Multifunctional Reactions

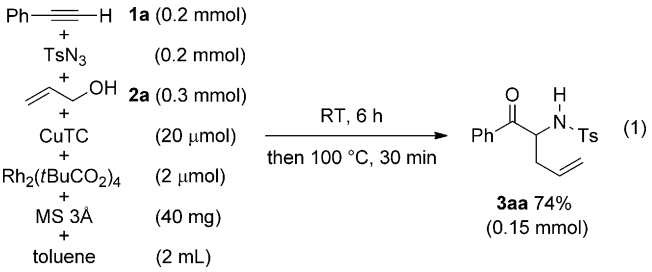
DOI: 10.1002/anie.201209603

One-Pot Procedure for the Introduction of Three Different Bonds onto Terminal Alkynes through *N*-Sulfonyl-1,2,3-Triazole Intermediates**

Tomoya Miura, Takamasa Tanaka, Tsuneaki Biyajima, Akira Yada, and Masahiro Murakami**

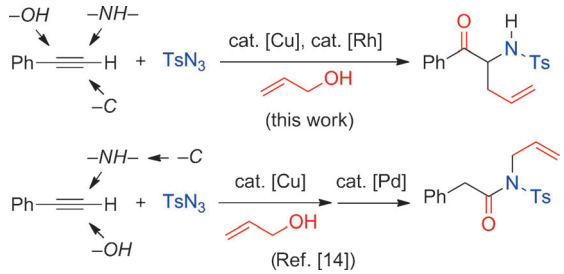
Alkynes constitute a fundamental class of organic compounds and a variety of alkynes can be readily synthesized by C–C bond-forming reactions of nucleophilic ethynyl species with electrophiles. The resulting alkynes provide versatile platforms for synthetic transformations.[1] In particular, a [3+2] dipolar cycloaddition reaction with azides to give triazoles has attracted much attention in the last decade.[2] Recent studies by the groups of Fokin and Gevorgyan, as well as our own, have disclosed that the resulting triazoles could act as precursors for reactive α-imino metal carbenoid species, which can subsequently couple with nitriles,[3] alkynes,[4] alkenes,[5] and alkanes.[6] A semi-pinacol rearrangement reaction is induced by the electrophilic nature of the α-imino carbenoid species.[7] Nucleophiles such as water[8] and arylboronic acids[9] also add to the electrophilic α-imino carbenoid species. The reaction with water regioselectively introduces amino and hydroxy groups in juxtaposition onto terminal alkynes. On the other hand, it has been reported by the groups of Wood[10] and Davies[11] that [3,3]- and [2,3]-sigmatropic rearrangements become feasible when α-diazo carbonyl compounds are reacted with allylic alcohols in the presence of rhodium(II) catalysts. Their studies prompted us to use allylic alcohols instead of water in the reaction of triazoles in pursuit of further functionalization with C–C bond formation through sigmatropic rearrangement. Herein, we report an extremely facile one-pot process to convert terminal alkynes into α-allyl-α-amino ketones through triazoles and allyl vinyl ether intermediates. During the one-pot process, three different bonds are regioselectively introduced onto the C≡C bond.[12]

Phenylethyne (**1a**), tosyl azide (TsN_3; 1.0 equiv), allyl alcohol (**2a**; 1.5 equiv), CuTC (10 mol%; TC = thiophene-2-carboxylate), $Rh_2(tBuCO_2)_4$ (1.0 mol%), 3 Å molecular sieves (MS 3 Å),[13] and toluene (2 mL) were put in a reaction vessel [Eq. (1)]. The reaction mixture was simply stirred at room temperature for 6 h, whereupon NMR analysis showed that both **1a** and tosyl azide were consumed. Next, the reaction



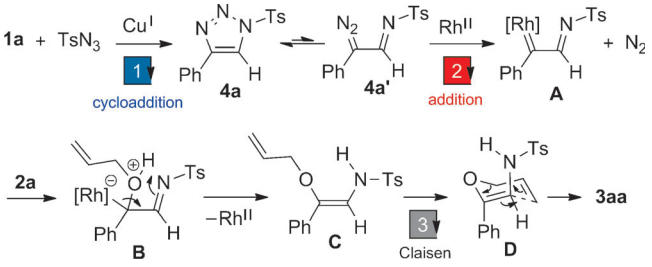
(1)

mixture was further stirred at 100 °C for 30 min, and then cooled. Isolation by preparative thin-layer chromatography furnished 2-allyl-2-tosylamino-1-phenylethanone (**3aa**) in 74% yield based on **1a**. Thus, terminal alkynes were regioselectively multifunctionalized with the formation of C–O, C–N, and C–C bonds in one pot. The outcome of this process stands in contrast to that of the reaction reported by Chang et al., which used the same substrates, but a different catalyst system (Scheme 1).[14,15]



Scheme 1. Two pathways of the reaction of phenylethyne (**1a**) with tosyl azide and allyl alcohol (**2a**).

Scheme 2 shows the proposed mechanism of the one-pot process, which consists of three steps. The first step is a [3+2] cycloaddition reaction of **1a** with tosyl azide, which has been reported by the groups of Fokin, Sharpless, and Chang to



Scheme 2. Proposed mechanism for the rhodium(II)-catalyzed synthesis of **3aa** from **1a**, tosyl azide, and **2a**.

[*] Dr. T. Miura, T. Tanaka, T. Biyajima, Dr. A. Yada, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University, Katsura, Kyoto 615-8510 (Japan)
E-mail: tmiura@sbchem.kyoto-u.ac.jp
murakami@sbchem.kyoto-u.ac.jp
Homepage: http://www.sbchem.kyoto-u.ac.jp/murakami-lab/

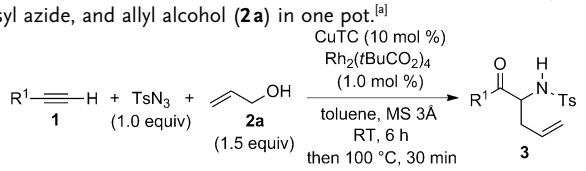
[**] This work was supported in part by MEXT (Grant-in-Aid for Scientific Research on Innovative Area Nos. 22105005 and 22106520, Young Scientists (A) No. 23685019), Takeda Science Foundation, and Asahi Glass Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209603.

occur at room temperature with copper(I) catalysis.[16] The resulting *N*-sulfonyl-1,2,3-triazole **4a** engages in the second step when heated to 100 °C. The second step, which forms **C** from **4a**, consists of a ring–chain tautomerization[17] and a subsequent rhodium(II)-catalyzed reaction with allyl alcohol **2a**.[18] The α-diazo imine **4a′**, which is formed from **4a** by the ring–chain tautomerization, reacts with the rhodium(II) dimer to afford α-imino rhodium(II) carbenoid **A**, along with the release of molecular nitrogen. Compound **2a** then adds to the electrophilic carbene center of **A** to furnish zwitterionic intermediate **B**. The anionic rhodium releases an electron pair, which eventually results in the imine moiety abstracting a proton from the oxygen. Thus, (*Z*)-allyl vinyl ether **C** is stereoselectively formed. The third and final step is a Claisen-type [3,3]-sigmatropic rearrangement, which proceeds via six-membered chairlike transition state **D**, to give product **3aa**. Although the copper(I) and rhodium(II) catalysts coexist in the reaction media, they scarcely interfered with each other in playing their catalytic roles in the cycloaddition and carbene reactions.

Various other terminal alkynes **1** were subjected to reaction with **2a** to demonstrate the generality of the one-pot process (Table 1). The corresponding products, which include alkyl-substituted ketones, were obtained in yields ranging from 53% to 80%.

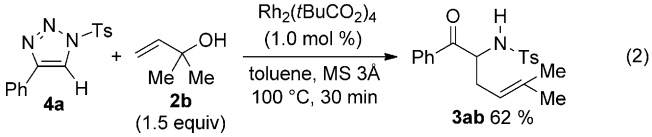
Table 1: Synthesis of α-allyl-α-amino ketones **3** from terminal alkynes **1**, tosyl azide, and allyl alcohol (**2a**) in one pot.[a]



Entry	**1**	R^1	**3**	Yield [%][b]
1	**1b**	4-Me-C_6H_4	**3ba**	80
2	**1c**	4-MeO-C_6H_4	**3ca**	73
3	**1d**	4-CF_3-C_6H_4	**3da**	69
4	**1e**	4-EtO_2C-C_6H_4	**3ea**	58[c]
5	**1f**	3-thienyl	**3fa**	72
6	**1g**	*n*-hexyl	**3ga**	53[d]
7	**1h**	*iso*-butyl	**3ha**	64[d]
8	**1i**	$(CH_2)_4OBz$	**3ia**	66[d]
9	**1j**	$(CH_2)_4N$(Phth)	**3ja**	72[d]

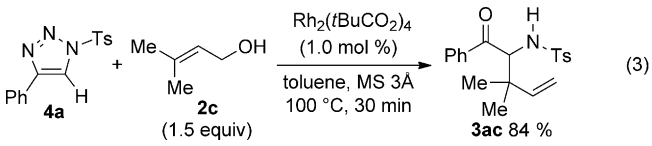
[a] Conditions: **1** (0.2 mmol), TsN_3 (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), CuTC (20 μmol), $Rh_2(tBuCO_2)_4$ (2 μmol), and MS 3 Å (40 mg) in toluene (2 mL) were stirred at RT for 6 h, then at 100 °C for 30 min unless otherwise noted. [b] Yield of isolated product (average of 2 runs). [c] The reaction was stirred at RT for 12 h. [d] Using $Rh_2(tBuCO_2)_4$ (5 μmol) in $CHCl_3$ (0.5 mL), then at 100 °C for 1 h under microwave (MW) irradiation. Bz = benzoyl, Phth = phthaloyl.

The second and third steps were examined in more detail using isolated triazole **4a**. Thus, a mixture of **4a** and α-disubstituted allylic alcohol **2b** (1.5 equiv) in toluene was heated at 100 °C for 30 min in the presence of $Rh_2(tBuCO_2)_4$ (1.0 mol%) and MS 3 Å. Chromatographic purification afforded 2-(3,3-dimethylallyl)-2-tosylamino-1-phenylethanone [**3ab**; Eq. (2)]. On the other hand, the reaction of γ-disubstituted allylic alcohol **2c** gave 2-(1,1-dimethylallyl)-2-



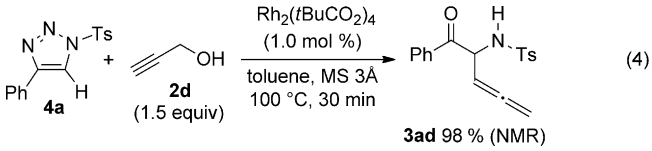
(2)

tosylamino-1-phenylethanone [**3ac**; Eq. (3)]. These results confirmed that the C–C bond was formed regioselectively at the γ position of allylic alcohols, which supports the involvement of a [3,3]-sigmatropic rearrangement in the mechanism.



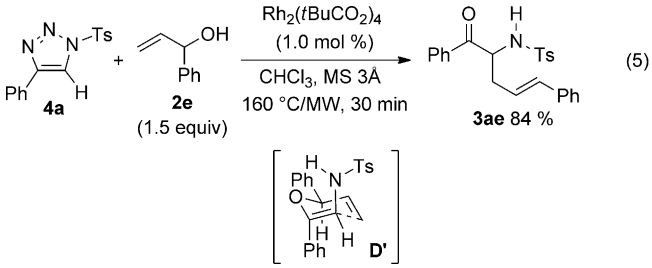
(3)

The γ-selectivity even led to the production of α-allenyl-substituted compound **3ad** from propargyl alcohol (**2d**) [Eq. (4)].



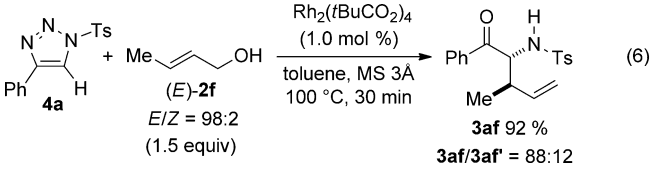
(4)

The stereochemical aspects were also investigated. The configuration of the double bond of product **3ae**, which was produced from α-substituted allylic alcohol **2e**, was obtained with an exclusively *E* orientation [Eq. (5)]. This outcome is well accounted for by assuming six-membered chairlike transition state **D′** with an α-substituent at the pseudo-equatorial position.

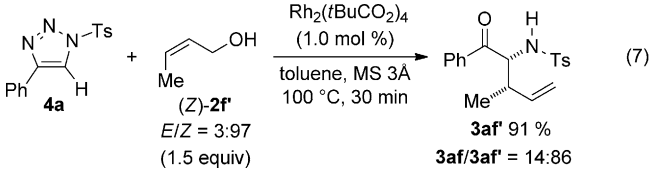


(5)

The use of an *E*/*Z* crotyl alcohol resulted in moderate stereospecificity [Eqs. (6) and (7)]. These results implied that the initially formed *Z* isomer, which corresponds to **C** in



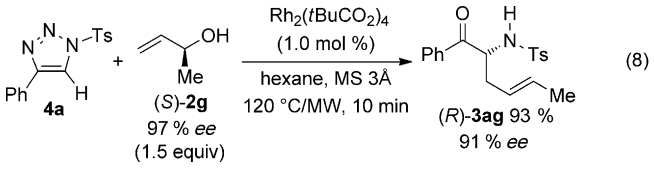
(6)



(7)

Scheme 2, partially isomerized to the *E* isomer before the [3,3]-sigmatropic rearrangement.

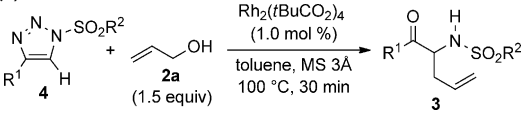
When (*S*)-1-methyl-2-propen-1-ol (**2g**) was used, a good level of chirality transfer was observed [Eq. (8)].



(8)

The substrate scope of triazoles **4** was also examined in the reaction with the allyl alcohol (**2a**; Table 2). Triazoles **4a** and **4g**, which are substituted with 4-phenyl- and 4-(*n*-hexyl) groups, respectively, reacted to afford the corresponding

Table 2: Rh^{II}-catalyzed denitrogenative reaction of 4-substituted 1-(*N*-sulfonyl)-1,2,3-triazoles **4** with **2a**.[a]

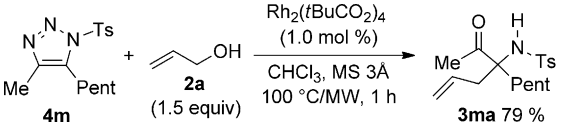


Entry	**4**	R^1	R^2	**3**	Yield [%][b]
1	**4a**	Ph	4-Me-C_6H_4	**3aa**	91
2	**4g**	*n*-hexyl	4-Me-C_6H_4	**3ga**	77[c]
3	**4k**	OEt	4-Me-C_6H_4	**3ka**	75[d]
4	**4l**	H	4-Me-C_6H_4	**3la**	13[e]
5	**4n**	Ph	4-MeO-C_6H_4	**3na**	91
6	**4o**	Ph	4-Br-C_6H_4	**3oa**	93
7	**4p**	Ph	Me	**3pa**	94
8	**4q**	Ph	$(CH_2)_2SiMe_3$	**3qa**	94

[a] Conditions: **4** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv), $Rh_2(tBuCO_2)_4$ (2 μmol), and MS 3 Å (40 mg) in toluene (2 mL) were heated at 100 °C for 30 min, unless otherwise noted. [b] Yield of isolated product (average of 2 runs). [c] Using $Rh_2(tBuCO_2)_4$ (5 μmol) and MS 3 Å (10 mg) in $CHCl_3$ (0.5 mL) for 1 h under MW irradiation. [d] Using $Rh_2(tBuCO_2)_4$ (1 μmol) and **2a** (1.0 mmol, 5.0 equiv). [e] Yield determined by ^1H NMR spectroscopy.

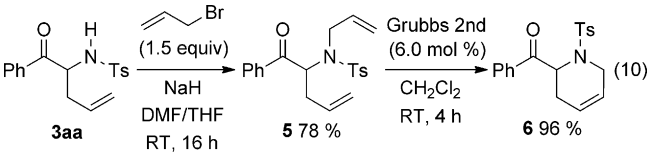
products **3aa** and **3ga** in 91 % and 77 % yields, respectively (entries 1 and 2). The yield of **3ga** was slightly lower because β-hydride migration occurred with the rhodium carbenoid intermediate, which corresponds to **A** in Scheme 2, to give α,β-unsaturated *N*-tosyl imine as a by-product,[7] as was the case with the one-pot reaction (Table 1, entry 6). 4-Ethoxy-substituted triazole **4k**, which was prepared from ethoxyethyne, afforded α-amino acid derivative **3ka** (Table 2, entry 3). As for the sulfonyl groups, not only arylsulfonyl groups, but also alkylsulfonyl groups were suitable (entries 5–8). Thus, the reaction was highly general with respect to the R^1 and R^2 groups.

Whereas the reaction of unsubstituted triazole **4l** was sluggish (Table 2, entry 4), 4,5-disubstituted triazole **4m** was reactive enough to furnish the product **3ma**, which possesses a quaternary α-carbon in 79 % yield [Eq. (9)].[19]



(9)

The synthetic utility of α-allyl-α-amino ketones was exemplified by further transformation [Eq. (10)]. Allylation of **3aa** with allyl bromide and subsequent ring-closing metathesis using the 2nd generation Grubbs catalyst afforded 3,4-dehydropiperidine **6**.



(10)

In conclusion, we have developed an extremely facile method for the synthesis of α-substituted α-amino ketones, which are often key substructures of bioactive compounds,[20] as well as synthetic intermediates for α-amino alcohols,[21] both in general and in various natural products.[22] Terminal alkynes are functionalized with three different bonds using sulfonyl azides and allylic alcohols, which would otherwise require multiple synthetic steps. High generality with respect to the terminal alkyne substituents, as well as a good level of chirality transfer from chiral allylic alcohols, are observed. The three starting materials are readily accessible, even from commercial sources. This one-pot synthetic method is environmentally benign, as the only waste generated throughout the entire process is molecular nitrogen.

Experimental Section

Typical procedure for the one-pot reaction of terminal alkynes with allylic alcohols [Eq. (1)]: **1a** (20.4 mg, 0.2 mmol), TsN_3 (39.4 mg, 0.2 mmol; Ts = *p*-toluenesulfonyl), **2a** (17.4 mg, 0.3 mmol), CuTC (3.8 mg, 20 μmol), $Rh_2(tBuCO_2)_4$ (1.2 mg, 2 μmol), MS 3 Å (40 mg), and toluene (2 mL) were added to an oven-dried 4 mL-vial equipped with a stir bar. The vial was capped with Teflon film. The reaction mixture was stirred at room temperature for 6 h, and then, heated at 100 °C for 30 min. Afterwards, the reaction mixture was cooled and passed through a cotton stopper with CH_2Cl_2, the filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography ($CHCl_3$/ethyl acetate 25:1) to give product **3aa** as a white solid (48.8 mg, 0.15 mmol, 74 %).

Received: November 30, 2012
Published online: February 25, 2013

Keywords: allylation · copper · rhodium · terminal alkynes · triazoles

[1] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, **1999**, pp. 563 – 606.

[2] For recent reviews, see: a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302; b) A. Qin, J. W. Y. Lam, B. Z. Tang, *Macromolecules* **2010**, *43*, 8693; c) D. Astruc, L. Liang, A. Rapakousiou, J. Ruiz, *Acc. Chem. Res.* **2012**, *45*, 630.

[3] a) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972. For a review on transannulation reactions of triazoles, see: b) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem.* **2012**, *124*, 886; *Angew. Chem. Int. Ed.* **2012**, *51*, 862.

[4] a) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470; b) B. Chattopadhyay, V. Gevorgyan, *Org. Lett.* **2011**, *13*, 3746.

[5] a) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher, V. V. Fokin, *J. Am. Chem. Soc.* **2009**, *131*, 18034; b) N. Grimster, L. Zhang, V. V. Fokin, *J. Am. Chem. Soc.* **2010**, *132*, 2510; for a related report, see: c) E. Lourdusamy, L. Yao, C.-M. Park, *Angew. Chem.* **2010**, *122*, 8135; *Angew. Chem. Int. Ed.* **2010**, *49*, 7963.

[6] a) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352. For a related report, see: b) N. Selander, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 2477.

[7] a) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17440; b) N. Selander, B. T. Worrell, V. V. Fokin, *Angew. Chem.* **2012**, *124*, 13231; *Angew. Chem. Int. Ed.* **2012**, *51*, 13054; for a related report, see: c) R. Liu, M. Zhang, G. Winston-McPherson, W. Tang, *Chem. Commun.* **2013**, DOI: 10.1039/c2cc34609e.

[8] T. Miura, T. Biyajima, T. Fujii, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 194.

[9] N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 14670.

[10] a) J. L. Wood, B. M. Stoltz, H.-J. Dietrich, D. A. Pflum, D. T. Petsch, *J. Am. Chem. Soc.* **1997**, *119*, 9641; b) J. L. Wood, G. A. Moniz, *Org. Lett.* **1999**, *1*, 371; c) J. L. Wood, G. A. Moniz, D. A. Pflum, B. M. Stoltz, A. A. Holubec, H.-J. Dietrich, *J. Am. Chem. Soc.* **1999**, *121*, 1748.

[11] a) Z. Li, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 396; b) B. T. Parr, Z. Li, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 2378; c) Z. Li, B. T. Parr, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 10942.

[12] For intramolecular 1-allyl-1,2-aminohydroxylation of 2-alkynyl arylazides with allyl alcohol catalyzed by gold(I), see: A. Wetzel, F. Gagosz, *Angew. Chem.* **2011**, *123*, 7492; *Angew. Chem. Int. Ed.* **2011**, *50*, 7354.

[13] In the absence of 3 Å molecular sieves, a small amount of 2-tosylamino-1-phenylethanone (> 5 %) was formed as a by-product by hydration.

[14] E. J. Yoo, I. Bae, S. H. Cho, H. Han, S. Chang, *Org. Lett.* **2006**, *8*, 1347.

[15] For selected reviews on multicatalyst cooperative systems, see: a) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; c) L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373; for recent examples, see: d) M. Asikainen, N. Krause, *Adv. Synth. Catal.* **2009**, *351*, 2305; e) G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609; f) B. M. Trost, X. Luan, *J. Am. Chem. Soc.* **2011**, *133*, 1706; g) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem.* **2011**, *123*, 9255; *Angew. Chem. Int. Ed.* **2011**, *50*, 9089; h) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 551; *Angew. Chem. Int. Ed.* **2012**, *51*, 536; i) D. Fuchs, G. Rousseau, L. Diab, U. Gellrich, B. Breit, *Angew. Chem.* **2012**, *124*, 2220; *Angew. Chem. Int. Ed.* **2012**, *51*, 2178.

[16] a) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless, S. Chang, *Angew. Chem.* **2007**, *119*, 1760; *Angew. Chem. Int. Ed.* **2007**, *46*, 1730; b) J. Raushel, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4952; c) Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao, Y. Hu, *Tetrahedron* **2011**, *67*, 6294.

[17] a) P. Grünanger, P. V. Finzi, *Tetrahedron Lett.* **1963**, *4*, 1839; b) R. E. Harmon, F. Stanley, Jr., S. K. Gupta, J. Johnson, *J. Org. Chem.* **1970**, *35*, 3444; c) G. Himbert, D. Frank, M. Regitz, *Chem. Ber.* **1976**, *109*, 370.

[18] For the addition of alcohols to rhodium carbenoids, see: a) R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, P. Teyssié, *Tetrahedron Lett.* **1973**, *14*, 2233; b) P. Bulugahapitiya, Y. Landais, L. Parra-Rapado, D. Planchenault, V. Weber, *J. Org. Chem.* **1997**, *62*, 1630; c) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 15497, and references therein.

[19] For the synthesis of 4,5-disubstituted 1-(*N*-sulfonyl)-1,2,3-triazoles, see: M. E. Meza-Aviña, M. K. Patel, C. B. Lee, T. J. Dietz, M. P. Croatt, *Org. Lett.* **2011**, *13*, 2984.

[20] a) D. M. Perrine, J. T. Ross, S. J. Nervi, R. H. Zimmerman, *J. Chem. Educ.* **2000**, *77*, 1479; b) K. F. Foley, N. V. Cozzi, *Drug Dev. Res.* **2003**, *60*, 252.

[21] a) R. D. Pace, G. W. Kabalka, *J. Org. Chem.* **1995**, *60*, 4838; b) S. Sengupta, D. Das, S. Mondal, *Synlett* **2001**, 1464; c) R. V. Hoffman, N. Maslouh, F. Cervantes-Lee, *J. Org. Chem.* **2002**, *67*, 1045; d) N. Arai, H. Ooka, K. Azuma, T. Yabuuchi, N. Kurono, T. Inoue, T. Ohkuma, *Org. Lett.* **2007**, *9*, 939.

[22] a) M. Anada, M. Tanaka, T. Washio, M. Yamawaki, T. Abe, S. Hashimoto, *Org. Lett.* **2007**, *9*, 4559; b) M. Tanaka, S. Nakamura, M. Anada, S. Hashimoto, *Heterocycles* **2008**, *76*, 1633.

