

The chemistry of **phenols**

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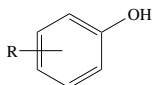
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The chemistry of **phenols**

Part 1

Edited by

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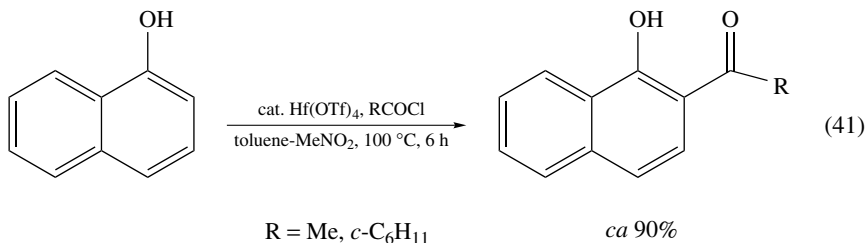
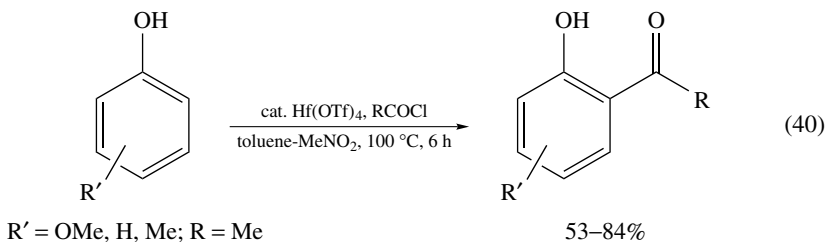
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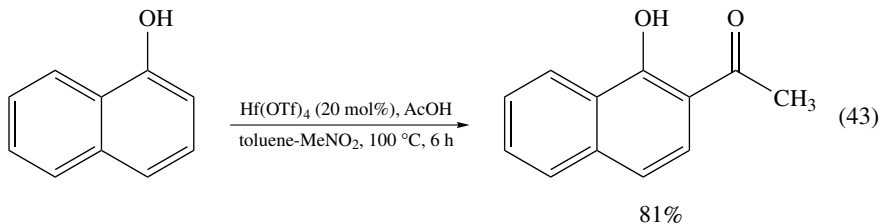
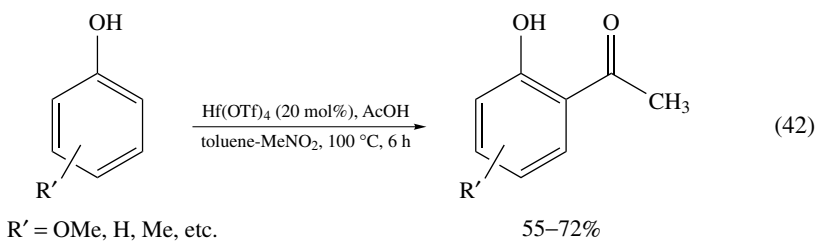
Such sulfonated polymers are conventionally prepared by the free-radical polymerization of polystyrene, followed by sulfonation.

III. FRIEDEL–CRAFTS ACYLATIONS

Regioselective direct acylation of phenol and naphthol derivatives with acid chlorides was achieved by using hafnium triflate, $\text{Hf}(\text{OTf})_4$ (5 to 20 mol%), as a catalyst (equations 40 and 41)⁶⁵.



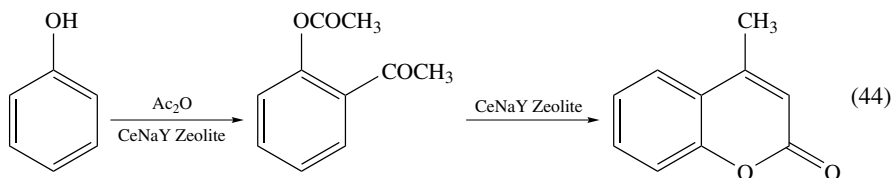
The $\text{Hf}(\text{OTf})_4$ is also effective in the *ortho*-acylation of phenols using carboxylic acids instead of the acid chlorides, although somewhat lower yields are obtained and larger amounts of the catalyst are required (equations 42 and 43)⁶⁶.



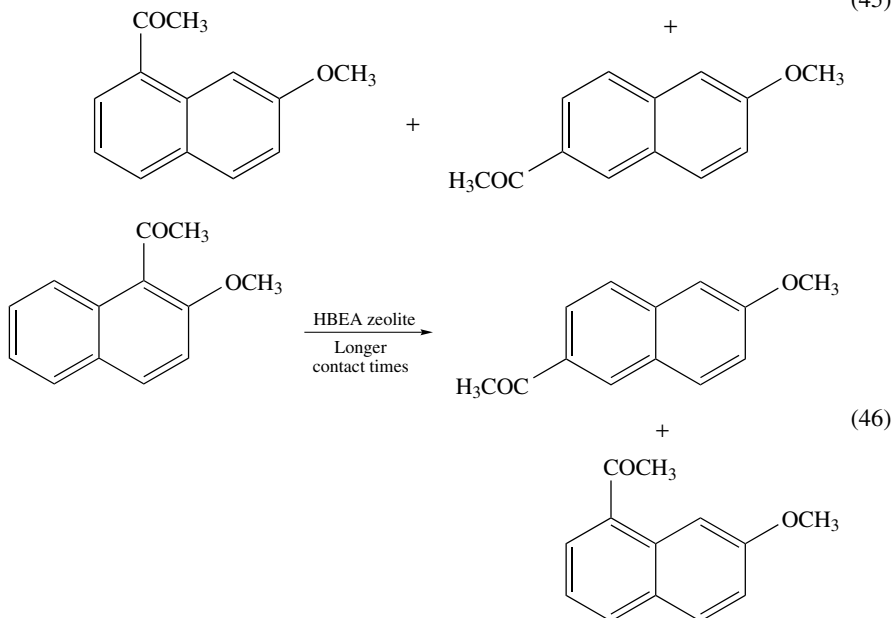
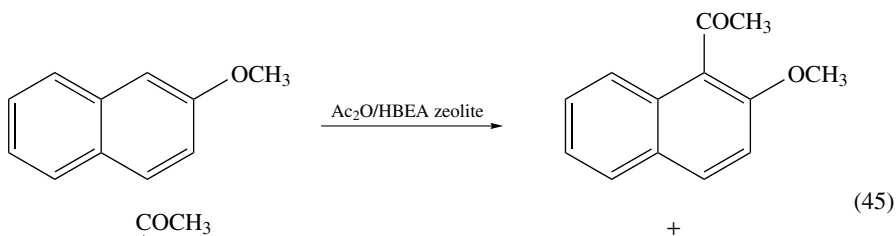
Similarly, scandium triflate ($\text{Sc}(\text{OTf})_3$), zirconium triflate ($\text{Zr}(\text{OTf})_4$) and titanium chloro(tris)triflate ($\text{TiCl}(\text{OTf})_3$) were also used for the *ortho*-acylation of phenols and 1-naphthols using acid chlorides^{67,68}.

By using suitable protecting groups, *meta*-acylation of phenols and ansioles was made possible using acetyl chloride and aluminium chloride⁶⁹.

Phenol reacts with acetic anhydride to give 4-methylcoumarin in a process involving O-/C-diacylation and cyclization over CeNaY zeolite in high yields (equation 44)⁷⁰.



Acetylation of 2-methoxynaphthalene by acetic anhydride over HBEA zeolite gives 1-acetyl-2-methoxynaphthalene, 2-acetyl-6-methoxynaphthalene and a small amount of 1-acetyl-7-methoxynaphthalene (equation 45)⁷¹. The 1-acetyl-2-methoxynaphthalene rearranges to the other isomers under longer contact times, probably involving both intermolecular transacylation and intramolecular rearrangements (equation 46).

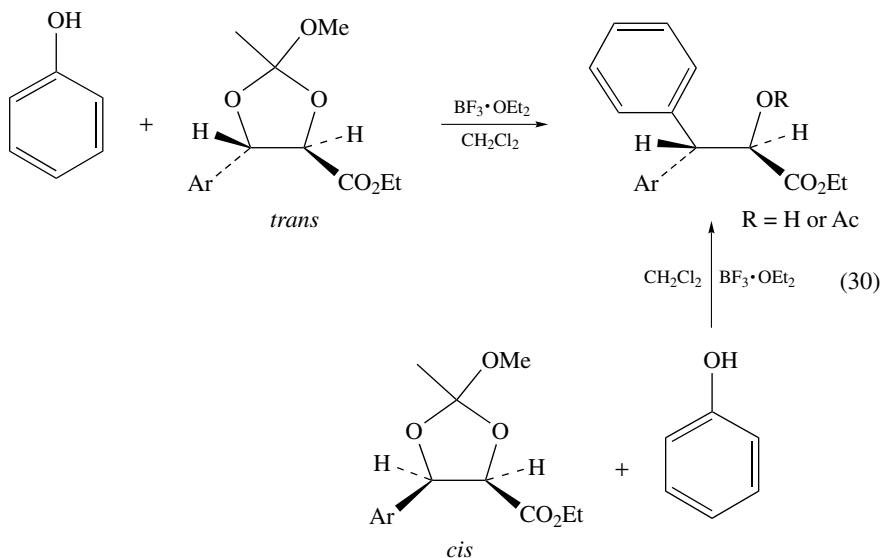


B. C–C Bond Formation

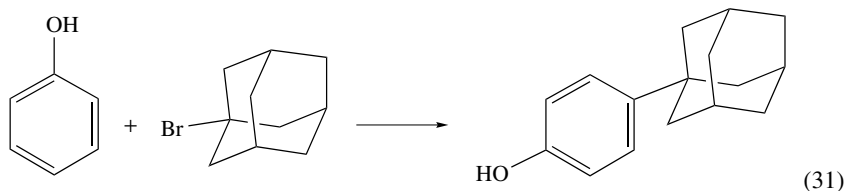
Among many C–C bond forming reactions of phenols, the classical Friedel–Crafts method is still important, since it possesses an advantage of converting aromatic C–H bonds to C–C bonds without any synthetic intermediate. However, there are drawbacks of (i) employing strong Lewis acids often in stoichiometric amounts, and (ii) being effective only for C-alkylation or C-acylation and not, for example, C-ethynylation or C-ethynylation. Alkylation of halogenated phenols has become useful based on the development of various organometallic reactions such as the Suzuki coupling, the Heck reaction, the Stille coupling and the Sonogashira coupling. This methodology, however, requires extra steps for the preparation of halogenated phenols in a regioselective manner, and the hydroxy group generally must be protected prior to the organometallic reaction. A demand therefore exists for new synthetic methodologies, which directly convert aromatic C–H bonds of phenol to C–C bonds, employing catalytic amounts of reagents. The hydroxy group of phenol serves as a directing group in such aromatic C–H bond activation and C–C bond formation.

1. C-alkylation: Bond formation with sp^3 carbon

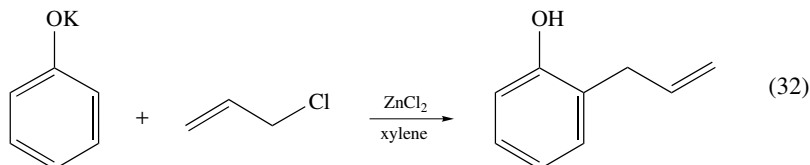
The C–C bond formation between the aromatic sp^2 carbons of phenol and sp^3 carbons can be conducted either under basic or acidic conditions, and can compete with O-alkylation. The *o/p*-selectivity is another matter of interest. Although the classical reaction of alkali metal phenoxides with alkyl halides generally takes place at the oxygen atom, C-alkylation occurs in some cases depending on solvent, counter cation and heterogeneity of the reaction system¹¹⁷. The regio- and stereoselectivity of the phenol alkylation was examined using a chiral *ortho*-ester under acidic conditions (equation 30)¹¹⁸. The C- and O-alkylation is controlled by the electronic nature of the substituent on the *ortho*-ester; an electron-rich aryl group induces the C-alkylation. The stereochemistry at the benzyl carbon is retention of configuration for the *trans*-isomer and inversion for the *cis*-isomer, which is explained by the involvement of free carbocation. Heating a mixture of



phenol and 1-adamantyl halides at 100–200 °C for several hours to days gives C-alkylated phenols, in which a small amount of the acid formed during the reaction may be catalyzing the generation of the tertiary carbocations (equation 31)¹¹⁹. Adamantyl bromide gives predominantly the *p*-isomer while the chloride gives the *o*-isomer. Secondary alkyl halides such as 2-bromoadamantane, bromocyclohexane or 2-bromonorbornane can also be used.



Several methods were reported for C-allylation of phenol, which is an alternative to the Claisen rearrangement^{120,121}. The reaction sometimes competes with chroman formation by the addition of the phenol hydroxy group to the olefin. Potassium phenoxides in the presence of ZnCl_2 react with allyl halides giving *o*-allylphenols (equation 32)¹²². In the absence of the zinc salt, a modest yield of *O*-allylated phenol is obtained. Stoichiometric amounts of copper metal and copper(II) perchlorate also promote the *o*-allylation¹²³. Molybdenum complexes $[\text{Mo}(\text{CO})_4\text{Br}_2]_2$ or $\text{Mo}(\text{CO})_3(\text{CH}_3\text{CN})_2(\text{SnCl}_3)\text{Cl}$ catalyze allylation of phenol with allyl acetate, and $(\text{acac})_2\text{Mo}(\text{SbF}_6)_2$ allyl alcohol, in which the formation of a π -allyl molybdenum complex is proposed^{124,125}. Treatment of allyl alcohols with Brønsted acids in general provides chromans, for which two mechanisms are suggested: (i) initial *O*-allylation followed by cyclization, and (ii) initial C-allylation^{126–128}. Conjugated 1,3-dienes are used for the C-allylation in the presence of Lewis acid, zeolite or a transition metal complex^{129–131}. Rhodium catalysis found by Bienaymé and coworkers couples β -springene and a phenol giving the C-allylated phenol (equation 33)¹³². Cleavage of a vinylcyclopropanecarboxylate with tin phenoxide was reported to give an *o*-allylated product¹³³.



Inoue, Sato and coworkers studied a [2,3]sigmatropic rearrangement for the synthesis of *o*-alkylphenol. Reaction of a sulfoxide and phenol in the presence of dehydrating reagents such as thionyl chloride or benzenesulfonyl chloride provides phenoxysulfonium salts, which on treatment with triethylamine are converted to *o*-(α -alkylthioalkyl)phenols^{134,135}. Since the benzylic thio group can be readily removed, the overall transformation provides the *o*-alkylated phenols. Later, a method to treat sulfides with sulfonyl chloride was developed for the same transformation (equation 34)¹³⁶, which is more effective than the original Gassmann's method employing *N*-chlorosuccinimide.

Posner and Canella used the directed metalation technology for phenol C-alkylation (equation 35); phenol was dimetalated at both the hydroxy group and the *o*-position with *t*-butyllithium, and treatment with methyl iodide gave *o*-cresol¹³⁷. Brandsma and coworkers employed a complex reagent of butyllithium, *N,N,N',N'*-tetramethylethylenediamine, and potassium *t*-butoxide for the metalation¹³⁸. Bates and Siahaan metalated cresols with butyllithium and potassium *t*-butoxide, and the *o*- and *m*-isomers gave the organometallic intermediate in good yield, while the yield was fair for the *p*-isomer¹³⁹. The Simmons–Smith