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Rhenium-Catalyzed Regioselective Alkylation of Phenols

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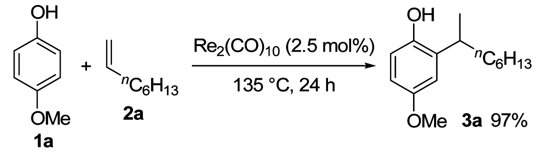
Selective introduction of substituent(s) into aromatic rings offers a direct and efficient method to synthesize substituted-aromatic compounds. Well known examples of such a transformation are the Friedel−Crafts reaction[1] and the hydroarylation of olefins.[2] However, in both cases, it is usually difficult 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 $Re_2(CO)_{10}$ 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, $Re_2(CO)_{10}$, 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.

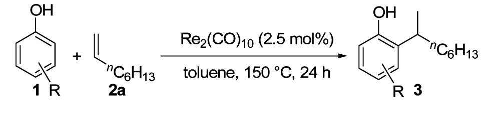


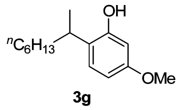
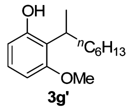
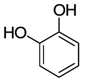
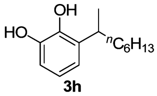
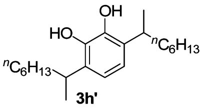
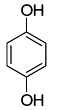
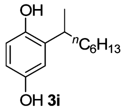
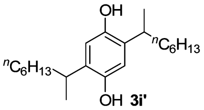
(1)

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

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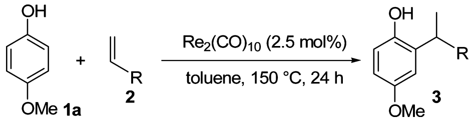
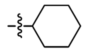
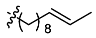
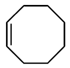
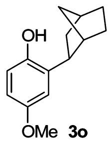
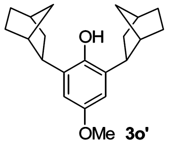
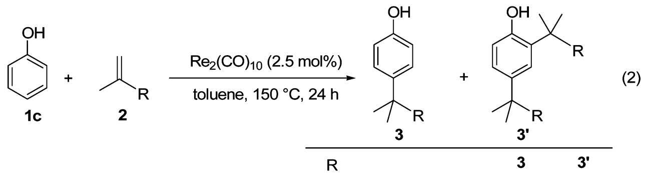
Table 2. Reactions between Phenol **1a** and Several Olefins **2**^{a}



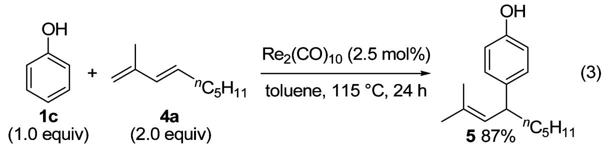
entry	R	product	yield / %^{b}
1	 **2b**	**3j**	97
2	$(CH_2)_4OEt$ **2c**	**3k**	87
3	$(CH_2)_4OCOEt$ **2d**	**3l**	83
4	 **2e**	**3m**	70
5	 **2f**	**3n**	93
6	 **2g**	 **3o**  **3o'**	91 [82:18]^c

^{a} **2** (1.5 equiv). ^{b} Isolated yield. ^{c} The ratio between **3o** and **3o′**.

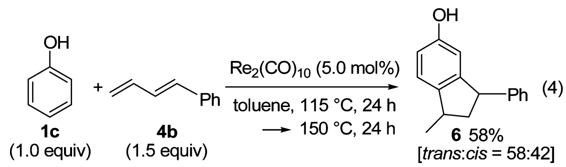


R		3	3'
$^nC_9H_{19}$	**2h** (1.0 equiv)	**3p** 89%	**3p'** 4%
Ph	**2i** (1.5 equiv)	**3q** 86%	**3q'** 8%

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.

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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.

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(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.
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