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Ruthenium-Catalyzed Conversion of sp^3 C–O Bonds in Ethers to C–C Bonds Using Triarylboroxines

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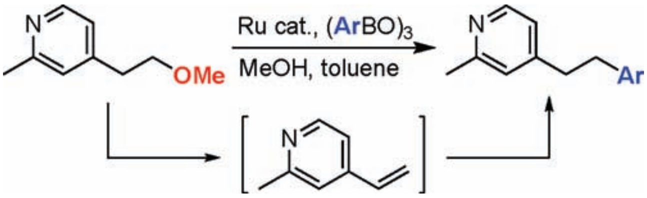
ABSTRACT



Catalytic conversion of unreactive sp^3 C–O bonds in alkyl ethers to C–C bonds is described. Alkyl ethers bearing 2- or 4-pyridyl groups were coupled with triarylboroxines in the presence of a ruthenium catalyst. Triarylboroxines bearing a variety of functional groups including electron-withdrawing and -donating groups can be used for the reaction. No additional base was required for the coupling with the organoboron reagents, and base-sensitive groups can be tolerated. The reaction is considered to proceed via dehydroalkoxylation followed by addition of triarylboroxines to form C–C bonds.

A transition-metal-catalyzed C–C bond formation via selective cleavage of unreactive C–O bonds has been rigorously investigated because of its potential utility in organic synthesis. C–O bonds in ethers are among the most unreactive because alkoxides are considered poor leaving groups.[1] Concerning sp^3 C–O bonds in ethers,[2–5] several catalytic conversions to C–C bonds have been reported, but the bonds used for the examples are limited to relatively activated ones such as allylic[2] or benzylic[3] sp^3 C–O bonds.

Here we describe a ruthenium-catalyzed conversion of unreactive sp^3 C–O bonds in alkyl ethers to C–C bonds using triarylboroxines. The reaction is considered to proceed via dehydroalkoxylation, followed by coupling with triarylboroxines to form C–C bonds.

Initially, we envisioned that the chelation-assistance strategy used for cleavage and functionalization of sp^2 C–O bonds in aryl ethers, reported by our group,[1e,g] may be applicable to the reaction of sp^3 C–O of alkyl ethers, and we chose 2-(2-methoxyethyl)pyridine (**1a**) as the substrate for catalyst screening. When a reaction of **1a** with

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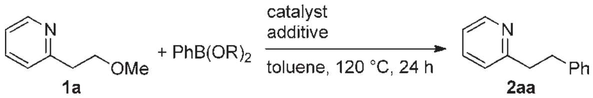
(1) Conversion of sp^2 C–O bonds in ethers: (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535. (b) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (c) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Org. Chem.* **1984**, *49*, 4894. (d) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235. (e) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (f) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (g) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (h) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (i) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866. (j) Yu, D.-G.; Yu, M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, *11*, 3374. (k) Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2009**, *11*, 4890.

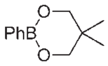
(2) Conversion of sp^3 C–O bonds in allyl ethers: (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. (b) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, *14*, 121. (c) Commercon, A.; Eourgain, M.; Delaumeny, M.; Normant, J. F.; Villieras, J. *Tetrahedron Lett.* **1975**, *16*, 3837. (d) Hayashi, T.; Konishi, M.; Yokota, K.-I.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1981**, 313. (e) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (f) Lu, X.; Jiang, X. *J. Organomet. Chem.* **1989**, *359*, 139. (g) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273. (h) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713. (i) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 15. (j) Manabe, K.; Nakada, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1499. (k) Yasui, H.; Mizutani, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 1410. (l) Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103.

(3) Conversion of sp^3 C–O bonds in benzyl ethers: (a) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268. (b) Wang, B.-Q.; Xiang, S.-K.; Sun, Z.-P.; Guan, B.-T.; Hu, P.; Zhao, K.-Q.; Shi, Z.-J. *Tetrahedron Lett.* **2008**, *49*, 4310. (c) Taylor, B. L. H.; Swift, E. C.; Wartzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389.

10.1021/ol2012007

Table 1. Coupling of Dialkyl Ether **1a** with Phenylboron Reagents[a]



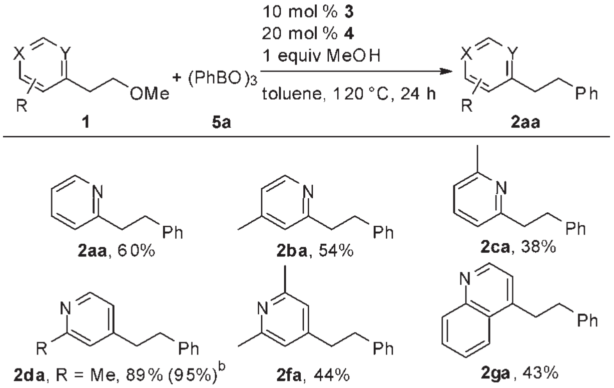
entry	catalyst	$PhB(OR)_2$	additive	yield[b]
1	$RuH_2(CO)(PPh_3)_3$	$PhB(OH)_2$	–	trace
2	Ru(cod)(cot)	$PhB(OH)_2$	–	trace
3	$[RuCl_2(p\text{-cymene})]_2$ (**3**)/PPh_3 (1:2)	$PhB(OH)_2$	–	16%
4[c]	$Ni(cod)_2/PCy_3$ (1:2)	$PhB(OH)_2$	–	nd[c,d]
5	$RhCl(PPh_3)_3$	$PhB(OH)_2$	–	3%
6[e]	**3**/$P(OMe)_3$ (1:2)	$PhB(OH)_2$	–	3%
7	**3**/$P(OPh)_3$ (**4**) (1:2)	$PhB(OH)_2$	–	25%
8	**3**/**4** (1:2)		–	nd[d]
9	**3**/**4** (1:2)	$(PhBO)_3$ (**5a**)	–	47%
10	**3**/**4** (1:2)	**5a**	H_2O	24%
11	**3**/**4** (1:2)	**5a**	MeOH	61%
12	**3**/**4** (1:2)	**5a**	EtOH	54%

[a] Reaction conditions: 0.5 mmol of **1a**, 1.0 mmol of $PhB(OR)_2$ (0.33 mmol in the case of **5a**), 0.1 mmol of metal catalyst (0.05 mmol in the case of **3**), 0.1 mmol of ligand (if any), 0.5 mmol of additive (if any), toluene 0.5 mL, 120 °C, 24 h. [b] GC yield. [c] 0.2 mmol of PCy_3 was used. [d] Not detected. [e] 65 h.

$PhB(OH)_2$ was performed with $RuH_2(CO)(PPh_3)_3$ as a catalyst, only a trace amount of the desired phenylation product **2aa** was detected by GC analysis (Table 1, entry 1). Ru(cod)(cot) gave a similar result (entry 2), but the use of $[RuCl_2(p\text{-cymene})]_2$ (**3**) with PPh_3 increased the yield to 16% (entry 3). Catalysts of other transition metals such as $RhCl(PPh_3)_3$ and $Ni(cod)_2/PCy_3$ were not effective for this transformation (entries 4 and 5). The ligands were screened for the reaction using **3** as a catalyst.[6] The reaction with $P(OMe)_3$ resulted in a 3% yield of **2aa** (entry 6), but the use of $P(OPh)_3$ (**4**) led to an increase of the yield to 25% (entry 7). Next, other phenylboron reagents were examined for the reaction. While the 2,2-dimethyl-1,3-propanediol ester did not react with **1a** to give **2aa** (entry 8), the coupling with triphenylboroxine (**5a**) provided **2aa** in 47% yield (entry 9). Finally, additives were examined for the reaction. Addition of H_2O decreased the yield (entry 10), but the reaction in the presence of 1 equiv of MeOH or EtOH further increased the yield to 61% and 54%, respectively (entries 11 and 12).[7]

Monitoring of the coupling of **1a** with **5a** in the presence of **3** and **4** by ^1H NMR spectroscopy revealed that 2-vinylpyridine was generated during the reaction. Coupling of 2-vinylpyridine with **5a** was catalyzed by the combination of **3** and **4** in the presence of 1 equiv of MeOH to give **2aa** in 37% yield. Metal-catalyzed coupling of 2- and 4-vinylpyridines and arylboronic acids has been reported by Lautens and co-workers using a rhodium catalyst.[8] Shintani and Hayashi also reported that ruthenium catalysts can be used for 1,4-addition of boronic acids to α,β-unsaturated ketones.[9,10] Based on these results, we speculated that the reaction may proceed via formation of 2-vinylpyridines as an intermediate formed by dehydromethoxylation of **1a**, which was possibly assisted by coordination of the pyridine nitrogen to a ruthenium or boron atom.

Scheme 1. Ruthenium-Catalyzed Coupling of Various Pyridylethyl Ethers **1** with **5a**[a]



[a] Reaction conditions: 0.50 mmol of **1**, 0.33 mmol **5a**, 0.05 mmol of **3**, 0.10 mmol of **4**, 0.5 mmol of MeOH, toluene 0.5 mL, 120 °C, 24 h. The numbers shown are isolated yields. [b] Isolated yield obtained using 0.025 mmol of **3** and 0.05 mmol of **4**.

Examination of various methyl ether substrates bearing pyridyl groups was then performed (Scheme 1). The reactions of substrates with 2-pyridyl- or 4-methyl-2-pyridyl groups afforded phenylation products **2aa** and **2ba** in 60% and 54% isolated yields, respectively. Increasing the steric bulk around the pyridine nitrogen using the 6-methyl-2-pyridyl group lowered the product yield to 38%. As we expected that the dehydromethoxylation may be accelerated as well for substrates with 4-pyridyl groups, the reaction was also examined with several methyl ethers bearing 4-pyridyl moieties. Although no reaction occurred in the case of 4-(2-methoxyethyl)pyridine, the reaction of 4-(2-methoxyethyl)-2-methylpyridine (**1d**) afforded

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(4) Catalytic reduction of sp^3 C–O bonds in alkyl ethers: (a) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919. (b) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 6179. (c) Yang, J.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2008**, *130*, 17509. (d) Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12554.

(5) Recent reviews on conversion of sp^3 C–X bonds in alkyl electrophiles such as alkyl halides: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347. (b) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(6) Detailed results are shown in the Supporting Information (Table S1).

(7) After the optimization of conditions, catalysts used for entry 2–5, Table 1, were again tested for the reaction, but only low yields of product **2aa** were obtained.

(8) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

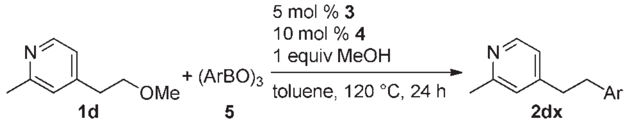
(9) Shintani, R.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 724.

(10) Reviews on addition of organoboron reagents to electron-deficient olefins: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Shintani, R.; Hayashi, T. *Aldrichim. Acta* **2009**, *42*, 31. (e) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093.

phenylation product **2da** in 89% isolated yield. In this case, lowering of the catalyst loading (5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 10 mol % of $P(OPh)_3$) slightly improved the product yield to 95%. The coupling of the substrate bearing a 2-phenyl-4-pyridyl group (**1e**) also provided product **2ea** in 52% yield. When substrates with 2,6-dimethyl-4-pyridyl and 4-quinolinyl groups were used for the reaction, the corresponding phenylation products **2fa** and **2ga** were obtained in 44% and 43% yields, respectively. In contrast, the reaction of neither 3-(2-methoxyethyl)-6-methylpyridine nor (2-methoxyethyl)benzene gave any corresponding phenylation products. Therefore, the methoxyethyl group on the aromatic ring should be on the 2- or 4-position of the pyridine ring to achieve the phenylation.

The generality of triarylboroxines **5** was next investigated for the coupling reaction using **1d** (Table 2). A variety of triarylboroxines bearing electron-withdrawing and -donating groups at the para positions were coupled with methyl ether **1d** to give mostly excellent yields of arylation product **2db**−**dh** (entries 1−7). One of the striking features of this reaction is that no additional base was required for the coupling of the organoboron reagents. This feature is demonstrated by the result that relatively base-sensitive groups such as acetyl and methoxycarbonyl groups are tolerated to give 96% and 71% yields, respectively (entries 3 and 4). In the case of tris(*p*-methoxyphenyl)boroxine **5h**, the product yield became moderate, and the deboronation product, anisole, was detected by GC (entry 7). Meta-substituted triarylboroxines were successfully coupled with **1d** to give high yields of the desired products (entries 8 and 9). In contrast, the reaction with tri(*o*-tolyl)boroxine **5k** did not give any detectable arylation product, probably because of severe steric congestion (entry 10). The coupling of **1d** with tri(2-naphthyl)boroxine **5l** proceeded smoothly to give arylation product **2dl** in 91% yield (entry 11).

Table 2. Ruthenium-Catalyzed Coupling of Ether **1d** with Various Triarylboroxines **5**[a]

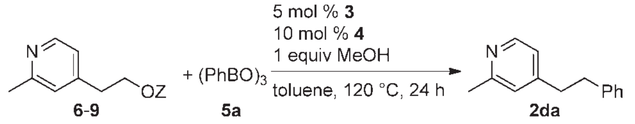


	Ar	product	isolated yield[b] (%)
1	p-$NO_2C_6H_4$	**2db**	88
2	p-$CF_3C_6H_4$	**2dc**	93
3	p-AcC_6H_4	**2dd**	95
4[c]	p-$MeOC(O)C_6H_4$	**2de**	71
5	p-BrC_6H_4	**2df**	91
6	p-MeC_6H_4	**2dg**	97
7	p-$MeOC_6H_4$	**2dh**	51
8	m-MeC_6H_4	**2di**	96
9	m-$MeOC_6H_4$	**2dj**	87
10	o-MeC_6H_4	**2dk**	nd[d]
11	2-naphthyl	**2dl**	91

[a] Reaction conditions: 0.5 mmol of **1d**, 0.33 mmol of **5**, 0.025 mmol of **3**, 0.05 mmol of **4**, 0.5 mmol of MeOH, toluene 0.5 mL, 120 °C, 24 h. [b] Isolated yield. [c] 0.5 mmol of **5**. [d] Not detected.

The applicability of substrates with leaving groups other than methoxy was also examined (Table 3). The reaction of ethyl ether **6** with **5a** proceeded to give **2da** in 77% yield (entry 1). Alcohol **7** can also be coupled with **5a** in 40% yield (entry 2). Phenoxy and acetoxy groups are generally regarded as better leaving groups than alkoxy groups and these were examined for the coupling reaction. The reaction of phenyl ether **8** provided coupling product **2da** in 78% yield (entry 3). However, ester **9** gave only 3% of the desired product (entry 4), possibly because of the high acidity of the generated conjugate acid or the low Lewis basicity of the leaving group to activate boroxines.

Table 3. Ruthenium-Catalyzed Coupling of Substrates with Various Oxygen Leaving Groups **6**−**9** with **5a**[a]



entry	substrate	−OZ	GC yield (%)
1	**6**	−OEt	77
2	**7**	−OH	40
3	**8**	−OPh	78
4	**9**	−OAc	3

[a] Reaction conditions: 0.5 mmol of **6**−-**9**, 0.33 mmol of **5a**, 0.025 mmol of **3**, 0.05 mmol of **4**, 0.5 mmol of MeOH, toluene 0.5 mL, 120 °C, 24 h.

^1H NMR monitoring of the reaction of **1d** with **5a** showed the generation of 2-methyl-4-vinylpyridine (**10**) at the early stage of the reaction.[11] Coupling of **10** with **5a** can also be catalyzed by the combination of **3** and **4** in the presence of MeOH. When the coupling of ether **1d** with **5a** was performed using CD_3OD, formation of the corresponding arylation product containing deuterium atoms **2da-*d*$_n$** was observed (Table 4). After 1 h, significant deuterium incorporation was only observed at the methylene next to the pyridine ring (C_3 position).[12] But after the reaction was complete, a small increase of the amount of deuterium atoms were observed at C_1 and C_2 positions as indicated in Table 4, while the deuterium incorporation at the C_3 position was slightly decreased probably via slow H/D exchange.[13] These results strongly suggest the intermediacy of **10** for the coupling reaction.

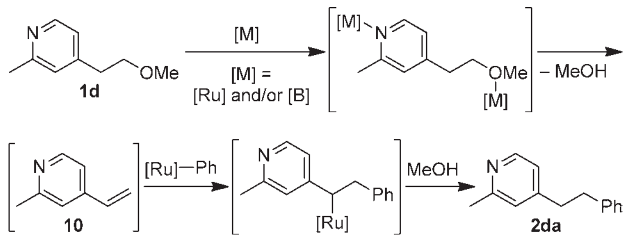
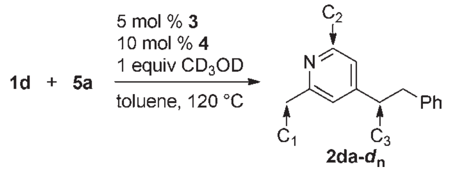


Figure 1. Possible reaction pathway for the ruthenium-catalyzed coupling of **1d** with **5a**.

Table 4. Coupling of **1d** with **5a** in the Presence of CD_3OD[a]



				incorporated D atoms[b,c]		
entry	time (h)	conversion[b] (%)	isolated yield (%)	C_1 (3H)	C_2 (1H)	C_3 (2H)
1	1	37	13	nd[d]	nd[d]	0.73D
2	24	quant	quant	0.25D	0.07D	0.51D

[a] Reaction conditions: 0.5 mmol of **1a**, 0.33 mmol of **5a**, 0.025 mmol of **3**, 0.05 mmol of **4**, 0.5 mmol of CD_3OD, toluene 0.5 mL, 120 °C. [b] Determined by ^1H NMR analyses. [c] Deuterium incorporation was also confirmed by ^2H NMR analyses. [d] Not detected.

Although the detailed mechanism is unclear at this point, a possible mechanism of the coupling reaction is shown in Figure 1 using **1d** and **5a** as a substrate. First, both the pyridine nitrogen and ethereal oxygen coordinate to a ruthenium or boron atom.[14] Dehydroalkoxylation of **1d** is facilitated by the coordination and proceeds to give vinylpyridine **10**. The presence of methanol assists transmetalation of the phenyl group from the boron atom to the ruthenium complex, and carboruthenation of **10**, followed by protodemetalation, proceeds to give phenylation product **2da**.

In summary, an unprecedented catalytic conversion of unreactive sp^3 C–O bonds in alkyl ethers to C–C bonds was described. Alkyl ethers bearing a 2- or 4-pyridyl group were coupled with triarylboroxines in the presence of a ruthenium catalyst. Triarylboroxines bearing a variety of functional groups including electron-withdrawing and -donating groups can be used for the reaction. No additional base was required for the coupling with organoboron reagents and base-sensitive groups can be tolerated. ^1H NMR monitoring of the reaction indicated that it proceeds via a novel mechanism for catalytic functionalization of ethers, dehydroalkoxylation, followed by coupling with triarylboroxines to form C–C bonds. Further studies are in progress to develop catalytic functionalization of other types of alkyl ethers using the dehydroalkoxylation/coupling strategy.

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Supporting Information Available. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Vinylpyridine **10** was not observed when the reaction was performed without either **3** and **5a**. Heating ether **1d** in toluene at 120 °C also failed to give **10**. These results suggest both ruthenium complex **3** and boronate **5a** are required for efficient formation of vinylpyridine intermediate **10**.

(12) Selective deuterium incorporation at the C_3 position was also observed for the reaction of vinylpyridine **10** with **5a**. See the Supporting Information for details.

(13) The slow H/D exchange at the C_1 and C_2 positions was supported by the result that deuterium incorporation at these positions was observed for **2da** when the reaction of **1d** with **5d** was performed in the presence of **2da**. See the Supporting Information for details.

(14) When ether **1d** was mixed with ruthenium complex **3** and phosphite **4** in toluene-d_8, a low-field shift (0.24 ppm) of the ^1H NMR signal was observed for the proton at the 6-position on the pyridine ring. The ^1H NMR spectrum of a mixture of **1d** and boroxine **5a** also showed a significant low-field shift (0.26 ppm) of the pyridyl proton at the 6-position as well as high-field shifts of the protons around the ethereal oxygen up to 0.09 ppm. The results suggest that both the nitrogen and the oxygen of substrate **1d** can interact with the ruthenium catalyst or boroxines under the conditions for the catalytic reaction.