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Continuous Chemoselective Methylation of *m*-Cresol and Phenol with Supercritical Methanol over Solid Acid and Base Metal Oxide Catalysts

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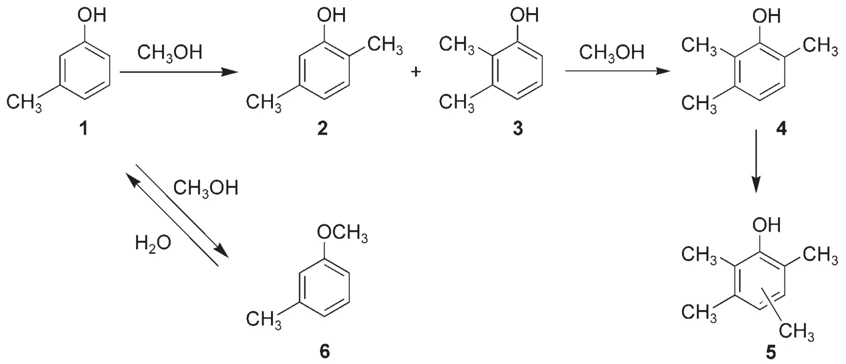
Abstract: The chemoselective methylation of *m*-cresol and phenol with supercritical methanol ($scCH_3OH$) promoted by metal oxide catalysts (MgO, ZrO_2, Cs–P–Si and Fe–V/SiO_2) was investigated in a continuous flow fixed bed reactor. The use of $scCH_3OH$ as a carrier medium led to a significant change in the product selectivity compared to that attained in the gas phase reaction, and caused a marked suppression of the degradation of CH_3OH during the reaction, resulting in an improvement in the catalyst lifetime. The chemoselective outcome of the reaction was highly influenced by the acid-base character on the solid catalysts examined under supercritical conditions.

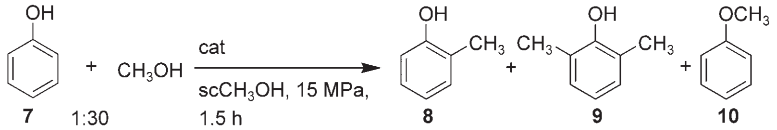
Keywords: *m*-cresol; phenol; selective methylation; solid catalyst; supercritical methanol

The use of supercritical fluids (SCFs) as compressed carrier media for heterogeneous catalysts can offer a great opportunity to manipulate the outcome of reactions in terms of the reactivity and selectivity mainly because of pressure tunable fluid properties.[1] In fact, the high solubilizing power of SCFs compared to normal gases allows a significant improvement in catalyst lifetime and activity by removing the deposited higher molecular weight products in the catalyst pores or on the catalyst surface. The enhanced diffusivity of solid organic compounds in SCFs can allow the effective removal of the reaction products from the catalyst surface.[1] In addition, the favorable heat transfer properties of SCFs can remove heat generated by the highly exothermic alkylation to minimize undesired side reactions.[1] Thus, heterogeneous catalysis with high product selectivities in SCFs has received considerable attention in the quest to achieve highly efficient molecular transformations. For example, we have recently reported the chemoselective methylation of functionalized amines over solid acid-base catalysts with $scCH_3OH$ using a continuous flow, fixed-bed, tubular reactor, where $scCH_3OH$ acts as a methylating agent and a reaction medium.[2] Changing the pressure of $scCH_3OH$ resulted in a significant increase in product selectivity. We have now expanded the scope of the methylation with $scCH_3OH$ and found that selective *ortho*-methylation of *m*-cresol (**1**) with $scCH_3OH$ over the solid catalysts proceeded rapidly to give the desired C–C bond formation product, 2,3,6-trimethylphenol (**4**) through 2,5-xylenol (**2**) and 2,3-xylenol (**3**) in good to excellent yields. Fine-tuning the supercritical reaction conditions, as well as the selection of catalysts, led to the achievement of the highly efficient *ortho*-methylation of phenol derivatives as shown in Scheme 1.

Screening of various solid metal oxide catalysts for the reaction of **1** with $scCH_3OH$ using a continuous flow, fixed-bed, tubular reactor at 300–500 °C and a pressure range of 0.1 to 15 MPa, (flow rate, W/F = 55–111 g-cat h/*m*-cresol mol, **1**:CH_3OH molar ratio of 13.5) revealed that the metal oxide catalysts ZrO_2[3] and Fe-V/SiO_2,[4] effected *ortho*-methylation under supercritical conditions to give predominantly a mixture of the *C*-methylated products **2**, **3**, and **4** in high yields (see Experimental Section) in addition to a small amount of tetramethyl-substituted phenols (**5**). Table 1 lists some typical examples of this reaction including the productivity based on STY, product selectivity, and material balance with methanol. Similarly, the reaction of phenol (**7**) over Fe-V/SiO_2 with $scCH_3OH$ proceeded smoothly to give the corresponding *ortho*-methylated phenols (**8** and **9**) in high selectivity (99%) as shown in Scheme 2. When a base catalyst, MgO, was used at 400 °C under otherwise identical conditions, the reaction of **1** with $scCH_3OH$ gave *ortho*-methylated phenols with 74% selectivity albeit with a high conversion of **1** (up to 89%) compared



Scheme 1.



cat	temp [°C]	conv [%]	yield [%] 8	9	10
Fe–V/SiO$_2$	350	65	48	17	1
Fe–V/ZrO$_2$	320	99	6	87	0.5

Scheme 2.

Table 1. Reaction of **1** with methanol over various metal oxide catalysts at 1:13.5 molar ratio at 4 h^{-1} of LHSV.

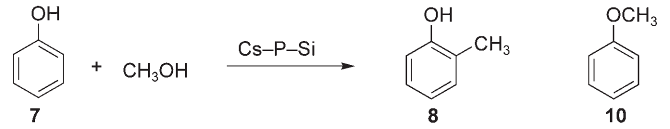
	Catalyst	Temp. [°C]/ Press. [MPa]	Conversion [%]	Yield [%] 2	3	4	Selectivity [%] 2–4	5	6	CH_3OH eff[a] [%]
1	ZrO$_2$[b]	400/0.1	26	14	8	1	87	7	0	88
2	"	400/8.2	96	41	10	36	91	6	3	94
3	Fe-V/SiO$_2$	350/0.1	9	7	2	1	99	0	0	96
4	"	350/8.2	36	24	8	3	97	2	1	100
5	"	350/8.2[c]	94	46	9	38	98	1	1	98
6	MgO	400/0.1	9	7	2	0	99	0	0	93
7	"	500/0/1	84	41	11	28	94	1	1	79
8	"	400/8.2	89	40	8	19	74	7	3	100
9	"	400/15	92	32	7	18	62	13	5	100

[a] Methanol efficiency: material balance based on methanol.
[b] The calcination temperature of catalyst precursor, $ZrO(OH)_2$, was 850 °C.
[c] Reaction of **1** with a molar ratio of 1:CH_3OH = 1:30 at 4 h^{-1} of LHSV.

with those attained in the gas phase reaction (9% conversion).

On the other hand, a ternary mixed oxide catalyst, Cs–P–Si, having both very weak acidic and basic sites, selectively gave the *O*-methylation products **8** and **9**, anisole **10** with good conversion and high selectivity, 49% and 98%, respectively as listed in Table 2.[5] Recently, we reported that the *N*-methylation of 2-aminoethanol over the same mixed oxide catalyst was promoted significantly with high conversion and excellent selectivity.[2a, b] The conversion of phenol was similarly enhanced in scCH_3OH, but the selectivity for *O*-methylation largely did not change with increasing pressure as described in Table 2. Since the *O*-methylation of phenol with CH_3OH proceeds *via* a formal intermolecular dehydration to give the desired products and H_2O as a concomitant product, water strongly inhibits *O*-methylation possibly because of the relatively stronger interaction of water with the active sites on the catalyst surface compared with methanol.[6] No degradable compound of

Table 2. Reaction of **7** with methanol over Cs–P–Si mixed metal oxide catalyst at 4 h^{-1} of LHSV.



	Temp. [°C]/ Press. [MPa]	**7**:CH_3OH	Conversion [%]	Selectivity [%]		CH_3OH eff[a] [%]
				8	**10**	
1	300/0.1	1:20	3	0	99	100
2	300/8.2	1:20	36	0	99	100
3	300/8.2	1:40	49	0	98	100
4	300/8.2	1:100	71	1	92	100

[a] Methanol efficiency: material balance based on methanol.

methanol can be detected under the reaction conditions tested.

A visual inspection of the inside of the reactor (a 10-mL high pressure vessel equipped with sapphire windows) confirmed that the reactants or expected reaction products are all dissolved in the scCH_3OH to make a single supercritical phase under the reaction conditions examined here. The use of supercritical conditions successfully improved the conversion of the starting phenols compared to those of the gas phase reaction, which gave only low conversion as shown in Table 1. In addition, it should be noted that under supercritical conditions, a material balance based on methanol (methanol efficiency) during the reaction was significantly improved to 100% possibly because of the unique properties of SCFs. In contrast to the supercritical phase reaction, serious decomposition of methanol was observed to provide the carbon deposition or heavier materials on the catalyst surface,[7] leading to quick catalyst deactivation in the gas phase. In fact, the commercial gas phase methylation process with the conventional catalysts MgO[8] and Fe-V/SiO_2[9] is reported to suffer from serious catalyst deactivation, possibly because of the decomposition of methanol.

Noticeably, the regiochemical outcome of the methylation of **1** or **7** was found to be affected by the catalyst properties as well as the reaction conditions. The base catalyst, MgO, which exhibited the best catalyst performance for *ortho* methylation of **1** in the gas phase at 500 °C, as discussed above,[8] gave a mixture of both *C*- and *O*-methylated products under supercritical conditions even at a lower temperature (400 °C) although with high reactivity. However, when the weaker acid-base bifunctional catalyst ZrO_2 was employed in the supercritical phase, the chemoselectivity of the methylation with scCH_3OH at 400 °C and 8.2 MPa has proven to have a strong correlation with the calcination temperatures of the catalyst precursors ranging from 430 to 1,000 °C, which correlates with the acid-base character on the surface measured by pyridine titration, as shown in Figure 1. The selectivity of *ortho*-methylation decreased after reaching a maximum at around 500 °C and increased again at around 700 °C with a decrease in the amount of pyridine adsorption on the surface. It has been reported that the acid-base character of the surface of ZrO_2 varied depending on the temperature of the calcination of the precursor, $ZrO(OH)_2$.[10] These results indicate that *ortho*-methylation of phenols predominantly proceeds possibly over the basic site of ZrO_2, while the reversible etherification to give **6** should be promoted by the acidic site of ZrO_2. The acidic property more perceptibly promoted the etherification to **6** in the scCH_3OH phase than in the gas phase, leading to non-regioselective methylation with the catalyst tested herein. Therefore, the balance between acidity and basicity on the catalyst surface is crucial for attaining the best catalyst performance in terms of reactivity and chemoselectivity. The use of the tunable acid-base catalyst ZrO_2 un-

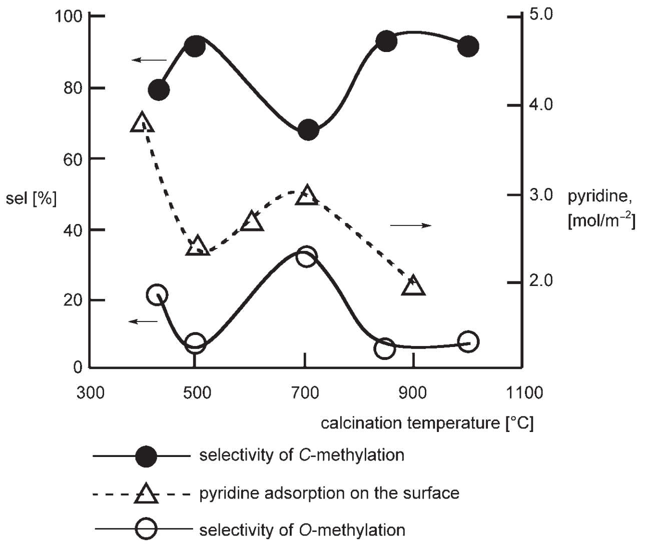


Figure 1. Calcination temperature effect on chemoselectivity over ZrO_2 catalysts.

der supercritical conditions resulted in not only a marked increase in the reactivity and methanol efficiency but also in the selectivity of *ortho* methylation as listed in Table 1. This selective methylation process is more appealing when ZrO_2 was used as a supported material; a combination of Fe-V oxide with ZrO_2 caused a significant improvement in the catalytic activity with up to 99% conversion from 65% with the silica supported Fe-V catalyst as shown in Scheme 2.

Thanks to pressure tunable fluid properties, optimum combinations of the liquid-like density and gas-like diffusivity can be realized to maintain catalyst activity, leading to an enhancement of the catalyst lifetime.[1] A continuous flow reaction over the Fe-V mixed oxide on a silica catalyst at 350 °C and a 1:30 molar ratio under otherwise identical conditions to those described in Table 1 revealed that the catalytic activity of Fe-V/SiO_2 did not suffer from serious deactivation under supercritical conditions compared to those attained under gas phase conditions as shown in Figure 2. Although the catalyst activity of the gas phase reaction deteriorated quickly in several hours and almost reached a steady state within 12 hours, giving 14% conversion, the use of supercritical conditions caused a significant improvement in the catalyst lifetime with an increase in pressure, the activity remaining for several days. ^{13}C Magic-angle-spinning NMR spectroscopy of the deposited materials on the catalyst surface after 72 hours of reaction showed that the carbon species on the tested catalysts in $scCH_3OH$ originated from an aromatic carbon, while the gas phase reaction gave the material consisting of aliphatic compounds, indicating that the deactivation of the Fe-V/SiO_2 catalyst might be caused by deposition of aliphatic carbons originating from methanol degradation.[8] A significant improvement in catalyst lifetime could be attained by retarding methanol degradation, reducing reaction temperature and effectively extracting the aliphatic precursors of coke from the catalyst surface with liquid-like $scCH_3OH$.

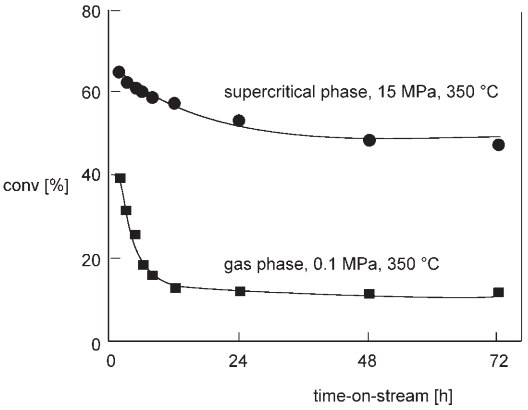


Figure 2. The catalyst lifetime: Influence of time-on-stream on the catalytic activity as a function of conversion of *ortho*-methylation of phenol under supercritical and gas phase conditions for several days.

In conclusion, we have reported the practical example of the chemoselective methylation of **1**, which can be tuned by using $scCH_3OH$ as a methylating agent and a reaction medium. Using $scCH_3OH$ can improve the efficiency of methanol and catalyst lifetime by lowering the reaction temperature, effectively removing of the deposition of higher molecular weight products from degradation of CH_3OH and extracting coke precursors from the catalyst surface. A suitable choice of a catalyst combining the weaker acidic and basic properties of solid metal oxides allowed the desired chemoselectivity for the $scCH_3OH$ methylation of phenols to be realized.

Experimental Section

The magnesium oxide catalyst, MgO, was prepared by calcination of magnesium carbonate at 540 °C under a nitrogen atmosphere for 5 hours. ZrO_2, prepared by precipitation from the reaction of $ZrO(NO_3)_2$ and aqueous ammonium hydroxide followed by calcination at 430, 500, 700, 850 and 1,000 °C under a nitrogen atmosphere for 5 hours. The Fe-V mixed oxide on SiO_2 was prepared by impregnating a homogenous methanol solution of $Fe(NO_3)_3$ and VOC_2O_4 into synthesized amorphous silica powder (Sylysia 350, Fuji Silysia Chemical Ltd.), followed by calcination at 750 °C under air for 5 hours. Except for amorphous SiO_2, the triclinic $FeVO_4$ phase was detected using powder X-ray diffraction analysis.

The methylation reaction of **1** in the gas or supercritical phase was carried out isothermally in a continuous up-flow, tubular reactor (SUS316 tubular reactor with a Swagelok VCR joint, 1/2 inch × 10 mm × 135 mm). The reactor, loaded with catalyst particles, was placed in an oven. A mixture of phenol and methanol was supplied to the reactor using an HPLC pump (PU1580, Jasco Co.) through the preheating coil. The pressure in the reaction system was controlled with an automatic back pressure regulator (880–81, Jasco Co.) at 0.1 to 15 MPa. Standard reaction conditions were used [5.0 mL catalyst, 300 °C, 8.2 MPa, molar ratio of methanol:amine = 13.5:1 or 20:1 and the LHSV (mL-liquid/mL-cat·h), which is the space velocity as normal liquid flow rate of mixed solution of reactants, is $4\ h^{-1}$). The reaction products were identified by Agilent 5973N-6890N (Agilent Technologies) GC-MS analysis. The selectivity and chemical yield of the products were determined by gas chromatography analysis (GC-17A; Shimadzu Co., FID detector and DB-1701 (J&W) capillary column).

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[6] The reaction of phenol with scCH_3OH was strongly repressed when water was added, while the inverse reaction of anisole with water in scCH_3OH did not proceed. Therefore, the use of a large excess of CH_3OH under supercritical conditions caused an enhancement of productivity as shown in Table 1, possibly because scCH_3OH might allow the effective desorption of the generated water from the catalyst surface.[2a]

[7] After 72 hours, the deposited materials on the catalysts tested were measured by elemental analysis and differential thermal analysis in air as well as ^{13}C MAS-NMR spectroscopy. The ^{13}C MAS-NMR spectra of used catalysts under supercritical and gas phase reactions showed broad peaks around $\delta = 125$ ppm due to aromatic carbons and $\delta = 48$ ppm due to aliphatic carbons. In fact, the extracted materials from the catalysts used with CH_2Cl_2 were found to include 2-hydroxy 3-methylbenzaldehyde, 2-hydroxybenzaldehyde and diethyl phthalate as byproducts as well as *ortho*-methylated products.

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