J|A|C|S
COMMUNICATIONS

Rhenium-Catalyzed Regioselective Alkylation of Phenols

Yoichiro Kuninobu,* Takashi Matsuki, and Kazuhiko Takai*

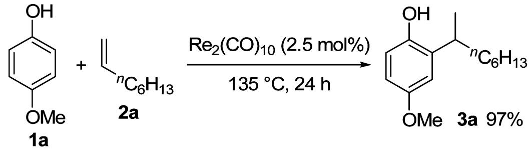
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Kita-ku, Okayama 700-8530, Japan

Received May 29, 2009; E-mail: kuninobu@cc.okayama-u.ac.jp; ktakai@cc.okayama-u.ac.jp

Selective introduction of substituent(s) into aromatic rings offers a direct and efficient method to synthesize substituted-aromatic compounds. Well known examples of such a transformation are the Friedel−Crafts reaction[1] and the hydroarylation of olefins.[2] However, in both cases, it is usually difficult to introduce only one alkyl group into the aromatic rings regioselectively.

Phenols are one of the most important aromatic compounds. Although several examples of *ortho*-alkylation of phenols and related compounds have been reported,[3] a number of problems remain: (1) a mixture of mono- and multialkylated products is formed;[4] (2) in some cases, a stoichiometric amount of a metal salt is necessary to promote the reaction;[5] and (3) there are limitations in the types of substrates that can be used.[4,6] During an investigation of the catalytic activities of rhenium complexes,[7,8] we found that monoalkylation of phenols proceeded only at the *ortho*- or *para*-position of the hydroxyl group selectively using $\mathrm{Re_2(CO)_{10}}$ as a catalyst.

By heating 4-methoxyphenol (**1a**) in a 1-octene (**2a**) solvent in the presence of a catalytic amount of a rhenium complex, $\mathrm{Re_2(CO)_{10}}$, the *ortho*-alkylated phenol derivative **3a** was obtained in 97% yield (eq 1). In this reaction, only the monoalkylated product **3a** was yielded as a single product despite using an excess amount of 1-octene (**2a**). This result is interesting because a mixture of mono- and multialkylated products is usually formed by the Friedel−Crafts reaction.

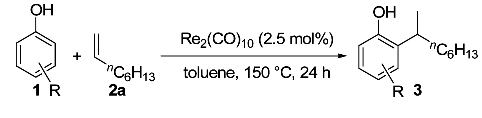


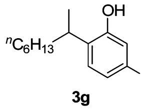
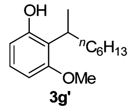
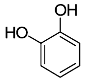
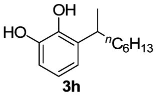
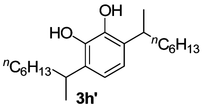
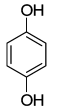
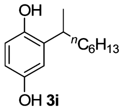
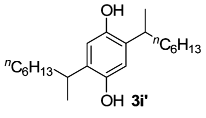
(1)

The reaction also proceeded quantitatively in toluene using 1.5 equiv of 1-octene (**2a**).[9] Although the rhenium complex $\mathrm{ReBr(CO)_5}$ also showed catalytic activities, the yield of the alkylated phenol **3a** was only 23%. Rhenium complexes, $\mathrm{[ReBr(CO)_3(thf)]_2}$ and $\mathrm{ReCl_3}$, gave a mixture of polyalkylated products.[10]

Next, we investigated the scope and limitations of phenol derivatives (Table 1). Treatment of 4-methylphenol (**1b**) with 1-octene (**2a**) in toluene at 135 °C gave *ortho*-alkylated phenol **3b** in 59% yield; however, the yield of **3b** increased at 150 °C, and **3b** was obtained in 82% yield (entry 1). Phenol (**1c**) produced *ortho*-alkylated phenol **3c** in 76% yield (entry 2).[11,12] *ortho*-Alkylated phenols **3d**, **3e**, and **3f** were obtained using 4-fluoro-, 4-chloro-, and 4-bromo-phenols (**1d**, **1e**, and **1f**) without losing the halogen atom (entries 3−5). When 3-methoxyphenol (**1g**) was employed, the alkylation reaction did not afford a single product, and a mixture of **3g** and **3g′** was formed (entry 6). Mono- and dialkylated catechols **3h** and **3h′** were yielded using catechol (**1h**) (entry 7). By using hydroquinone (**1i**) a mixture of mono- and dialkylated products **3i** and **3i′** was produced in 54% yield (entry 8).[13] The selectivity of **3i′** was improved dramatically by increasing the amount of olefin **2a** (entry 9).

Table 1. Reactions between Phenols **1** and 1-Octene (**2a**)[a]



entry	1		product		yield / %^{b}
1	R = *p*-Me	**1b**	**3b**		82
2	H	**1c**	**3c**		76
3	*p*-F	**1d**	**3d**		96
4	*p*-Cl	**1e**	**3e**		84
5	*p*-Br	**1f**	**3f**		61^{c}
6	*m*-MeO	**1g**	 **3g**	 **3g′**	$83\ [71{:}29]^{c,d}$
7		**1h**	 **3h**	 **3h′**	$50\ [81{:}19]^{c,e}$
8		**1i**	 **3i**	 **3i′**	$54\ [51{:}49]^{f,g}$
9		**1i**	**3i**	**3i′**	$84\ [<1{:}>99]^{g,h}$

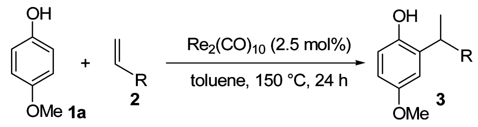
[a] **2a** (1.5 equiv), **1** (2.0 M). [b] Isolated yield. [c] **1** (4.0 M). [d] The ratio between **3g** and **3g′** is given in square brackets. [e] The ratio between **3h** and **3h′** is given in square brackets. [f] **2a** (1.0 equiv). [g] The ratio between **3i** and **3i′** is given in square brackets. [h] **2a** (4.5 equiv).

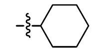
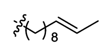
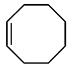
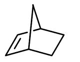
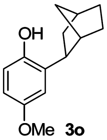
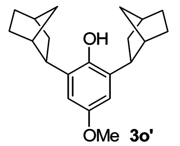
Next, we investigated several alkenes (Table 2). Secondary alkyl-substituted olefin **2b** afforded an *ortho*-alkylated phenol **3j** in 97% yield (entry 1). Olefins bearing a functional group could also be employed as substrates (entries 2−4). Ether and ester groups did not inhibit the reaction, and phenols **3k** and **3l** were obtained in 87% and 83% yields, respectively (entries 2 and 3).[14] By using an olefin with an olefin moiety at the internal position, **2e**, the reaction proceeded only at the terminal olefin position, and *ortho*-alkylated phenol **3m** was produced in 70% yield (entry 4). In this reaction, the internal olefin moiety remained unchanged during the reaction. The internal alkenes, *cis*-cyclooctene (**2f**) and norbornene (**2g**), also reacted with phenol **1a** and generated *ortho*-alkylated phenol **3n** and a mixture of *ortho*-alkylated phenols **3o** and **3o′** in 93% and 91% yields, respectively (entries 5 and 6). By using styrene, a mixture of mono- and di-, and *ortho*- and *meta*-alkylated phenols (4 isomers) was produced in quantitative yield.[15,16]

In contrast to the terminal alkenes, the regioselectivity of the substitution changed markedly when *gem*-disubstituted alkenes were employed. When *gem*-disubstituted olefins **2h** and **2i** were used, no *ortho*-monoalkylated phenols were formed, and instead, *para*-alkylated phenols **3p** and **3q**, and *ortho*- and *para*-disubstituted phenols **3p′** and **3q′** were obtained in 89% and 86%, and 4% and 8% yields, respectively (eq 2).

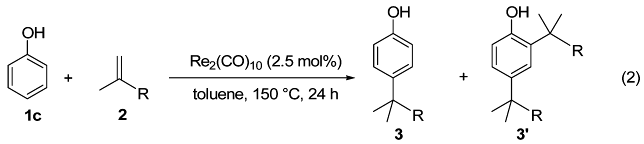
10.1021/ja904360k CCC: $40.75

Table 2. Reactions between Phenol **1a** and Several Olefins **2**[a]



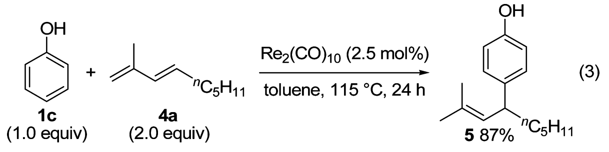
entry	R		product	yield / %[b]
1		**2b**	**3j**	97
2	$(CH_2)_4OEt$	**2c**	**3k**	87
3	$(CH_2)_4OCOEt$	**2d**	**3l**	83
4		**2e**	**3m**	70
5		**2f**	**3n**	93
6		**2g**	 **3o**  **3o'**	91 [82:18][c]

[a] **2** (1.5 equiv). [b] Isolated yield. [c] The ratio between **3o** and **3o′**.

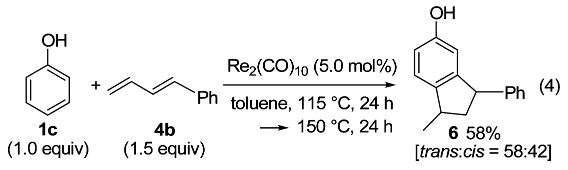


R		3	3'
$^nC_9H_{19}$	**2h** (1.0 equiv)	**3p** 89%	**3p'** 4%
Ph	**2i** (1.5 equiv)	**3q** 86%	**3q'** 8%

By treatment of phenol (**1c**) with diene having a methyl group at the β-position of the diene moiety, **4a**, the reaction occurred at the δ-position of diene **4a**, and **5** was obtained in 87% yield (eq 3).



On the other hand, by the reaction of phenol (**1c**) with diene **4b** in the presence of a rhenium catalyst, $Re_2(CO)_{10}$, an annulation reaction proceeded and indane **6** was obtained in 58% yield (eq 4). This reactivity is quite different from the previous reports in which dihydrobenzofuran and/or dihydrobenzopyran derivatives are produced.[17]



In summary, we have succeeded in regioselective alkylation of phenols in good to excellent yields. In this reaction, monoalkylated phenols are obtained selectively, offering advantages over the standard Friedel−Crafts alkylation, in which a complex mixture of *ortho*- and *para*-substituted, and mono- and multisubstituted phenols is usually formed. The details of the reaction mechanism is under investigation. We hope that this reaction will become a useful method to synthesize substituted phenols.

Acknowledgment. This work was partially supported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: General experimental procedure and characterization data for phenol derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Calloway, N. O. *Chem. Rev.* **1935**, *17*, 327.

(2) (a) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1991, p 479. (b) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414. (c) Periana, R. A.; Liu, X. Y.; Bhalla, G. *Chem. Commun.* **2002**, 3000.

(3) For *para*-selective alkylation of phenols, see: (a) Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2779. (b) Hekmatshoar, R.; Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Bamoharram, F. F. *Catal. Commun.* **2008**, *9*, 837.

(4) (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Dorta, R.; Togni, A. *Chem. Commun.* **2003**, 760. (c) Sarish, S.; Devassy, B. M.; Bohringer, W.; Fletcher, J.; Halligudi, S. B. *J. Mol. Catal. A* **2005**, *240*, 123.

(5) (a) Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 4491. (b) Sartori, G.; Bigi, F.; Maggi, R.; Arienti, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 257.

(6) (a) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. (b) Carrión, M. C.; Cole-Hamilton, D. J. *Chem. Commun.* **2006**, 4527.

(7) We have recently reported on rhenium-catalyzed transformations. See: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (b) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (c) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368. (d) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376. (e) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2006**, *35*, 1376. (f) Kuninobu, Y.; Yu, P.; Takai, K. *Chem. Lett.* **2007**, *36*, 1162. (g) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609. (h) Kuninobu, Y.; Ueda, H.; Takai, K. *Chem. Lett.* **2008**, *37*, 878. (i) Kuninobu, Y.; Nishina, Y.; Matsuki, T.; Takai, K. *J. Am. Chem. Soc.* **2008**, *130*, 14062. (j) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9318.

(8) Other groups have also reported on rhenium-catalyzed reactions. See: (a) Kühn, F. E.; Scherbaum, A.; Herrmann, W. A. *J. Organomet. Chem.* **2004**, *689*, 4149. (b) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760. (c) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *127*, 12462. (d) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (e) Ouh, L. L.; Müller, T. E.; Yan, Y. K. *J. Organomet. Chem.* **2005**, *690*, 3774.

(9) When this reaction was carried out using 1.0 equiv of 1-octene (**2a**) and octane as a solvent, **3a** was formed in 85% yield. Friedel−Crafts reactions are usually performed in halogenated solvents. From this viewpoint, the reaction here is environmentally friendly.

(10) The product **3a** was not formed by a manganese complex, $Mn_2(CO)_{10}$. Other transition metal carbonyl complexes, such as $Cr(CO)_6$, $W(CO)_6$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, and $Ir_4(CO)_{12}$, did not give alkylated phenol **3a**. Iron(III) chloride, $FeCl_3$, aluminum chloride, $AlCl_3$, and trifluoroborane, $BF_3 \cdot OEt_2$, which are usually used in Friedel−Crafts reactions, were employed as catalysts; however, $FeCl_3$ did not produce alkylated products, and $AlCl_3$ and $BF_3 \cdot OEt_2$ afforded a mixture of **3a** ($AlCl_3$ 44%; $BF_3 \cdot OEt_2$ 11%) and polyalkylated isomers.

(11) Anisol, 1,2-dimethoxybenzene, and 1,2,3-trimethoxybenzene did not provide an alkylated product. This result shows that a hydroxyl group of phenols is indispensable to promote the reaction.

(12) Investigation of several rhenium complexes: $ReBr(CO)_5$ 32%; $[ReBr(CO)_3(thf)]_2$ 31%; $ReCl_3$ 32%; $ReCl_5$ 12%; $ReCl_3(PPh_3)_2(NCMe)$ 0%; $ReCl_3O(PPh_3)_2$ 0%; $ReIO_2(PPh_3)_2$ 3%. In each cases, polyalkylation of phenol (**1c**) also occurred.

(13) 2,6-Dimethylphenol, 2-methylphenol, 4-methoxyaniline, 2-hydroxypyridine, 3-hydroxypyridine, and 4-hydroxypyridine did not promote the reaction. 4-Trifluoromethylphenol and 4-methoxythiophenol produced complex mixtures.

(14) Investigation of several acid catalysts in the reaction between phenol **1a** and olefin bearing an ester moiety, **2d**: $AlCl_3$ 0%; $Al(OPh)_3$ 0%; $BF_3 \cdot OEt_2$ 10%; *para*-toluenesulfonic acid 10%. In the case of $AlCl_3$, the reaction was inhibited by the ester group. See: ref 10.

(15) The reaction did not proceed using 3,3-dimethyl-1-butene, 4-phenyl-1-buten-3-yne, *trans*-5-decene, and 2-ethylhexyl acrylate.

(16) There are several reports on *ortho*-selective alkylation of phenols with styrene. See: (a) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033. (b) Chu, C.-M.; Huang, W.-J.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2007**, *48*, 6881.

(17) (a) Nguyen, R.-V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397. (b) Youn, S. W.; Eom, J. I. *J. Org. Chem.* **2006**, *71*, 6705.

JA904360K