JOC*Note*

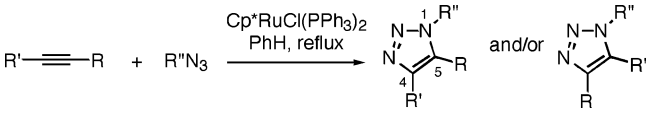
A Study of the Scope and Regioselectivity of the Ruthenium-Catalyzed [3 + 2]-Cycloaddition of Azides with Internal Alkynes

Max M. Majireck and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

smw@chem.psu.edu

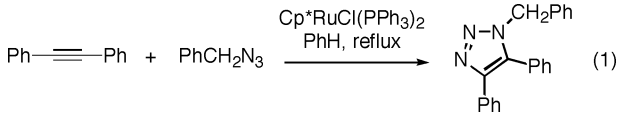
Received August 14, 2006



[3 + 2]-Cycloadditions of alkyl azides with various unsymmetrical internal alkynes in the presence of $Cp^*RuCl(PPh_3)_2$ as catalyst in refluxing benzene have been examined, leading to 1,4,5-trisubstituted-1,2,3-triazoles. Whereas alkyl phenyl and dialkyl acetylenes undergo cycloadditions to afford mixtures of regioisomeric 1,2,3-triazoles, acyl-substituted internal alkynes react with complete regioselectivity. In addition, propargyl alcohols and propargyl amines were found to react with azides to afford single regioisomeric products.

1,2,3-Triazoles are nitrogen heteroarenes which have found a range of important applications in the pharmaceutical and agricultural industries.[1] The most widely used method for synthesis of 1,2,3-triazoles has involved the thermal 1,3-dipolar cycloaddition of organic azides with alkynes pioneered by Huisgen.[2] However, there are major problems commonly associated with this methodology, including the need for long reaction times and high temperatures, as well as the formation of regioisomeric mixtures of products when using unsymmetrical alkynes. It was recently reported that it is possible to impart some regioselectivity into these thermal cycloadditions by utilizing sterically or electronically biased alkynes.[3] As part of the work by the Sharpless group on so-called "click" reactions,[4] whereby heteroatom links between molecules can be generated under mild conditions, it was found that cycloadditions of terminal alkynes with alkyl azides catalyzed by Cu(I) can be conducted at room temperature and are highly regioselective.[5,6] This methodology was also independently discovered by Meldal et al. at about the same time.[7] Thus, cycloadditions of alkynes **1** with azides **2** under conditions such as those shown in Scheme 1 lead exclusively to 4-substituted-1,2,3-triazoles **3** in high yields. This type of copper catalysis, however, does not promote the cycloadditions of internal alkynes. Mechanistic studies have demonstrated that these reactions involve terminal copper acetylides and proceed via a stepwise non-concerted process.[5b]

More recently, it was discovered that the reaction of terminal alkynes with alkyl azides is catalyzed by $Cp^*RuCl(PPh_3)_2$ in refluxing benzene to afford exclusively the 1,5-disubstituted-1,2,3-triazoles 4 (Scheme 1).[8] In contrast to the click reactions promoted by copper, the ruthenium complex was also reported to catalyze the cycloaddition reaction of internal alkynes, although only a single case which involved a symmetrical system was described (eq 1).



It was suggested that this transformation probably occurs by initial coordination of the alkyne and azide with catalyst **5** to afford intermediate **6**, which then undergoes cyclotrimerization to afford metallacycle **7** or **8** (Scheme 2). The formation of the former metallacycle **7** seems most likely due to unfavorable steric interactions in isomer **8**. Reductive elimination of this intermediate then leads to the 1,2,3-triazole and regenerates the catalyst. No rationale was presented, however, for the preference for the observed formation of the 1,5-disubstituted triazole system **4** when using terminal alkynes. As part of our recent interest in 1,2,3-triazoles,[9] we decided to explore the generality and scope of the Ru-catalyzed cycloadditions of alkyl azides with internal alkynes.

Initial experiments were conducted with benzyl azide and commercially available alkynes to form 1,4,5-trisubstituted-1,2,3-triazoles (**A** and/or **B**) as outlined in Table 1. The reactions were all run with 10 mol % of ruthenium catalyst **5** in refluxing benzene. In the majority of cases, the cycloadditions proceeded to completion within 2.5 h using ~1.5 equiv of acetylene relative

(1) For reviews of 1,2,3-triazoles, see: (a) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 4, pp 1−126. (b) Dehne, H. In *Methoden der Organischen Chemie (Houben-Weyl*); Schaumann, E., Ed.; Thieme: Stuttgart, 1994; Vol. E8d, pp 305−405. (c) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339.

(2) For reviews, see: (a) L'Abbe, G. *Chem. Rev.* **1969**, *69*, 345. (b) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; p 559. (c) Sha, C.-K.; Mohanakrishnan, A. K. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; p 623.

(3) See for example: (a) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184. (b) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469. (c) Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143.

(4) For reviews of "click chemistry", see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. **2006**, 51.

(5) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210. (c) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(6) For recent improved experimental procedures, see: (a) Lee, B.-Y.; Park, S. R.; Jeon, H. B.; Kim, K. S. *Tetrahedron Lett*. **2006**, *47*, 5105. (b) Reddy, K. R.; Rajgopal, K.; Kantam, M. L. *Synlett* **2006**, 957.

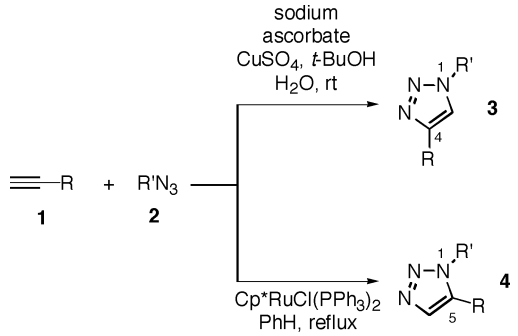
(7) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(8) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

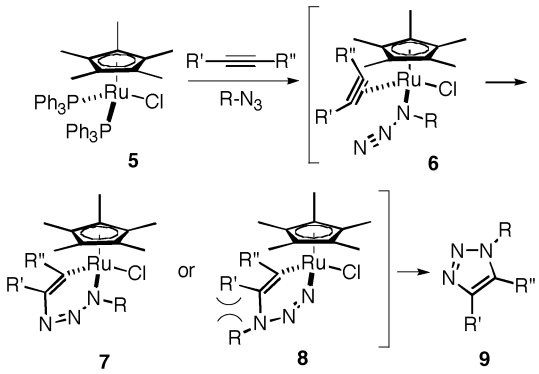
(9) Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035.

10.1021/jo061688m CCC: $33.50
Published on Web 10/05/2006

SCHEME 1



SCHEME 2



to azide, giving good yields of products. In reactions which were slower, however, the amount of alkyne was increased, as was the reaction time. In cases where regioisomers were formed, NMR integration of the crude reaction mixture prior to chromatographic separation was utilized to determine product ratios. The regiochemistry of the purified products was then established by ^{1}H NMR NOE experiments. In the cases of phenyl alkyl acetylenes (entries 1 and 2), moderate regioselectivity was observed in favor of isomers **B**. With unsymmetrical methyl propyl acetylene (entry 7), the **A**/**B** ratio was about 1/2. In the case of hindered methyl *t*-butyl acetylene, the cycloaddition proved to be quite slow, and although only one regioisomeric triazole **B** was detected, the yield was low.

A few unsymmetrical disubstituted alkynes which bear a carbonyl group were also investigated (entries 3, 4, 11, and 12), and in all cases, the cycloadditions were totally regioselective, affording only triazole isomers **A**. It should be noted that thermal (uncatalyzed) cycloadditions of electron-deficient alkynes with azides usually produce mixtures of regioisomeric products,[2b] although isomers such as **A** usually predominate, presumably for polarity reasons. It has recently been found that, if these thermal reactions are conducted in water, isomers of type **A** are produced cleanly with both terminal and internal alkynes.[3c]

We were surprised to find that propargylic alcohols undergo Ru-catalyzed cycloadditions to afford exclusively 1,2,3-triazoles of type **B** (entries 5 and 14). On the other hand, in the case of a homopropargyl alcohol (entry 10), the regioselectivity is low and is similar to that found with a simple dialkyl acetylene (cf. entry 7). Moreover, the alkynyl acetal in entry 6 showed no regioselectivity in the cycloaddition, which would seem to preclude any type of heteroatom−metal coordination.[10] The same high regioselectivity in favor of triazole **B** was observed with a propargyl amine (entry 13). It should also be noted that attempted cycloaddition of benzyl azide with phenyl trimethylsilyl acetylene provided a complex mixture of products.

The cycloaddition of benzhydryl azide[11] with methyl phenyl acetylene was also examined. This secondary azide reacts more slowly than does benzyl azide, but affords the same ratio of adducts **A**/**B** (entry 15). In the case of highly hindered, tertiary adamantyl azide, the reaction is extremely slow and provides a single product of type **B**, but only in very low yield (entry 16).

We have shown that the reaction of internal alkynes with azides catalyzed by Cp*RuCl(PPh$_3$)$_2$ (**5**) is a general process. These cycloadditions proceed under mild conditions, affording 1,4,5-trisubstituted-1,2,3-triazoles in good yields. Depending upon the alkyne substitution pattern, the reactions can be highly regioselective. At present, however, we are unable to offer a compelling mechanistic rationale for these regiochemical results.

Experimental Section

General Procedure for Ru-Catalyzed Cycloadditions. A mixture of azide (1.0 equiv, 0.5 mmol), alkyne (1.2−5.0 equiv), Cp*RuCl(PPh$_3$)$_2$ (0.1 equiv, 0.05 mmol), and 2.5 mL of anhydrous benzene was refluxed at 80 °C for 2.5−40 h. The progress of the reaction was monitored by TLC. The mixture was then cooled and evaporated under reduced pressure. The product was purified by flash column chromatography using a mixture of ethyl acetate and hexanes. Ratios of regioisomers (see Table 1) were determined on the crude reaction mixture by ^{1}H NMR integration prior to chromatography. Numbers of structures below refer to Table 1. Compounds **1A**,[12] **1B**,[13] **3A**,[14] **4A**,[13,15] and **9B**[12] have been previously prepared.

1-Benzyl-4-methyl-5-phenyl-1*H*-[1,2,3]triazole (entry 1A) and 1-Benzyl-5-methyl-4-phenyl-1*H*-[1,2,3]triazole (entry 1B). Benzyl azide (67 mg, 0.50 mmol), prop-1-ynylbenzene (125 mg, 1.08 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The products were obtained as a yellow oil (42 mg of **1A**) and a white solid (78 mg of **1B**) in a total yield of 95%. **1A:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.46−7.44 (m, 3H), 7.30−7.25 (m, 3H), 7.20−7.15 (m, 2H), 7.07−7.03 (m, 2H), 5.45 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.1, 135.9, 135.1, 129.9, 129.7, 129.3, 129.1, 128.5, 127.7, 52.5, 11.1; LRMS-ES+ *m*/*z* (relative intensity) 250 (MH$^+$, 65); HRMS-ES+ ($C_{16}H_{15}N_3$) calcd 250.1344 (MH$^+$), found 250.1349. **1B:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74−7.71 (m, 2H), 7.49−7.21 (m, 8H), 5.57 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.4, 135.3, 132.0, 129.6, 129.5, 129.1, 128.7, 128.1, 127.59, 127.57, 52.5, 9.6; LRMS-ES+ *m*/*z* (relative intensity) 250 (MH$^+$, 65); HRMS-ES+ ($C_{16}H_{15}N_3$) calcd 250.1344 (MH$^+$), found 250.1349.

1-Benzyl-5-phenyl-4-propyl-1*H*-[1,2,3]triazole (entry 2A) and 1-Benzyl-4-phenyl-5-propyl-1*H*-[1,2,3]triazole (entry 2B). Benzyl azide (67 mg, 0.50 mmol), pent-1-ynylbenzene (110 mg, 0.76 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). Both products were obtained as yellow oils (14 mg of **2A**; 96 mg of **2B**) in a total yield of 80%. **2A:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44−7.01 (m, 10H), 5.41 (s, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.67 (sextet, J = 7.6 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.3, 136.1, 130.2, 129.6, 129.3, 129.2, 129.1, 128.4, 128.0, 127.8, 52.4, 27.5, 23.3, 14.3; LRMS-ES+ *m*/*z* (relative intensity)

(10) See for example: Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887.

(11) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110.

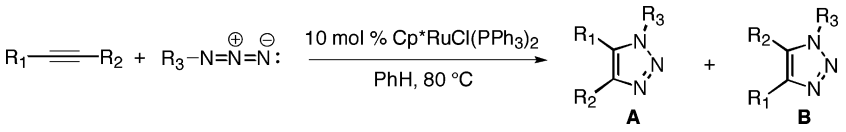
(12) (a) Olsen, C. E. *Acta Chem. Scand.* **1973**, *27*, 2983. (b) Olsen, C. E. *Acta Chem. Scand. B* **1975**, *29*, 953.

(13) Cottrell, I. F.; Hands, D.; Houghton, P. G.; Humphrey, G. R.; Wright, S. H. B. *J. Heterocycl. Chem.* **1991**, *28*, 301.

(14) (a) Prager, R. H.; Razzino, P. *Aust. J. Chem.* **1994**, *47*, 1375. (b) Cwiklicki, A.; Rehse, K. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 156.

(15) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, *8*, 1314.

TABLE 1. Preparation of 1,4,5-Trisubstituted-1,2,3-triazoles via Ru-Catalyzed Cycloadditions of Azides with Internal Alkynes



entry	R_1	R_2	R_3	equiv of alkyne	time (h)	% yield	**A:B** ratio
1	Ph	Me	CH_2Ph	2.0	2.5	95	38:62
2	Ph	Pr	CH_2Ph	1.5	2.5	80	13:87
3	Ph	CO_2Et	CH_2Ph	2.0	2.5	85	100:0
4	Ph	COMe	CH_2Ph	1.5	2.5	100	100:0
5	Ph	CH_2OH	CH_2Ph	1.5	5.0	70	0:100
6	Ph	$CH(OEt)_2$	CH_2Ph	1.5	2.5	75	50:50
7	Me	Pr	CH_2Ph	3.0	16	75	32:68
8	Et	Et	CH_2Ph	2.0	6.0	85	N/A
9	Me	*t*-Bu	CH_2Ph	5.0	36	15	0:100
10	Me	CH_2CH_2OH	CH_2Ph	1.5	8.0	90	23:77
11	Bu	CO_2Me	CH_2Ph	1.2	2.5	90	100:0
12	Et	COMe	CH_2Ph	1.5	2.5	90	100:0
13	Me	CH_2NEt_2	CH_2Ph	1.5	2.5	70	0:100
14	Et	CMe_2OH	CH_2Ph	1.5	5.0	80	0:100
15	Ph	Me	$CHPh_2$	3.0	20	65	33:67
16	Ph	Me	1-adamantyl	5.0	40	10	0:100

278 (MH^+, 100); HRMS-ES+ ($C_{18}H_{20}N_3$) calcd 278.1657 (MH^+), found 278.1638. **2B:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.70 (m, 2H), 7.48−7.21 (m, 8H), 5.58 (s, 2H), 2.72 (t, J = 6.3 Hz, 2H), 1.43 (sextet, J = 8.1 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 135.7, 133.9. 132.2, 129.4, 129.1, 128.7, 128.1, 127.51, 127.47, 52.5, 25.6, 22.3, 14.4; LRMS-ES+ *m*/*z* (relative intensity) 278 (MH^+, 100); HRMS-ES+ ($C_{18}H_{20}N_3$) calcd 278.1657 (MH^+), found 278.1638.

1-Benzyl-5-phenyl-1*H*-[1,2,3]triazole-4-carboxylic Acid Ethyl Ester (entry 3A). Benzyl azide (67 mg, 0.50 mmol), phenylpropynoic acid ethyl ester (165 mg, 0.95 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). The product was obtained as an off-white solid (131 mg) in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.41 (m, 3H), 7.28−7.18 (m, 5H), 7.01−6.98 (m, 2H), 5.44 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 141.7, 137.5, 135.0, 130.5, 130.2, 129.2, 128.9, 128.8, 127.9, 126.4, 61.4, 52.6, 14.5; LRMS-ES+ *m*/*z* (relative intensity) 308 (MH^+, 100); HRMS-ES+ ($C_{18}H_{17}N_3O_2$) calcd 308.1399 (MH^+), found 308.1377.

1-(1-Benzyl-5-phenyl-1*H*-[1,2,3]triazol-4-yl)-ethanone (entry 4A). Benzyl azide (67 mg, 0.50 mmol), 4-phenylbut-3-yn-2-one (110 mg, 0.76 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (140 mg) in 100% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.43 (m, 3H), 7.29−7.25 (m, 3H), 7.23−7.21 (m, 2H), 7.04−7.02 (m, 2H), 5.43 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 144.2, 140.0, 135.1, 131.0, 130.1, 129.3, 129.1, 128.9, 128.0, 126.4, 52.4, 28.5; LRMS-ES+ *m*/*z* (relative intensity) 300 (M + Na^+, 95); HRMS-ES+ ($C_{17}H_{16}N_3O$) calcd 278.1293 (MH^+), found 278.1312.

(3-Benzyl-5-phenyl-3*H*-[1,2,3]triazol-4-yl)methanol (entry 5B). Benzyl azide (67 mg, 0.50 mmol), 3-phenylprop-2-yn-1-ol (100 mg, 0.75 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). The product was obtained as an off-white solid (93 mg) in 70% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (m, 2H), 7.39−7.23 (m, 8H), 5.62 (s, 2H), 4.69 (s, 2H), 3.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 135.4, 132.6, 130.9, 129.4, 129.2, 128.8, 128.7, 128.1, 128.0, 52.9, 52.7; LRMS-ES+ *m*/*z* (relative intensity) 266 (MH^+, 100); HRMS-ES+ ($C_{16}H_{16}N_3O$) calcd 266.1293 (MH^+), found 266.1273.

1-Benzyl-4-diethoxymethyl-5-phenyl-1*H*-[1,2,3]triazole (entry 6A) and 1-Benzyl-5-diethoxymethyl-4-phenyl-1*H*-[1,2,3]triazole (entry 6B). Benzyl azide (67 mg, 0.50 mmol), (3,3-diethoxyprop-1-ynyl)benzene (155 mg, 0.76 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). The products were obtained as a yellow oil (45 mg of **6A**) and a clear oil (80 mg of **6B**) in a total yield of 75%. **6A:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.40 (m, 3H), 7.26−7.20 (m, 5H), 7.04−7.01 (m, 2H), 5.60 (s, 1H), 5.43 (s, 2H), 3.71−3.64 (m, 2H), 3.59−3.52 (m, 2H), 1.12 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 135.7, 130.4, 129.8, 129.1, 128.9, 128.5, 127.8, 127.2, 96.8, 61.9, 52.3, 15.4; LRMS-ES+ *m*/*z* (relative intensity) 338 (MH^+, 100); HRMS-ES+ ($C_{20}H_{24}N_3O_2$) calcd 338.1869 (MH^+), found 338.1855. **6B:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.70 (m, 2H), 7.50−7.33 (m, 8H), 5.82 (s, 2H), 5.64 (s, 1H), 3.66−3.56 (m, 2H), 3.43−3.35 (m, 2H), 1.09 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 136.5, 131.2, 131.1, 128.9, 128.8, 128.6, 128.3, 128.2, 96.2, 63.6, 53.7, 15.2; LRMS-ES+ *m*/*z* (relative intensity) 338 (MH^+, 100); HRMS-ES+ ($C_{20}H_{24}N_3O_2$) calcd 338.1869 (MH^+), found 338.1855.

1-Benzyl-5-methyl-4-propyl-1*H*-[1,2,3]triazole (entry 7A) and 1-Benzyl-4-methyl-5-propyl-1*H*-[1,2,3]triazole (entry 7B). Benzyl azide (67 mg, 0.50 mmol), hex-2-yne (125 mg, 1.5 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). Both products were obtained as clear oils (25 mg of **7A**; 56 mg of **7B**) in 75% total yield. **7A:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (m, 3H), 7.17−7.15 (m, 2H), 5.48 (s, 2H), 2.60 (t, J = 7.4 Hz, 2H), 2.09 (s, 3H), 1.70 (q, J = 7.5 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.0, 135.5, 129.3, 128.6, 127.50, 127.47, 52.3, 27.5, 23.2, 14.2, 8.3; LRMS-ES+ *m*/*z* (relative intensity) 216 (MH^+, 100); HRMS-ES+ ($C_{13}H_{17}N_3$) calcd 216.1501 (MH^+), found 216.1495. **7B:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 3H), 7.16−7.14 (m, 2H), 5.47 (s, 2H), 2.46 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 1.36 (q, J = 7.6 Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 135.9, 133.6, 129.3, 128.6, 127.4, 52.3, 24.9, 22.1, 14.1, 11.0; LRMS-ES+ *m*/*z* (relative intensity) 216 (MH^+, 100); HRMS-ES+ ($C_{13}H_{17}N_3$) calcd 216.1501 (MH^+), found 216.1495.

1-Benzyl-4,5-diethyl-1*H*-[1,2,3]triazole (entry 8). Benzyl azide (67 mg, 0.50 mmol), hex-3-yne (82 mg, 1.0 mmol), and Cp*RuCl(PPh_3)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (90 mg) in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.27 (m, 3H), 7.15−7.11 (m, 2H), 5.45 (s, 2H), 2.62 (q, J = 7.6 Hz, 2H), 2.51 (q, J = 7.7 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 135.9, 134.4, 129.3, 128.5, 127.4, 52.2, 18.9, 16.3, 14.6, 13.7; LRMS-ES+ *m*/*z* (relative intensity) 216 (MH^+, 100); HRMS-ES+ ($C_{13}H_{18}N_3$) calcd 216.1501 (MH^+), found 216.1500.

1-Benzyl-5-*tert*-butyl-4-methyl-1*H*-[1,2,3]triazole (entry 9B). Benzyl azide (67 mg, 0.50 mmol), 4,4-dimethylpent-2-yne (245 mg, 2.5 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as a clear oil (17 mg) in 15% yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32−7.27 (m, 3H), 6.99−6.97 (m, 2H), 5.73 (s, 2H), 2.50 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.5, 140.1, 137.2, 129.2, 128.1, 126.5, 54.2, 31.9, 30.9, 15.0; LRMS-ES+ *m*/*z* (relative intensity) 230 (MH$^+$, 55); HRMS-ES+ (C$_{14}$H$_{20}$N$_3$) calcd 230.1657 (MH$^+$), found 230.1647.

2-(3-Benzyl-5-methyl-3*H*-[1,2,3]triazol-4-yl)-ethanol (entry 10A) and 2-(1-Benzyl-5-methyl-1*H*-[1,2,3]triazol-4-yl)-ethanol (entry 10B). Benzyl azide (67 mg, 0.50 mmol), pent-3-yn-1-ol (130 mg, 1.5 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The products were obtained as an inseparable mixture (99 mg) in 90% overall yield. **10A** + **10B:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33−7.27 (m, 3H *major* + 3H *minor*), 7.14−7.12 (m, 2H *major* + 2H *minor*), 5.55 (s, 2H *major*), 5.44 (s, 2H *minor*), 3.92 (t, J = 5.9 Hz, 2H *minor*), 3.72 (t, J = 6.1 Hz, 2H *major*), 2.81 (t, J = 5.9 Hz, 2H *minor*), 2.72 (t, J = 6.1 Hz, 2H *major*), 2.20 (s, 3H *major*), 2.04 (s, 3H *minor*); ^{13}C NMR (75 MHz, CDCl$_3$) major peaks δ 142.2, 135.5, 134.8, 132.2, 129.4, 129.3, 129.1, 128.8, 128.7, 127.8, 127.6, 65.0, 60.7, 52.7, 52.2, 30.1, 26.5, 14.1, 10.7; LRMS-ES+ *m*/*z* (relative intensity) 218 (MH$^+$, 100); HRMS-ES+ (C$_{12}$H$_{15}$N$_3$ONa) calcd 240.1113 (M + Na$^+$), found 240.1095.

1-Benzyl-5-butyl-1*H*-[1,2,3]triazole-4-carboxylic Acid Methyl Ester (entry 11A). Benzyl azide (67 mg, 0.50 mmol), hept-2-ynoic acid methyl ester (80 mg, 0.61 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (114 mg) in 90% yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34−7.32 (m, 3H), 7.17−7.15 (m, 2H), 5.53 (s, 2H), 3.92 (s, 3H), 2.85 (t, J = 8.0 Hz, 2H), 1.31−1.22 (m, 6H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.4, 143.3, 136.9, 134.9, 129.5, 129.0, 127.6, 52.5, 52.3, 30.7, 23.4, 22.9, 14.0; LRMS-ES+ *m*/*z* (relative intensity) 296 (M + Na$^+$, 100); HRMS-ES+ (C$_{15}$H$_{19}$N$_3$O$_2$) calcd 296.1375 (M + Na$^+$), found 296.1377.

1-(1-Benzyl-5-ethyl-1*H*-[1,2,3]triazol-4-yl)-ethanone (entry 12A). Benzyl azide (67 mg, 0.50 mmol), hex-3-yn-2-one (73 mg, 0.75 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (105 mg) in 90% yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35−7.28 (m, 4H), 7.18−7.16 (m, 2H), 5.51 (s, 2H), 2.89 (q, J = 7.5 Hz, 2H), 2.67 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 143.9, 142.7, 134.9, 129.5, 129.0, 127.6, 52.0, 28.1, 17.3, 12.6; LRMS-ES+ *m*/*z* (relative intensity) 252 (M + Na$^+$, 100); HRMS-ES+ (C$_{13}$H$_{15}$N$_3$ONa) calcd 252.1113 (MH$^+$), found 252.1113.

(3-Benzyl-5-methyl-3*H*-[1,2,3]triazol-4-ylmethyl)diethylamine (entry 13B). Benzyl azide (67 mg, 0.50 mmol), but-2-ynyldiethylamine (85 mg, 0.75 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (90 mg) in 70% yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32−7.25 (m, 3H), 7.17−7.15 (m, 2H), 5.85 (s, 2H), 3.36 (s, 2H), 2.42 (q, J = 7.1 Hz, 4H), 2.29 (s, 3H), 0.95 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.1, 136.2, 130.9, 129.1, 128.3, 127.6, 52.3, 46.7, 45.9, 11.7, 10.7; LRMS-ES+ *m*/*z* (relative intensity) 259 (MH$^+$, 100); HRMS-ES+ (C$_{15}$H$_{23}$N$_4$) calcd 259.1923 (MH$^+$), found 259.1907.

2-(3-Benzyl-5-ethyl-3*H*-[1,2,3]triazol-4-yl)-propan-2-ol (entry 14B). Benzyl azide (67 mg, 0.50 mmol), 2-methylhex-3-yn-2-ol (83 mg, 0.74 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as an off-white solid (96 mg) in 80% yield: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29−7.23 (m, 3H), 7.14−7.12 (m, 2H), 5.83 (s, 2H), 3.48 (s, 1H), 2.71 (q, J = 7.5 Hz, 2H), 1.51 (s, 6H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.6, 138.1, 137.7, 129.0, 128.0, 127.5, 69.8, 54.2, 31.2, 20.7, 14.8; LRMS-ES+ *m*/*z* (relative intensity) 246 (MH$^+$, 100); HRMS-ES+ (C$_{14}$H$_{20}$N$_3$O) calcd 246.1606 (MH$^+$), found 246.1604.

1-Benzhydryl-4-methyl-5-phenyl-1*H*-[1,2,3]triazole (entry 15A) and 1-Benzhydryl-5-methyl-4-phenyl-1*H*-[1,2,3]triazole (entry 15B). Benzhydryl azide[11] (105 mg, 0.50 mmol), prop-1-ynylbenzene (175 mg, 1.5 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). Both products were obtained as yellow solids (30 mg of **15A**; 70 mg of **15B**) in 65% overall yield. **15A:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50−7.48 (m, 3H), 7.34−7.31 (m, 6H), 7.24−7.19 (m, 6H), 6.55 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.3, 139.4, 135.7, 130.2, 129.8, 129.5, 129.0, 128.8, 128.5, 128.1, 66.2, 11.1; LRMS-ES+ *m*/*z* (relative intensity) 326 (MH$^+$, 100); HRMS-ES+ (C$_{22}$H$_{20}$N$_3$) calcd 326.1657 (MH$^+$), found 326.1666. **15B:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74−7.72 (m, 2H), 7.48−7.45 (m, 2H), 7.42−7.34 (m, 7H), 7.29−7.25 (m, 4H), 6.85 (s, 1H), 2.40 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.2, 138.2, 132.0, 130.0, 129.2, 129.0, 128.9, 128.7, 128.1, 127.8, 66.8, 10.0; LRMS-ES+ *m*/*z* (relative intensity) 326 (MH$^+$, 100); HRMS-ES+ (C$_{22}$H$_{20}$N$_3$) calcd 326.1657 (MH$^+$), found 326.1666.

1-Adamantan-1-yl-5-methyl-4-phenyl-1*H*-[1,2,3]triazole (entry 16B). 1-Azidoadamantane (95 mg, 0.50 mmol), prop-1-ynylbenzene (305 mg, 2.63 mmol), and Cp*RuCl(PPh$_3$)$_2$ (40 mg, 0.05 mmol). The product was obtained as a yellow oil (13 mg) in 10% yield: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64−7.61 (m, 2H), 7.48−7.44 (m, 2H), 7.38−7.37 (m, 1H), 2.62 (s, 3H), 2.44 (d, J = 3.0 Hz, 6H), 2.30 (m, 3H), 1.83 (t, J = 3.1 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 146.8, 132.3, 128.9, 128.5, 127.9, 62.3, 42.0, 36.4, 30.1, 12.4; LRMS-ES+ *m*/*z* (relative intensity) 293 (M$^+$, 100); HRMS-ES+ (C$_{19}$H$_{23}$N$_3$) calcd 293.1892 (MH$^+$), found 293.1888.

Acknowledgment. We are grateful to the National Institutes of Health (CA-034303) for financial support of this research. We also thank Amy Yap for conducting some preliminary experiments, and Dr. G. Jia for providing information on preparation of the ruthenium catalyst **5**.

Note Added after ASAP Publication. Table 1 had an incorrect ratio in the version published October 5, 2006; the correct version was published October 5, 2006.

Supporting Information Available: Copies of proton and carbon NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061688M