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923.
[8] a) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333; b) S.-I. Fukuzawa, E. Shimizu, K. Ogata, *Heterocycles* **2009**, *78*, 645.
[9] a) Y. M. Wu, J. Deng, Y. Li, Q. Y. Chen, *Synthesis* **2005**, 1314; b) L. Li, G. Zhang, A. Zhu, L. Zhang, *J. Org. Chem.* **2008**, *73*, 3630.
[10] a) I. Perez-Castro, O. Caamano, F. Fernandez, M. D. Garcia, C. Lopez, E. De Clercq, *Org. Biomol. Chem.* **2007**, *5*, 3805; b) Kuijpers et al. recently reported an elegant synthesis of 5-bromo-1,2,3-triazoles from 1-bromoalkynes, however reactions required 40 mol% Cu^{I}/Cu^{II}, elevated temperature or 16–50 h to reach completion; B. H. M. Kuijpers, G. C. T. Dijkmans, S. Groothuys, P. J. L. M. Quaedflieg, R. H. Blaauw, F. L. van Delft, F. P. J. T. Rutjes, *Synlett* **2005**, 3059.
[11] The regiochemistry of **3** was assigned by reducing the 5-iodo center to give 5-H-triazole **4**. See the Supporting Information for details.
[12] B. Gerard, J. Ryan, A. B. Beeler, J. A. Porco, Jr., *Tetrahedron* **2006**, *62*, 6405.
[13] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853.
[14] R. V. Rice, G. D. Beal, US Patent 2,290,710, **1943**.
[15] Addition of electrophilic iodinating reagents (*N*-iodomorpholine, ICl, *N*-iodosuccinimide, etc.) to a solution containing CuI–TTTA, the target azide and terminal alkyne rapidly gave the corresponding 1-iodoalkyne, but failed to promote the subsequent cycloaddition. This failure is likely to be a result of the disruption of the catalytically active complex, either through oxidation of the metal or displacement/destruction of the ligand.
[16] J. Deng, Y.-M. Wu, Q.-Y. Chen, *Synthesis* **2005**, 2730.
[17] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210.
[18] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
[19] a) M. Ahlquist, V. V. Fokin, *Organometallics* **2007**, *26*, 4389; b) B. F. Straub, *Chem. Commun.* **2007**, 3868.

