JOC Note
pubs.acs.org/joc

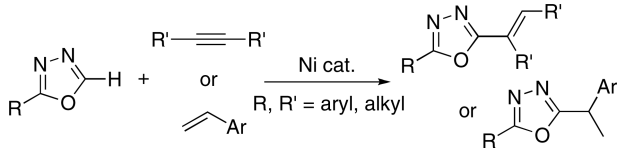
Nickel-Catalyzed C−H Alkenylation and Alkylation of 1,3,4-Oxadiazoles with Alkynes and Styrenes

Tomoya Mukai, Koji Hirano, Tetsuya Satoh, and Masahiro Miura*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

miura@chem.eng.osaka-u.ac.jp

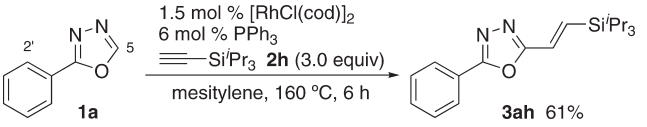
Received June 25, 2009



The addition reaction of 1,3,4-oxadiazoles to alkynes via C−H bond cleavage efficiently proceeds in the presence of a nickel catalyst. This direct coupling allows a facile access to alkenyl-substituted oxadiazoles. The reaction with styrenes in place of alkynes is also available to selectively afford the corresponding branched adducts.

Various aryl-substituted aromatic heterocycles are known to exhibit interesting biological activities and are also useful as π-conjugated organic materials.[1] 1,3,4-Oxadiazole is apparently among the most significant heterocycle cores. Thus, 1,3,4-oxadizole derivatives may act as ester and amide bioisosteres and, hence, are of interest in pharmaceutical and agrochemical fields.[2] Also, much attention has been focused on the oxadiazole core π-systems as electron-transporting and hole-blocking materials in the area of organic light-emitting diodes (OLEDs).[2c,3] Consequently, the development of effective methods for the rapid and concise synthesis and modification of the oxadiazole motif is of considerable importance in organic synthesis.

SCHEME 1. Rhodium-Catalyzed Alkenylation of 2-Phenyl-1,3,4-oxadiazole (1a) with Triisopropylsilylacetylene (2h)



1a **3ah** 61%

Recent advances in the transition metal-mediated direct functionalization of C−H bonds have had a significant impact on the various fields in synthetic chemistry.[4] In particular, since the pioneering work of Murai and co-workers,[5] a variety of catalytic systems have been explored for the direct alkenylation as well as alkylation of aromatic and heteroaromatic substrates with alkynes as well as alkenes via oxidative addition of their C−H bonds.[6] Herein, we report the nickel-catalyzed C−H alkenylation of 1,3,4-oxadiazoles with alkynes. The reaction provides an efficient approach to a variety of alkenyl-substituted oxadiazoles—high-yielding synthetic methods for which have so far been limited to selenium-mediated processes.[7] Moreover, the alkylation reaction with styrenes is also disclosed.[8]

Recently, we reported the rhodium-catalyzed and coordination-assisted direct ortho-alkenylation of *N*-heterocycle-substituted arenes with terminal silylacetylenes such as triisopropylsilylacetylene.[9] We applied the rhodium-based catalyst system to the reaction using 2-phenyl-1,3,4-oxadiazole (**1a**) and found that the alkenylation proceeded at the 5-position rather than the expected 2′-position proximal to the 3-nitrogen to afford the corresponding adduct **3ah** in good yield (Scheme 1). However, the reaction with other terminal and internal alkynes was unsuccessful.

We then turned our attention to the potential of nickel catalysts. Cavell reported the nickel-catalyzed addition of the acidic C−H bond at the 2-position of imidazolium salts to alkenes.[10] Nakao and Hiyama also described the efficient alkenylation and alkylation of the relatively acidic sp^2 C−H bond of heteroarenes and fluoroarenes under nickel catalysis.[11] Given the high acidity of the C−H bond at the 5-position of **1a**,[12] its effective activation by nickel complexes

(1) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(2) (a) Leung, D.; Du, W.; Hardouin, C.; Cheng, H.; Hwang, I.; Cravatt, B. F.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1423. (b) Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. *Eur. J. Med. Chem.* **1996**, *31*, 819. (c) Zarudnitskii, E. V.; Pervak, I. I.; Merkulov, A. S.; Yurchenko, A. A.; Tolmachev, A. A. *Tetrahedron* **2008**, *64*, 10431 and references cited therein.

(3) (a) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471. (b) He, G. S.; Tan, L.-S.; Zheng, Q.; Prasad, P. N. *Chem. Rev.* **2008**, *108*, 1245.

(4) Reviews: (a) Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 47. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (g) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (i) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (j) Chatani, N., Ed. Directed Metallation. In *Topics in Organometallic Chemistry*; Springer: Berlin, Germany, 2008; Vol. 24. (k) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (l) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (m) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.

(5) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(6) Selected examples: (a) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615. (b) Kakiuchi, F.; Sato, T.; Igi, K.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 386. (c) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (d) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (e) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102. (f) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329. (g) Tsukada, N.; Murata, K.; Inoue, Y. *Tetrahedron Lett.* **2005**, *46*, 7515. (h) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (i) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332.

(7) (a) Wang, Y.-G.; Huang, X.; Wu, Y.-Z. *Tetrahedron* **2007**, *63*, 7866. (b) Wang, Y.-G.; Xu, W. M.; Huang, X. *J. Comb. Chem.* **2007**, *9*, 513.

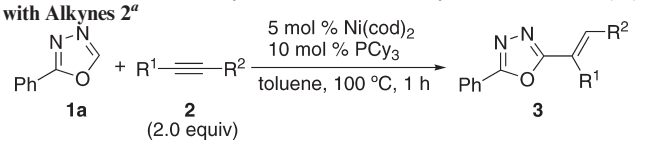
(8) Copper-mediated direct arylation of oxadiazoles: Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072.

(9) Katagiri, T.; Mukai, T.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2009**, *38*, 118.

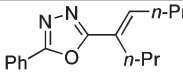
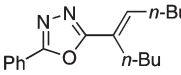
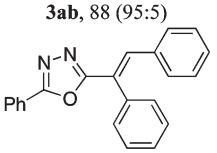
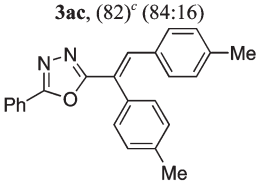
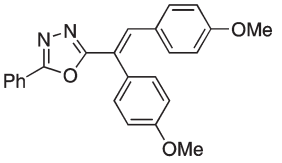
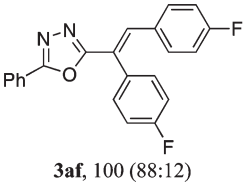
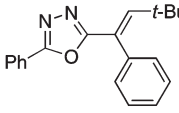
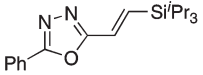
(10) (a) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845. (b) Normand, A. T.; Yen, S. K.; Huynh, H. V.; Hor, T. S. A.; Cavell, K. J. *Oganometallics* **2008**, *27*, 3153.

Published on Web 07/24/2009 DOI: 10.1021/jo901350j

TABLE 1. Nickel-Catalyzed Reaction of 2-Phenyl-1,3,4-oxadiazole (1a) with Alkynes 2[a]



1a **2** (2.0 equiv) **3**

entry	2	3, yield (%), (*E*/*Z*)[b]
1	$R^1 = R^2 =$ *n*-Pr **2a**	 **3aa**, 76 (99:1)
2	$R^1 = R^2 =$ *n*-Bu **2b**	 **3ab**, 88 (95:5)
3	$R^1 = R^2 =$ Ph **2c**	 **3ac**, (82)[c] (84:16)
4[d]	$R^1 = R^2 =$ 4-MeC_6H_4 **2d**	 **3ad**, 74 (86:14)
5[d]	$R^1 = R^2 =$ 4-MeOC_6H_4 **2e**	 **3ae**, 51 (79:21)
6[d]	$R^1 = R^2 =$ 4-FC_6H_4 **2f**	 **3af**, 100 (88:12)
7[e]	R^1 = Ph, R^2 = *t*-Bu **2g**	 **3ag**, 72 (99:1)
8	R^1 = H, $R^2 = Si^iPr_3$ **2h**	 **3ah**, 39 (99:1)

[a]Reaction conditions: [**1**]:[**2**]:[Ni(cod)$_2$]:[PCy$_3$] = 0.25:0.50:0.0125:0.025 (in mmol), in toluene (1.2 mL) under N_2 at 100 °C for 1 h. [b]*E*/*Z* ratio determined by ^{1}H NMR. [c]^{1}H NMR yield. [d]With 0.38 mmol of **2**. [e]With PPh$_3$ instead of PCy$_3$.

was anticipated. Indeed, treatment of **1a** with 2.0 equiv of 4-octyne (**2a**) in the presence of 5 mol % of Ni(cod)$_2$ and 10 mol % of PCy$_3$ in toluene at 100 °C for 1 h furnished the corresponding alkenylated product **3aa** in 76% yield with high stereoselectivity (Table 1, entry 1).[13] The longer alkyl chains of 5-decyne (**2b**) did not interfere with the reaction (entry 2). Diarylacetylenes were also available for use. The reaction with diphenylacetylene (**2c**) took place without any difficulties to produce the conjugated oxadiazole **3ac** in a similar yield albeit with the decrease of stereoselectivity to some extent (entry 3). While the electron-rich **2d** and **2e** showed lower reactivity (entries 4 and 5), the use of the electron-deficient **2f** quantitatively afforded **3af** (entry 6). The unsymmetrical internal alkyne **2g** could couple with **1a** to give alkenylated oxadiazole **3ag** exclusively, in which the oxadiazole core was connected selectively to the benzylic position (entry 7). In this case, the use of PPh$_3$ in place of PCy$_3$ gave a better result (ca. 20% with PCy$_3$). In addition, the terminal alkyne, triisopropylsilylacetylene (**2h**), could participate in the reaction (entry 8). However, other terminal alkynes including 1-octyne and phenylacetylene could not be employed.

Next, we examined the substituent effects of the 2-position of oxadiazole (Table 2). The oxadiazoles bearing 4-methylphenyl and 1-naphthyl groups as well as the simple phenyl one underwent alkenylation on treatment with diarylacetylenes to produce **3bd** and **3dd** in 61% and 63% yields, respectively. Notably, **3bd** was obtained essentially as the single stereoisomer. On the other hand, the reactions with 4-methoxyphenyl- and phenethyl-substituted **1c** and **1e** gave **3cc** and **3ef** with moderate yields.

Subsequently, we attempted the alkylation of 2-phenyl-1,3,4-oxadiazole (**1a**) with styrene (**4a**). It was of considerable interest that the reaction led to the exclusive formation of branched compound **5aa**, and no corresponding linear isomer was detected while the yield was only 17% (Table 3, entry 1). The observed regioselectivity was in marked contrast to that in the relevant rhodium- and ruthenium-catalyzed processes, where linear couplings usually predominate.[4] Therefore, an optimization study was performed by using a series of phosphine ligands. Change of PCy$_3$ to PPh$_3$ improved the yield to 40% with maintenance of the unique regioselectivity (entry 2). Other monodentate triarylphosphines such as P(4-MeOC_6H_4)$_3$ and P(4-FC_6H_4)$_3$ resulted in similar yields (entries 3 and 4). To our delight, use of xantphos was found to dramatically increase the yield (entries 5 and 6). Considering the observed lower efficiency of dppe and dppf (entries 7 and 8), the uniquely large bite angle of xantphos would play an important role in the catalytic cycle.

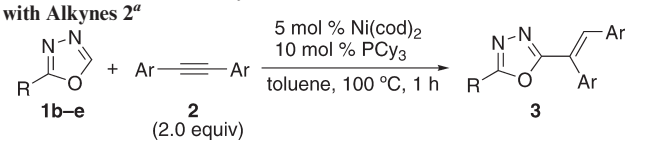
With the modified conditions in hand, the reaction of **1a** with a number of styrene derivatives was conducted (Table 4). Not only styrenes having an electron-donating substituent but also those with an electron-withdrawing substituent took part in the reaction to afford the corresponding coupled products in good to high yields (entries 2−4). Moreover, ester function was compatible under the reaction conditions although a prolonged reaction period was required for completion of the reaction (entry 5). Simple aliphatic alkenes and acrylate esters could not be used in the present reaction. The starting materials were recovered intact.

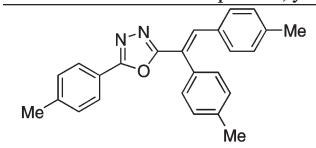
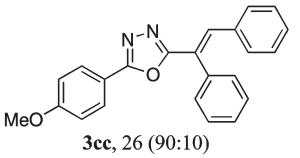
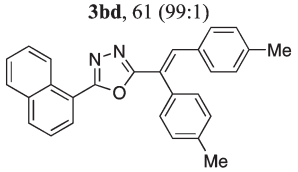
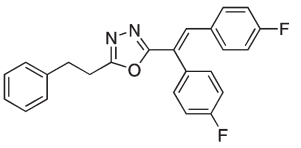
(11) (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Heterocycles* **2007**, *72*, 677. (c) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (d) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (e) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170.

(12) (a) Regel, E.; Büchel, K.-H. *Liebigs Ann. Chem.* **1977**, 159. (b) Tolmachev, A. A.; Zarudnitskii, E. V.; Yurchenko, A. A.; Pinchuk, A. M. *Chem. Heterocycl. Compd.* **1999**, *35*, 1117. (c) Zarudnitskii, E. V.; Pervak, I. I.; Merkulov, A. S.; Yurchenko, A. A.; Tolmachev, A. A.; Pinchuk, A. M. *Synthesis* **2006**, 1279. See also:(d) Fu, K. S. Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

(13) Other trialkylphosphines such as P(*t*-Bu)$_3$, P(*n*-Bu)$_3$, and PMe$_3$ were less effective (ca. < 10% yield).

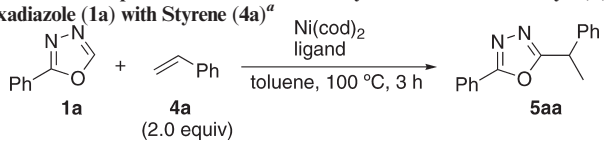
TABLE 2. Nickel-Catalyzed Reaction of Various 1,3,4-Oxadiazoles 1 with Alkynes 2[a]



product, yield (%), (*E*/*Z*)[b]	
 **3bd**, 61 (99:1)	 **3cc**, 26 (90:10)
 **3dd**, 63 (81:19)	 **3ef**, 49 (84:16)

[a]Reaction conditions: [**1**]:[**2**]:[Ni(cod)$_2$]:[PCy$_3$] = 0.25:0.50:0.0125:0.025 (in mmol), in toluene (1.2 mL) under N_2 at 100 °C for 1 h. **1b**: R = 4-MeC$_6$H$_4$; **1c**: R = 4-MeOC$_6$H$_4$; **1d**: R = 1-naphthyl; **1e**: R = phenethyl. [b]*E*/*Z* ratio determined by ^{1}H NMR.

TABLE 3. Optimization for Nickel-Catalyzed Reaction of 2-Phenyl-1,3,4-oxadiazole (1a) with Styrene (4a)[a]

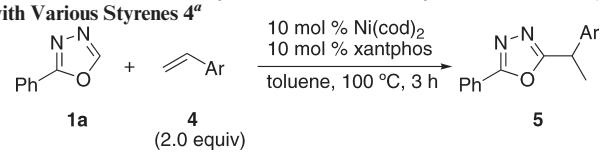


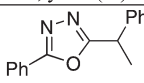
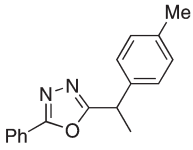
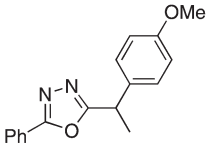
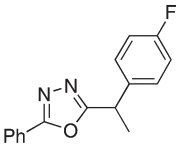
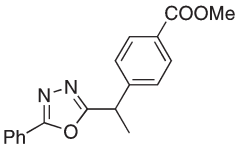
entry	ligand	**5aa**, yield (%)[b]
1	PCy$_3$	(17)
2	PPh$_3$	(40)
3	P(4-MeOC$_6$H$_4$)$_3$	(35)
4	P(4-FC$_6$H$_4$)$_3$	(31)
5[c]	xantphos	(89)
6[d]	xantphos	(86) 83
7	dppe	(12)
8	dppf	(8)

[a]Reaction conditions: **1a** (0.25 mmol), **4a** (0.50 mmol), Ni(cod)$_2$ (5 mol %), ligand (P/Ni = 2), in toluene (1.2 mL) under N_2 at 100 °C for 3 h. [b]GC yield is in parentheses. [c]Reaction for 6 h. [d]Ni(cod)$_2$ (10 mol %) and xantphos (10 mol %).

Although the exact reaction mechanism for the present nickel catalysis is not clear at this stage, the most plausible pathway based on the literature information[10,11] may involve a Ni(0)/Ni(II) redox through (i) oxidative addition of the sp^2 C−H bond of oxadiazoles (C_{azole}−H) to Ni(0) to generate C_{azole}−Ni(II)−H, (ii) insertion of alkynes or alkenes to the Ni−H bond in a *syn*-fashion, and (iii) reductive elimination leading to the corresponding coupled products and the starting nickel species (Scheme 2). The observed regioselectivity in the case of the unsymmetrical alkynes **2g** or **2h** (Table 1, entries 7 and 8) would originate from the strong preference of the metal being located at the position far from the *t*-Bu or Si^{i}Pr$_3$ group in the insertion step due to steric reasons. The unusual branch selectivity with styrenes would result from the preferable formation of the corresponding

TABLE 4. Nickel-Catalyzed Reaction of 2-Phenyl-1,3,4-oxadiazole (1a) with Various Styrenes 4[a]



entry	**4**	**5**, yield (%)
1	Ar = Ph **4a**	 **5aa**, 83
2	Ar = 4-MeC$_6$H$_4$ **4b**	 **5ab**, 67
3	Ar = 4-MeOC$_6$H$_4$ **4c**	 **5ac**, 84
4	Ar = 4-FC$_6$H$_4$ **4d**	 **5ad**, 91
5[b]	Ar = 4-(MeOCO)C$_6$H$_4$ **4e**	 **5ae**, 66

[a]Reaction conditions: [**1a**]:[**4**]:[Ni(cod)$_2$]:[xantphos] = 0.25:0.50:0.025:0.025 (in mmol), in toluene (1.2 mL) under N_2 at 100 °C for 3 h. [b]Reaction time was 6 h.

π-benzyl nickel intermediates.[11e,14] In addition, the π-benzyl intermediate formation would be crucial for the catalytic reaction so that the simple aliphatic alkenes and acrylate esters could not participate in the reaction.

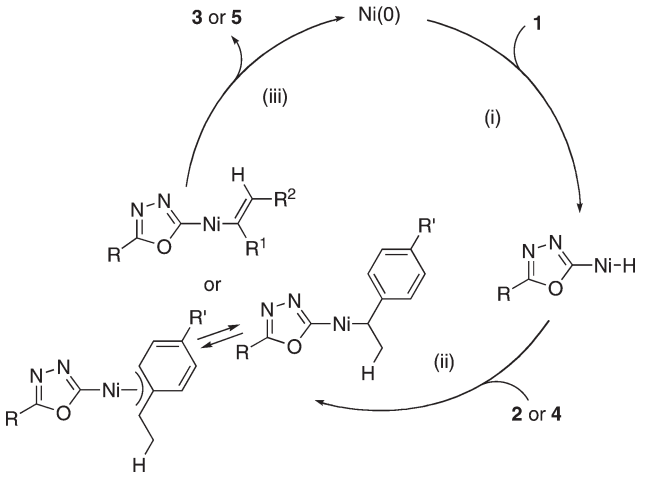
In summary, we have demonstrated that 2-aryl- and 2-alkyl-1,3,5-oxadiazoles efficiently undergo direct alkenylation at the 5-position upon treatment with alkynes in the presence of a nickel catalyst. Styrenes can also couple with the oxadiazoles to selectively afford branched compounds. Thus, the nickel catalysis appears to provide a facile approach to the substituted oxadiazoles that are of interest in both biological and physical properties.

Experimental Section

Typical Procedure for Nickel-Catalyzed Alkenylation of 1,3,4-Oxadiazoles 1 with Alkynes 2. The reaction of 2-phenyl-1,3,4-oxadiazole (**1a**) with 4-octyne (**2a**) is representative (Table 1, entry 1). With use of a glovebox filled with nitrogen, Ni(cod)$_2$ (0.021 M toluene solution, 0.60 mL, 0.0125 mmol) and PCy$_3$

(14) (a) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (b) Shirakura, M.; Suginome, M. *Org. Lett.* **2009**, *11*, 523.

SCHEME 2. Plausible Mechanism



(7.0 mg, 0.025 mmol) were placed in a reaction flask, and the flask was taken outside the glovebox. The solution was then stirred for 10 min at room temperature. A solution of **1a** (37 mg, 0.25 mmol), **2a** (55 mg, 0.50 mmol), and 1-methylnaphthalene (ca. 20 mg, internal standard) in toluene (0.60 mL) was added, and the mixture was heated at 100 °C for 1 h. After the consumption of **1a** was checked by GC analysis, the resulting mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate as an eluent (90:10, v/v) to furnish (*E*)-2-(4-octen-4-yl)-5-phenyl-1,3,4-oxadiazole (**3aa**, 49 mg, 0.19 mmol) in 76% yield. **3aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.50−1.67 (m, 4H), 2.26−2.32 (m, 2H), 2.60 (t, J = 8.0 Hz, 2H), 6.66 (t, J = 7.7 Hz, 1H), 7.48−7.51 (m, 3H), 8.06−8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (two signals merged), 21.2, 21.3, 28.3, 29.3, 123.2, 124.5, 125.8, 127.9, 130.4, 136.7, 162.8, 164.8; HRMS (EI) m/z (M) calcd for $C_{16}H_{20}N_2O$ 256.1576, found 256.1570.

Typical Procedure for Nickel-Catalyzed Alkylation of 1,3,4-Oxadiazoles 1 with Styrenes 4. The reaction of 2-phenyl-1,3,4-oxadiazole (**1a**) with styrene (**4a**) is representative (Table 4, entry 1). With use of a glovebox filled with nitrogen, Ni(cod)$_2$ (0.042 M toluene solution, 0.60 mL, 0.025 mmol) and xantphos (14 mg, 0.025 mmol) were placed in a reaction flask, and the flask was taken outside the glovebox. The solution was stirred for 10 min at room temperature, and a solution of **1a** (37 mg, 0.25 mmol), **4a** (52 mg, 0.50 mmol), and 1-methylnaphthalene (ca. 20 mg, internal standard) in toluene (0.60 mL) was then added. After being heated at 100 °C for 3 h, the consumption of **1a** was confirmed by GC analysis. The resulting mixture was cooled to room temperature, and evaporation followed by silica gel column purification produced 2-phenyl-5-(1-phenylethyl)-1,3,4-oxadiazole (**5aa**, 51 mg, 0.21 mmol) in 83% yield. **5aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (d, J = 7.3 Hz, 3H), 4.44 (q, J = 7.3 Hz, 1H), 7.26−7.31 (m, 1H), 7.35 (d, J = 4.4 Hz, 4H), 7.44−7.52 (m, 3H), 7.98−8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 36.5, 123.0 (two signals merged), 125.8, 126.3, 126.5, 127.9, 130.5, 139.3, 164.0, 167.7; HRMS (CI) m/z (M + H) calcd for $C_{16}H_{15}N_2O$ 251.1186, found 251.1187.

Acknowledgment. This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We are grateful to Profs. T. Hiyama and Y. Nakao of Kyoto University for useful discussion.

Supporting Information Available: Characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.