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Organic Transformations in Subcritical and Supercritical Water

Pengyu Wang

A dissertation submitted to
Kochi University of Technology
in partial fulfillment of the requirements
for the degree of

Doctor of Engineering

Graduate School of Engineering
Kochi University of Technology
Kochi, Japan

March, 2009

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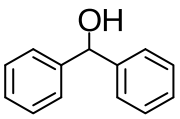
Abstract

The thesis deals with studies on organic transformations in subcritical and supercritical water (sub-CW and SCW, respectively). Quite unique organic transformations, such as non-catalytic oxidation of secondary alcohols benzhydrol (**1**) and benzoin (**2**) in SCW, non-catalytic Oppenauer oxidation of alcohols **1** and benzyl alcohol (**3**) under solvent-free conditions and in SCW, non-catalytic permethylation of catechol (**5**) and 4-methylcatechol (**6**) in sub-CW and SCW, and sub-CW assisted clean cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of $ZnCl_2$, are investigated to clarify the potential of sub-CW and SCW in organic transformations as reaction media.



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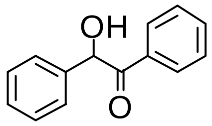

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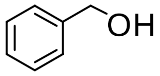

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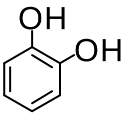

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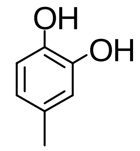

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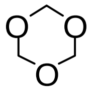

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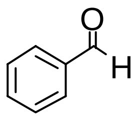

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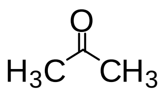

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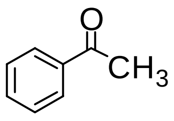

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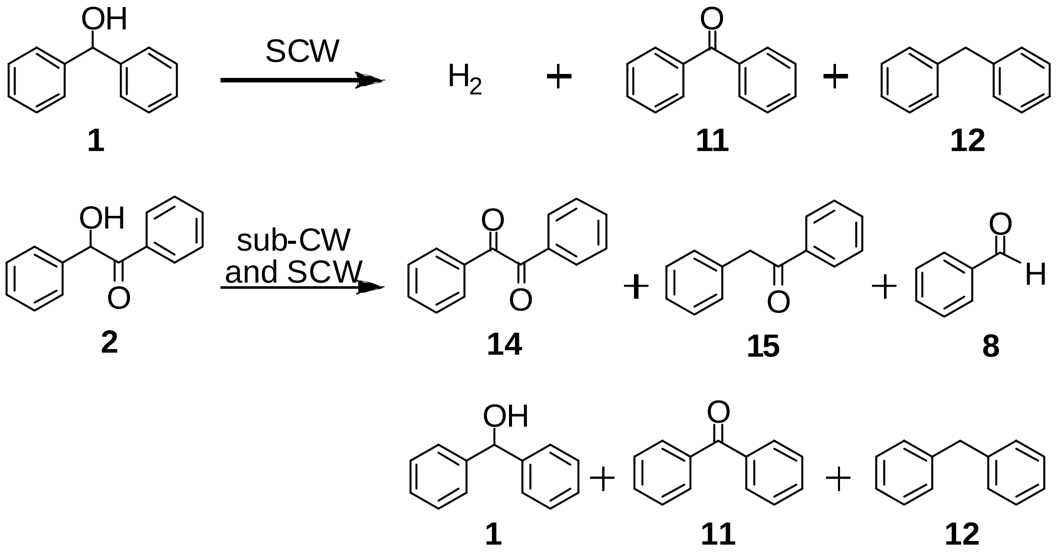
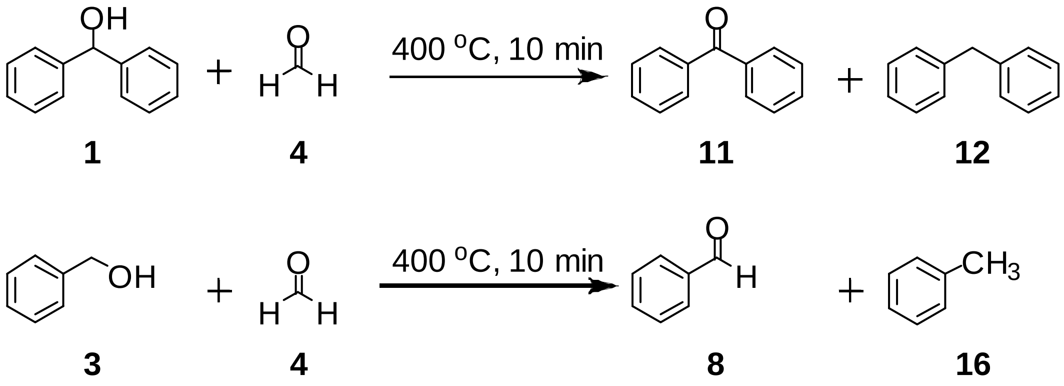
First, oxidation of secondary alcohols, such as benzhydrol (**1**) and benzoin (**2**), was investigated in the absence of any catalyst or oxidant in SCW. Reaction temperature and reaction time dependences were observed in both reactions. Higher temperature and longer reaction time caused higher conversions of **1** and **2** as well as higher yields of oxidation products, benzophenone (**11**) and benzil (**14**), and reduction products, diphenylmethane (**12**) and benzyl phenyl ketone (**15**), respectively. Water played a key role in the product distributions in these reactions. Reactions gave larger amounts of oxidation products, **11** and **14**, as well as smaller amounts of reduction products, **12** and **15**, respectively, in the presence of water, while the ratios of **11**:**12** and **14**:**15** were almost 1:1 in both cases in the absence of water. The best yield of **11** (63%) was achieved in the reaction of **1** at 460 °C for 180 min in 0.35 g mL^{-1} water density in an SUS 316 batch type tubular reactor. Hydrogen gas evolution was confirmed in the reaction of **1** in a quartz tubular



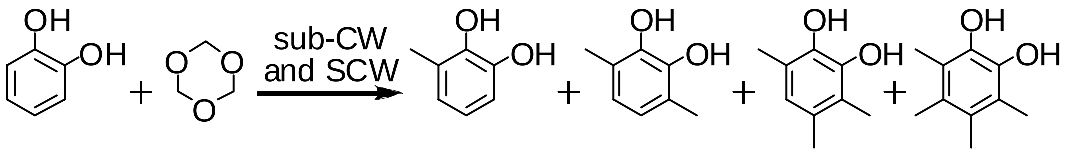
reactor. These facts, hydrogen gas evolution, water density dependence of alcohol reaction, and more oxidation products than reduction products in SCW, suggest that the water-catalyzed hydrogen generation mechanism is favourable to explain the reaction behaviour of alcohols in SCW.

Second, non-catalytic Oppenauer oxidation was applied for the oxidation of alcohols, such as benzhydrol (**1**) and benzyl alcohol (**3**), by use of a carbonyl compound, formaldehyde (**4**), as an oxidant in SCW in the SUS 316 batch type tubular reactor, and the results were compared to those under the most sustainable solvent-free conditions. Water was indispensable for the clean Oppenauer oxidation of **1** and **3** to produce almost pure oxidation products, benzophenone (**11**) and benzaldehyde (**8**), respectively, in both oxidations. Under solvent-free conditions, Oppenauer oxidation and disproportionation took place simultaneously in both reactions of **1** and **3** to afford oxidation products, **11** (64%) and **8** (95%), concomitant with small amounts of reduction products, diphenylmethane (**12**) (13%) and toluene (**16**) (2%), at 400 °C for 10 min in the SUS 316 batch type tubular reactor, respectively. Thus, lower yields of oxidation products, **11** (30%) and

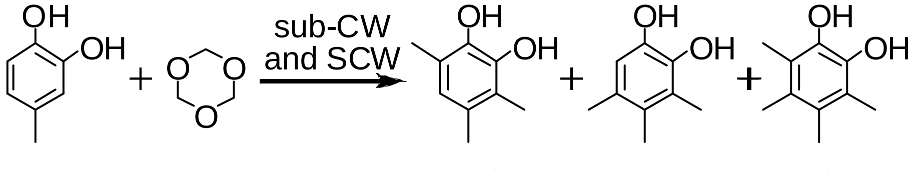


8 (66%), were obtained in SCW under the conditions of 400 °C, 10 min, and 0.35 g mL^{-1} water density, though the formations of reduction products, **12** (<1%) and **16** (<1%), were almost completely suppressed, respectively.

Third, simple and complete aromatic ring-methylation of catechol derivatives, such as catechol (**5**) and 4-methylcatechol (**6**), was investigated utilizing 1,3,5-trioxane (**7**) as a source of methyl groups in sub-CW and SCW without any catalyst. The formation of permethylation product, 3,4,5,6-tetramethylcatechol (**23**), was observed under all the conditions examined in sub-CW and SCW in both reactions of **5** and **6**. Permethylation product **23** was obtained as an almost sole product at 350 °C for 10 min in 3.5 mL water in the SUS 316 batch type tubular reactor in both reactions. Reaction temperature and time dependences were observed in the reaction of **6**. A higher temperature and a longer reaction time improved the yield of permethylation product **23** as well as the yields of other methylation products, 3,4,6-trimethylcatechol (**22**) and 3,4,5-trimethylcatechol (**24**). Water density dependence was also observed in the permethylation of **6**. In the



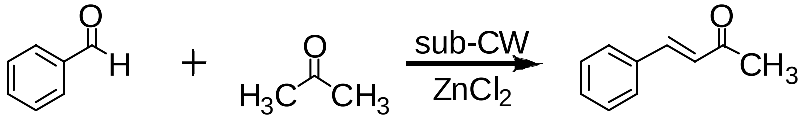
5 **7** **20** **21** **22** **23**



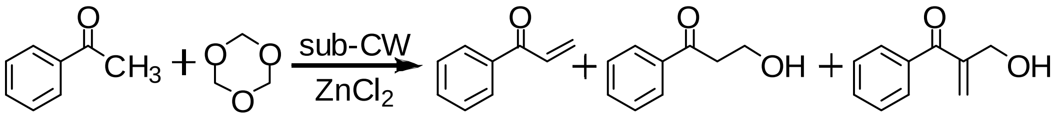
6 **7** **22** **24** **23**

absence of water, only a small amount of permethylation product **23** (4%) was obtained at 380 °C for 10 min. However, the formation of permethylation product **23** (13%) was improved in water under the conditions of 400 °C, 10 min, and 0.35 g mL^{-1} water density.

Finally, sub-CW assisted clean cross-aldol reaction was investigated through the reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of an inorganic additive, $ZnCl_2$. Clean cross-aldol reactions of **8**/**9** and **10**/**7** with $ZnCl_2$ were performed in sub-CW in the SUS 316 batch type tubular reactor with less waste of reagents and/or products as compared to the cases under the solvent-free conditions. In the absence of water, almost complete consumption of **8** and **10** (conversion: >99%) was observed, while no product was obtained at 250 °C for 20 and 5 min, respectively. However, the consumption of **8** and **10** was suppressed to 42 and 81%, respectively, in the presence of 3.5 mL water. Water assisted the cross-aldol reactions to afford a satisfactory yield (23%) of cross-aldol reaction product, benzalacetone (**32**), in the



8 **9** **32**



10 **7** **33** **34** **35**

reaction of **8** with **9** and a satisfactory total yield (63%) of 1-phenylprop-2-en-1-one (**33**), 3-hydroxy-1-phenylpropan-1-one (**34**), and 2-hydroxymethyl-1-phenylprop-2-en-1-one (**35**) in the reaction of **10** with **7** in the presence of $ZnCl_2$ under the conditions of 250 °C and 3.5 mL water in short reaction times (1–20 min).

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Chapter 1.

General Introduction

Water has been studied intensively as a medium for organic reactions to establish sustainable reaction systems, since water is not only a green solvent but also one of the most abundant substances on the earth.[1] Water shows different phases, such as solid phase, liquid phase, and gas phase, by changing temperature and pressure (Figure 1-1). In addition, water has a critical point (T_c = 374 °C, P_c = 22.1 MPa, and d_c = 0.32 g mL^{-1}) and supercritical phase situates at the region over the critical point. Supercritical water (SCW) is defined as the water which situates in the supercritical region, and subcritical water (sub-CW) is broadly defined as the water in liquid phase whose temperature (200–374 °C) is lower than the critical temperature.

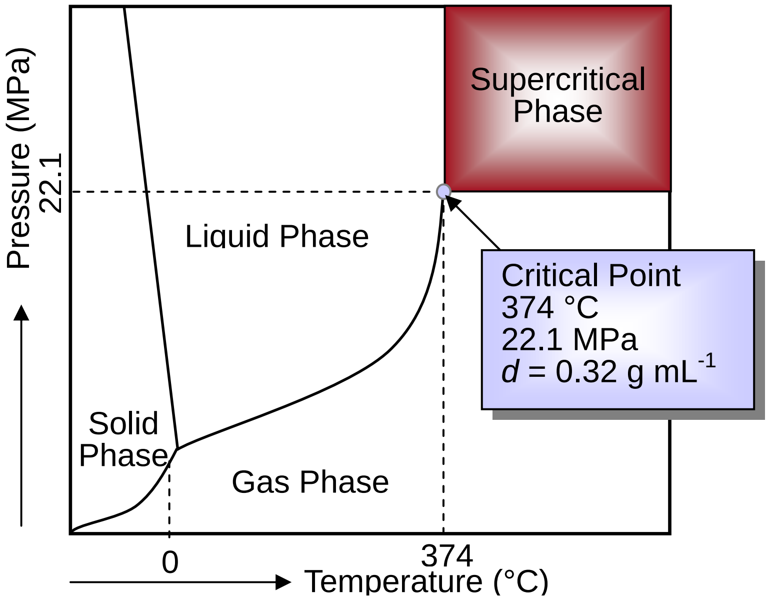


Figure 1-1. Water pressure-temperature phase diagram.

Although ambient water is an excellent reaction medium for many electrolytes, its very poor miscibility for many organic compounds due to the high polarity (ε_r = 79 at 25 °C and 0.1 MPa) limits its application for the organic reactions as a medium. However, the polarity of water is tunable simply by changing the temperature and pressure. With an increase of temperature and pressure, the dielectric constant of water decreases dramatically, especially, at the critical point. For example, the specific dielectric constant of water becomes 27 at 250 °C in 5 MPa and it decreases to 6 at 400 °C in 25 MPa.[2] Additionally, the specific dielectric constants (ε_r = 35, 20, 10, and 2) of water at 200, 300, 370, and 500 °C in a fixed pressure of 24 MPa are quite similar to those of ambient methanol (ε_r = 33), acetone (ε_r = 21), dichloromethane (ε_r = 9), and hexane (ε_r = 2), respectively.[3]

From a microscopic view, however, the aggregation state of SCW is fluctuated in time and space to afford a cluster structure of water molecules due to mutually exclusive events of the high pressure for aggregation and the high temperature for diffusion. When organic molecules are introduced into the fluctuated SCW, strong hydration due to high pressure occurs to afford water cages around the organic

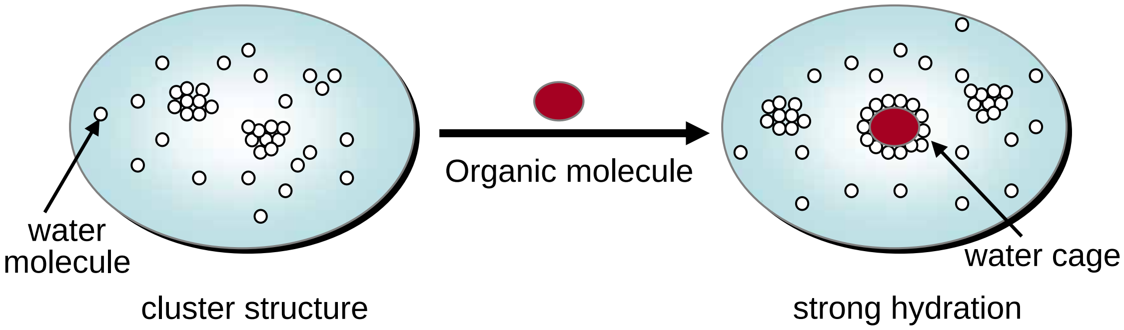
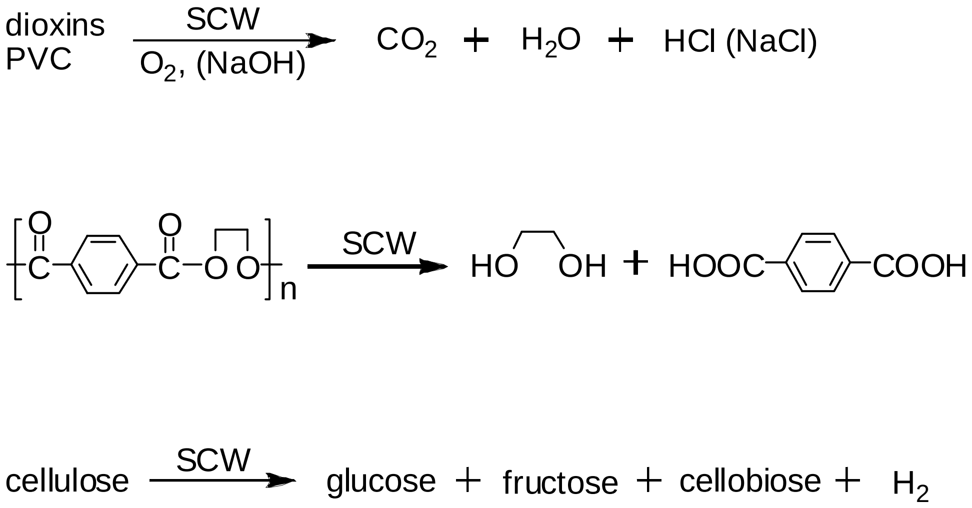


Figure 1-2. Water cage structure of supercritical water.

molecules (Figure 1-2).[4] Moreover, some special interactions between the organic and water molecules can be expected, due to vigorous vibrations of hydrated water molecules which surround the organic molecules closely at high temperatures. Furthermore, the ionic product of sub-CW and SCW is also bigger than that of ambient water. For example, the ionic product of water at the critical point become higher in 3 orders of magnitude than those of ambient water, which means higher concentrations of H^+ and OH^- than those of ambient water. Sub-CW and SCW is, therefore, very favorable for the acid-catalyzed or base-catalyzed reactions without any additional acid or base.[5] Some quite intriguing organic transformations have been reported concerning these quite unique properties of sub-CW and SCW.[5]

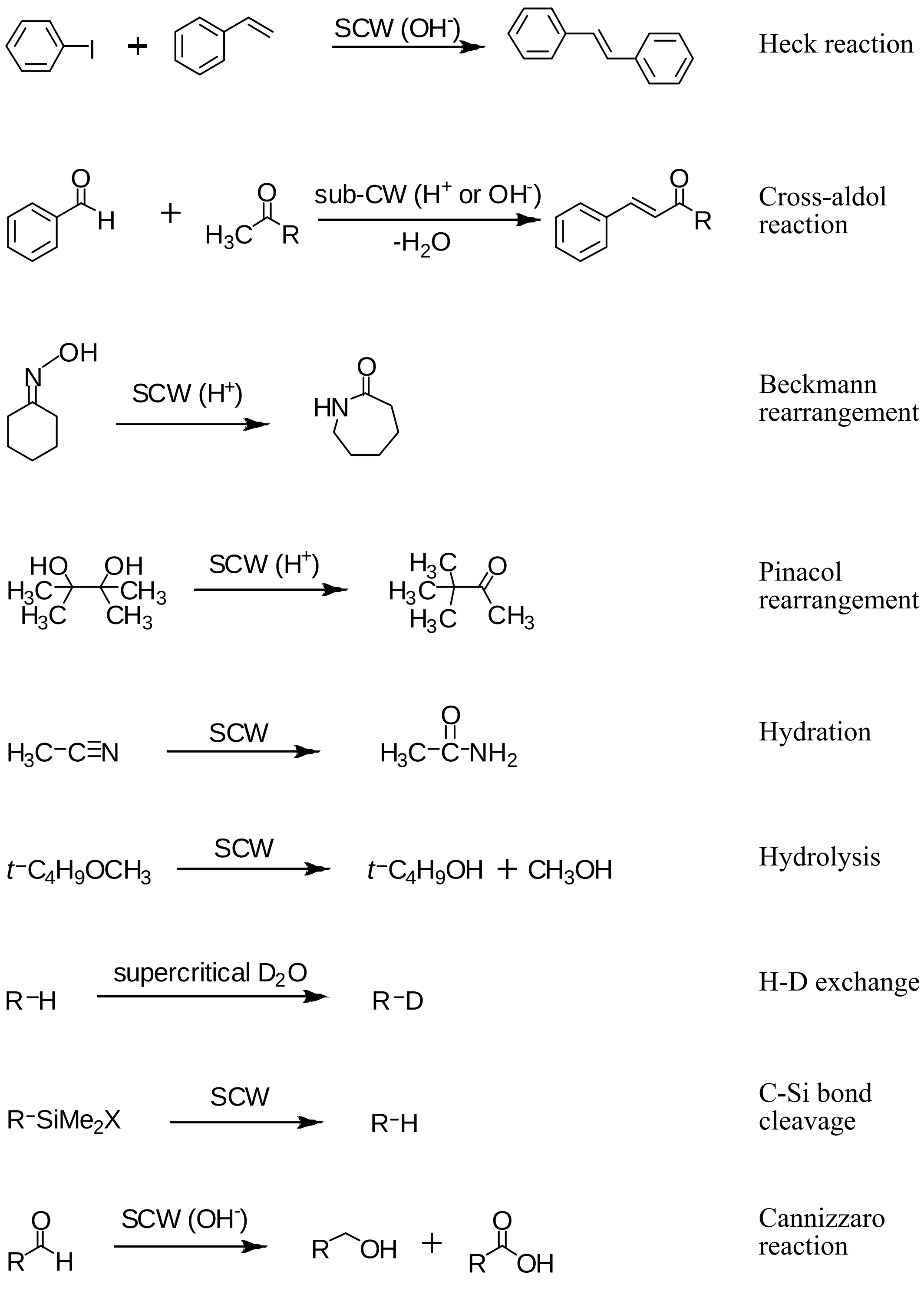
The application of sub-CW and SCW as reaction media started to grow in the early 1980s when Modell et al reported the complete oxidation of some hazardous organic materials in SCW.[6] For the last two decades with deep investigation of sub-CW and SCW, organic reactions in sub-CW and SCW became more and more important from the standpoints of science and engineering. It progressed very fast throughout the 1990s and 2000s with the further reorganization of sub-CW and SCW as media for the organic reactions in order to invent cleaner, safer, and more environmentally sustainable reaction systems.[7] Recently, sub-CW and SCW have been applied intensively for chemical synthesis, materials synthesis, wastes destruction, plastics recycling, and biomass processing as reaction media.[8] Among these applications, sub-CW and SCW are in common use in organic reactions as reaction systems.

In industrial chemistry, sub-CW and SCW have been investigated in the field of the waste treatment especially in the presence of a large excess amount of oxygen (Scheme 1-1). For example, dioxins and polyvinyl chloride (PVC) were oxidized completely to afford carbon dioxide, water, and hydrogen chloride (sodium chloride) without any catalyst.[9] Sub-CW and SCW were also utilized in the recovery of monomers from plastics, such as hydrolysis of polyethylene terephthalate (PET) to recover terephthalic acid and ethane-1,2-diol.[10] The degradation or gasification of cellulose was also reported to produce useful raw materials, such as glucose, fructose, cellobiose, and hydrogen gas, without any additive or catalyst in sub-CW and SCW.[11]



Scheme 1-1. Degradations of organic materials by subcritical and supercritical water.

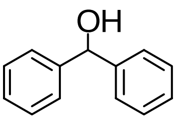
Recently, quite unique organic transformations in sub-CW and SCW have been investigated. For example, carbon-carbon bond formation reactions, such as non-catalytic Heck reaction of iodobenzene[12] and non-catalytic cross-aldol reaction of benzaldehyde with acetone or acetophenone in sub-CW and SCW, have been reported.[13] Several famous rearrangements, such as Beckmann rearrangement of cyclohexanone oxime,[14] pinacol rearrangement of 2,3-dimethyl-2,3-butanediol,[15] and benzil-benzilic acid rearrangement of benzil,[16] have been investigated in SCW in the absence of any catalyst. Hydration and hydrolysis, such as non-catalytic hydration and hydrolysis of nitriles in SCW[17] and non-catalytic hydrolysis of ethers, esters, and amides, in sub-CW and SCW have been studied.[18] Some other interesting organic transformations, such as H-D exchange of aromatic compound in supercritical deuterium oxide,[19] Cannizzaro reaction of formaldehyde or benzaldehyde, and C-Si bond cleavage,[20] have been studied in sub-CW and SCW without any catalyst. In addition, in these quite interesting organic transformations, water was not only a simple reaction solvent but also played a very curial role for these organic transformations in sub-CW and SCW. For example, water was a reactant in hydrolysis, hydration, and free radical oxidation chemistry.[17,18] On the other hand, water also participated as an acid/base catalyst in acid-catalyzed or base-catalyzed reactions and assisted as a catalyst in some transition states.[14-16] These interesting examples suggested that sub-CW and SCW are very suitable for organic transformations.



Scheme 1-2. Organic transformations in subcritical and supercritical water.

Although sub-CW and SCW have been investigated for the organic reactions as reaction media intensively, only a few examples such as oxidation of hazards wastes and degradation of organic materials have been applied on industry. Organic syntheses in sub-CW and SCW are still at the stage of laboratorial research. A lot of quite unique organic transformations in sub-CW and SCW should be investigated continuously to know the potential of using sub-CW and SCW as reaction media for organic synthesis and further to realize the organic syntheses in sub-CW and SCW on the industrial chemistry. In this thesis, the author investigates several quite unique organic transformations in sub-CW and SCW.

First, oxidation of alcohols to the corresponding ketones or aldehydes is one of the most important reactions in organic synthesis as well as industrial chemistry.[21] Usually, the oxidation of alcohols needs oxidants and catalysts.[22] Recently, Kajimoto et al reported a unique oxidation of ethanol in SCW at 450–500 °C in the absence of an oxidizing agent or a catalyst.[23] Takahashi et al proposed a water-catalyzed hydrogen formation mechanism consisting of a very unique 8-membered ring transition state with an ethanol molecule and two water molecules.[21] Unfortunately, side reactions, such as dehydration, occurred to give ethene simultaneously, which hindered the author from knowing the intrinsic



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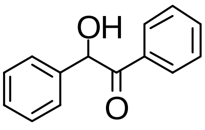

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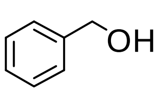
alcohol oxidation ability of SCW. Alternative alcohols with no such side reaction should be considered to discuss the inherent oxidation ability of SCW. In chapter 2, benzhydrol (**1**) and its higher homologue benzoin (**2**) are selected due to the advantages of the benzene subunits exhibiting high affinity to SCW[24] and of secondary alcohol with no hydrogen atom on the β-position of the hydroxyl group leading to dehydration, in order to evaluate the intrinsic alcohol oxidation ability of SCW.

Second, the Oppenauer oxidation of alcohol is one of the highly selective oxidation methods of alcohols producing the corresponding aldehydes or ketones. However, typical Oppenauer oxidation requires metal alkoxide as a catalyst to achieve good yields of desired ketones or aldehydes.[25] Recently, non-catalytic Meerwein-Ponndorf-Verley (MPV) reduction of ketones and aldehydes, which is an opposite reaction of Oppenauer oxidation, in supercritical alcohols have been reported.[26] The attractive non-catalytic MPV reduction of aldehydes and ketones in supercritical alcohols indicates that the Oppenauer oxidation of alcohols occurs in the presence of carbonyl compounds as oxidants under the similar reaction conditions in the absence of any catalyst. In chapter 3, the non-catalytic Oppenauer oxidation of alcohols, such as benzhydrol (**1**) and benzyl alcohol (**3**), is investigated by use of a small amount of formaldehyde (**4**) as an oxidant in SCW and the results



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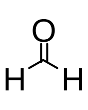

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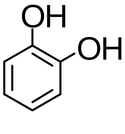
are compared to those under solvent-free conditions to accomplish a highly selective Oppenauer oxidation.

Third, alkylation of catechol derivatives is an important process in organic synthesis.[27] A typical alkylation method of catechol derivatives is the Friedel-Crafts process using strong acid catalysts.[28] Methylation of catechol derivatives is one of the most important processes, since methylcatechol derivatives, such as 3-methylcatechol, 4-methylcatechol, and 2,3,5-trimethylhydroquinone, are widely applied in the synthesis of agricultural chemicals and pharmaceuticals as intermediates.[27] In the methylation of catechol derivatives, permethylation processes are relatively difficult, while little was reported about non-catalytic permethylation of catechol derivatives. Recently, non-catalytic methylation of hydroquinone has been reported in supercritical methanol, while only a mono-methylation product, 2-methylhydroquinone, was observed even in the presence of an excess amount of methanol.[29] On the other hand, non-catalytic alkylation of phenol derivatives has been reported, such as non-catalytic methylation of phenol derivatives in supercritical methanol[30] and non-catalytic alkylation of phenol with propionaldehyde in SCW.[31] Among them, the alkylation of phenol with aldehyde in SCW requires a shorter reaction time than those in



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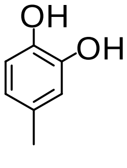

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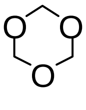

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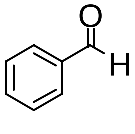
supercritical methanol, which suggests methylation with formaldehyde in SCW is more effective than that in supercritical methanol. In chapter 4, the author investigates permethylation of catechol derivatives, catechol (**5**) and 4-methylcatechol (**6**), with 1,3,5-trioxane (**7**)[32] as a source of methyl groups in sub-CW and SCW.

At last, organic reactions under solvent-free conditions have attracted much attention in organic synthesis, since it is one of the most sustainable reaction systems. Heating is one of the easiest methods to accelerate the reactions under solvent-free conditions, however it sometimes causes considerable decomposition of starting materials and/or reaction products because of the high temperature. On the other hand, SCW is another choice for green reaction systems, while the high temperature of SCW also leads to considerable decomposition of chemicals in the reactions. Meanwhile, sub-CW has a lower temperature (200–374 °C), which is easily anticipated to suppress the decomposition of organic compounds. In chapter 5, sub-CW assisted clean cross-aldol reaction is investigated using the cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of an inorganic additive, $ZnCl_2$, in sub-CW and the results are compared to those under solvent-free conditions.

The details of the researches are described in chapter 2, chapter 3, chapter 4,



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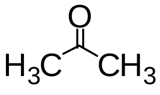

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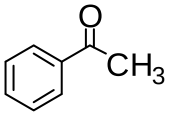

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and chapter 5. Chapter 2 treats with the investigation on non-catalytic oxidation of secondary alcohols, benzehydrol (**1**) and benzoin (**2**), in SCW. Chapter 3 describes non-catalytic Oppenauer oxidation of alcohols, **1** and benzyl alcohol (**3**), using formaldehyde (**4**) as an oxidant, both under solvent-free conditions and in SCW. Chapter 4 deals with a simple non-catalytic permethylation method of catechol derivatives, catechol (**5**) and 4-methylcatechol (**6**), with 1,3,5-trioxane (**7**) as a source of methyl group in sub-CW and SCW. At last, chapter 5 describes sub-CW assisted clean cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with **7** in the presence of an inorganic additive, $ZnCl_2$.

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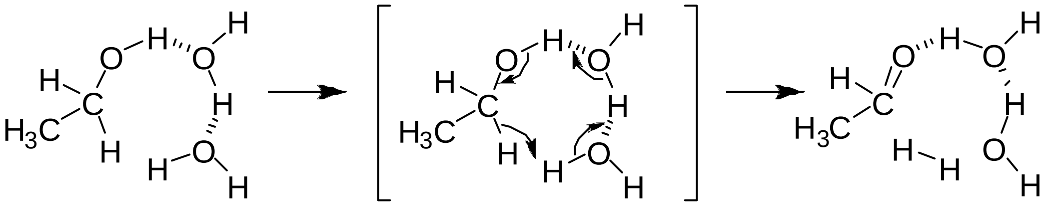
32 1,3,5-Trioxane (**7**) was selected instead of formaldehyde water solution as a reagent to avoid the potential influence of methanol which was added to the solution as a stabilizer.

Chapter 2.

Reaction Behavior of Secondary Alcohols in Supercritical Water

2-1 Introduction

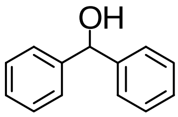
Alcohol oxidation affording ketone or aldehyde is one of the most important reactions in organic synthesis.[1] Usually, the oxidation of alcohols requires catalysts and considerable amounts of oxidants.[2] Recently, Kajimoto et al reported a quite unique oxidation of ethanol in SCW.[3] When ethanol was treated in SCW at 450–500 °C even without any oxidant or catalyst, oxidation occurred to give acetaldehyde concomitant with *hydrogen gas* generation. Concerning this reaction, Takahashi et al proposed a quite unique water-catalyzed hydrogen formation mechanism based on theoretical calculations.[4] The transition state of this mechanism consisted of an ethanol molecule and two water molecules, in which two water molecules catalyzed the reaction by making an eight-membered ring



Scheme 2-1. Water-catalyzed hydrogen formation mechanism.

bridging over two hydrogen atoms of the ethanol to give a H_2 molecule (Scheme 2-1). Unfortunately, dehydration of ethanol also occurred to give ethene simultaneously as a side reaction, which hindered us from knowing the intrinsic alcohol oxidation ability of SCW. In order to discuss the inherent oxidation ability of SCW, alternative substrates with no such side reaction should be considered.

Benzhydrol (**1**) and benzoin (**2**) were selected as substrates to evaluate the intrinsic alcohol oxidation ability of SCW due to advantages of (i) the benzene subunits exhibiting high affinity to SCW[5] and (ii) the secondary alcohol with no hydrogen atom on the β-position of the hydroxyl group leading to dehydration. In this chapter, the author investigates the alcohol oxidation property of SCW through secondary alcohols **1** and **2**.



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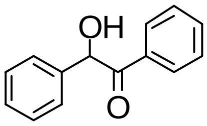

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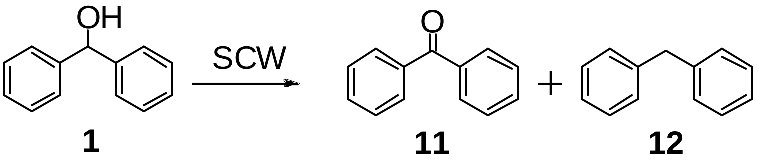
2-2 Results and Discussion

2-2-1 Reaction of benzhydrol (1) in supercritical water

Alcohol **1** was treated in SCW in an SUS 316 batch type tubular reactor under various conditions (Table 2-1).[6] Small amounts of benzophenone (**11**) and diphenylmethane (**12**) were produced, when **1** was treated at the temperature near

Table 2-1. Reaction of benzhydrol (**1**) in supercritical water[a)]



Entry	Mole of **1** (mmol)	Temperature (°C)	Water density (g mL^{-1})[b)]	Reaction time (Min)	Conversion (%)	Product (%)	
						11	**12**
1	0.272	380	0.35	180	19	6	4
2	0.272	400	0.35	180	26	16	5
3	0.272	420	0.35	180	77	46	4
4	0.272	440	0.35	180	87	53	9
5	0.272	460	0.35	180	>99	63	10
6	1.09	460	0.35	180	96	60	10
7	2.00	460	0.35	180	>99	60	17
8	0.272	460	0.35	20	38	16	<1
9	0.272	460	0.35	60	82	53	7
10	0.272	460	0.35	120	93	49	7
11	0.272	440	0	180	>99	48	53
12	0.272	440	0.05	180	86	50	29

a) Under N_2, in the SUS 316 batch type tubular reactor.

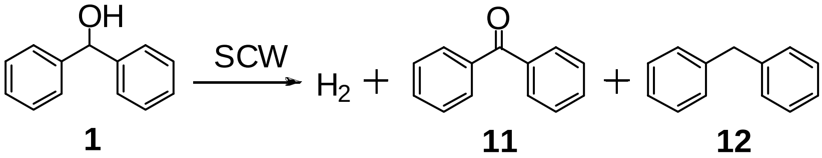
b) Value of water density water (g)/volume of the reactor.

the critical point (Entry 1). The conversion of **1** and yields of **11** and **12** became higher with an increase in the reaction temperature (Entries 1–5). A remarkable change was observed at 420 °C (Entry 3). Reaction time dependence was also examined in the reaction of **1** and the reaction almost finished within about 120 min (Entry 10). The best yield of oxidation product **11** was achieved at 460 °C for 180 min (Entry 5). The required high temperature (>420 °C) as well as long reaction time (>120 min) suggests that the activation energy of this reaction is quite high. Even though a higher concentration of alcohol **1** was used in this reaction, almost no influence on the conversion of **1** and the yield of **11** as well as a little influence on the yield of **12** was achieved (Entries 6 and 7). It is noteworthy that yields of **11** were always higher than those of **12** under all the conditions the author examined in water (Entries 5, 6, and 7).

The role of water was examined by changing the water density in this reaction. Almost same amounts of oxidation product **11** and reduction product **12** were obtained *in the absence of water* (Entry 11, pyrolysis), suggesting that disproportionation between two molecules of alcohol **1** took place thermally. However, *in the presence of water*, the ratio of **11**:**12** always exceeded unity and increased with increasing water density (Entries 11, 12, and 4). Even within shorter reaction times (Entries 8, 9, and 10), the yield of **11** was always higher than that of **12** at 460 °C in 0.35 g mL^{-1} water density. These observations imply that reaction of alcohol **1** proceeded via a new reaction pathway other than the disproportionation under the conditions of *higher water density and higher temperature*. Water must play a key role in the new reaction.

Next, in order to ascertain the gaseous products, a quartz tubular reactor was adopted instead of the SUS 316 one. Evolution of hydrogen gas was observed, along with oxidation product **11** and reduction product **12** in the reaction of **1** in SCW at 420 °C in the quartz tubular reactor (Table 2-2). However, slight differences of the product distributions were observed between the quartz tubular reactor and the SUS 316 one. These differences between the reactions would be explained by the different reactor materials of the SUS 316 and quartz as exemplified by Kajimoto et al.[3] Although smaller ratios of **11**:**12** were obtained in the quartz tubular reactor than those in the SUS 316 reactor, the oxidation product **11** was the major product in SCW in both reactors. On the other hand, the total amount of obtained H_2 and **12** was almost equal to the amount of **11**, showing no discrepancy supposing

Table 2-2. Generation of hydrogen gas in reaction of benzhydrol (**1**) in supercritical water[a)]



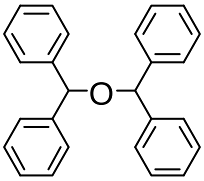
Entry	Temperature (°C)	Reaction time (min)	Conversion of **1** (%)[b)]	Products (%)		
				H_2	**11**	**12**
1	422	10	1	0.6	2.4	1.5
2	420	60	7	1.2	5.1	2.8

a) Reaction conditions: 0.272 mmol of **1** and 0.34 mL of water in 1 mL quartz batch type tubular reactor, water density 0.34 g mL^{-1}.

b) Conversions was suppressed with low level to avoid explosion of the quartz tubings by inner pressure of generated hydrogen gas.

that reduction product **12** was afforded via the reduction of **1** and/or **11** by the generated hydrogen in the reaction system. Then, influence of hydrogen gas on the product distributions was examined. When alcohol **1** was treated with and without additional hydrogen gas in SCW (**1**: 0.054 mmol, H_2: 0 or 0.29 mmol, at 440 °C for 180 min in 0.35 g mL^{-1} water density in the SUS 316 reactor), no difference in the product distributions was observed between the reactions with and without additional hydrogen gas (with H_2, **11**: 24%, **12**: 15%; without H_2, **11**: 25%, **12**: 13%). These results indicate that **1** and/or **11** may not be reduced by hydrogen gas generated *in situ* but may be reduced by nascent hydrogen under the reaction conditions. Katritzky et al reported, in a related study, that **1** and **11** were successfully reduced to give **12** in 15% aqueous formic acid or 15% aqueous sodium formate under supercritical conditions (460 °C, 60 min).[7] Prolonged reaction time led to higher conversion of **1** and higher yields of hydrogen gas, **11**, and **12** (Entry 2).[8] The yields of **11** were almost two times higher than those of **12** in both reactions.

Hatano et al studied a similar reaction using the same substrate **1** in sub-CW and SCW in *a steel bomb reactor*.[9] The same products, **11** and **12**, were obtained as us, while the distributions of **11** and **12** were quite different from ours. The ratios of **11**:**12** were always almost 1:1 under all conditions they tested. The water density did not effect the product distributions in their experiments. On the other hand, they obtained ether **13** in the reaction at 200 °C. When ether **13** was treated under supercritical conditions as a starting material, same amounts of **11** and **12** were obtained. They concluded, therefore, that equal amounts of **11** and **12** were derived from disproportionation of ether **13**, which was produced at an early stage of the reaction.[10] The proposed reaction mechanism would be quite reasonable, if a 1:1 mixture of **11** and **12** were obtained even in our experiments. However, our experiments always gave larger amounts of **11** than those of **12**. The lability of **12** could result in the low yield of **12** in our experiments under the reaction conditions. A control experiment involving **12** was performed in SCW (460 °C, 180 min, 0.35 g mL^{-1} water density). However, complete recovery of **12** (>99%) was observed, indicating that compound **12** was quite stable under the reaction conditions. Especially, it is noteworthy that the yield of **11** exceeded 50% to reach 63% under the reaction conditions of Entry 5 in Table 2-1. The observed temperature and water density dependence of the reaction (Table 2-1) and the evolution of hydrogen are of considerable importance for discussion of the reaction mechanism. In our experiment, the formation of ether **13** could be suppressed by hydrolysis of **13** itself under extreme supercritical conditions, even if ether **13** was generated in the reactions. Concerning the difference between the results of Hatano's and ours, it is difficult to put forward a conclusive discussion. The crucial differences could be resulted in the different materials of the metal reactors. Although the reaction



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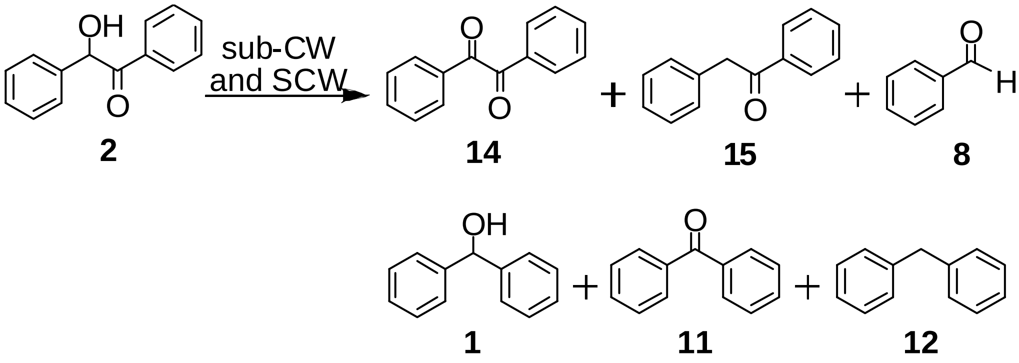
mechanism is not well understood, *the water-catalyzed hydrogen formation mechanism* seems to be the most favorable one at present for our experiment in SCW.

2-2-2 Reaction of benzoin (2) in subcritical and supercritical water

Another secondary alcohol, benzoin (**2**), which also has two benzene subunits, a secondary hydroxyl group, and a carbonyl group, was treated in sub-CW and SCW (Table 2-3). Oxidation product benzil (**14**) and reduction product benzyl phenyl ketone (**15**) with small amounts of benzaldehyde (**8**), which can be derived from decomposition of **2**, **14**, and/or **15**, were obtained even at low temperatures (Entries 1 (300 °C) and 2 (340 °C)) and in a short reaction time (10 min), indicating that the reactions of **2** in sub-CW and SCW proceed more easily as compared to those of **1**. With an increase in the reaction temperature, conversion of **2** and yields of **14** and **15** became higher (Entries 1, 2, and 6) and then saturated at 380 °C (Entry 10). Prolonged reaction time improved conversion of **2** as well as yields of **14** and **15**, concomitant with small amounts of **1**, which should be derived from the benzil-benzilic acid rearrangement of **14**, followed by decarboxylation, as reported by Comisar et al,[11] and quite small amounts of benzophenone (**11**) and diphenylmethane (**12**) from **1**, as discussed in the reaction of **1**. Water density effect was also observed in this reaction. *In the absence of water* (Entry 7, pyrolysis), however, a high conversion of **2** (95%) and almost same total yield of the oxidation products (~29%, defined as the sum of **14**, **1**, **11**, and **12**) and reduction product **15** (30%) were obtained, which was quite similar to the results of the pyrolysis of alcohol **1** (Entry 11 in Table 2-1). With an increase in the water density, conversion of **2** as well as yields of **14** and **15** became lower (Entries 7–10 and 6), which suggested that disproportionation of **2** was suppressed by water in the reaction. Again, total yield of the oxidation products as defined above was always larger than

Table 2-3. Reaction of benzoin (**2**) in subcritical and supercritical water[a]



Entry	Temperature (°C)	Water density (g mL^{-1})[b]	Reaction time (min)	Conversion (%)	Product (%)					
					14	**15**	**8**	**1**	**11**	**12**
1	300	0.35[c]	10	42	8	2	1	<1	—[d]	—[d]
2	340	0.35[c]	10	47	15	5	2	2	—[d]	—[d]
3	380	0.35	0[e]	27	10	1	<1	<1	—[d]	—[d]
4	380	0.35	1	36	15	3	1	1	—[d]	—[d]
5	380	0.35	5	59	16	6	4	4	<1	<1
6	380	0.35	10	66	19	9	6	6	<1	<1
7	380	0	10	95	26	30	6	<1	<1	<1
8	380	0.05	10	81	19	16	12	<1	<1	<1
9	380	0.15	10	73	18	10	12	2	<1	<1
10	380	0.25	10	68	16	7	8	3	<1	<1
11	400	0.35	10	67	18	9	15	7	<1	<1

a) Reaction conditions: 0.236 mmol of **2**, water, under N_2 in the SUS 316 batch type tubular reactor.

b) Value of water density: water (g)/volume of the reactor.

c) Reaction medium was not homogeneous, because reaction temperature was under the critical temperature of water.

d) Not detected.

e) As soon as the temperature reached 380 °C, the reaction was quenched by rapid cooling of the reactor in ice water.

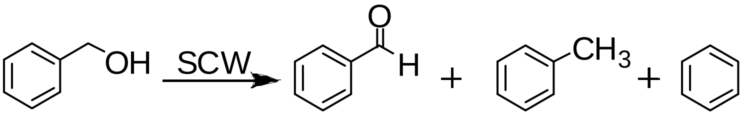
the yield of reduction product **15** in every reaction *in the presence of water*.

As a conclusion, the reactivity of **2** was higher than that of **1** in sub-CW and SCW. The temperature-dependence and time-dependence in the reaction of **2** in SCW were also observed. Alcohol **2** reacted more rapidly than alcohol **1** with an increase in reaction temperature up to 380 °C. Prolonged reaction time caused higher conversion of **2** and higher yields of products. The total yield of oxidation product **14** and its secondary products (**1**, **11**, and **12**) was always higher than that of reduction product **15** in the presence of water.

2-2-3 Reaction of benzyl alcohol (3) in supercritical water

The reaction behaviour of a primary alcohol, benzyl alcohol (**3**), in SCW, was compared to those of **1** and **2**. When alcohol **3** was treated in SCW under the conditions of 380–440 °C, 180 min, and 0.35 g mL^{-1} water density in the SUS 316 batch type tubular reactor, oxidation product benzaldehyde (**8**) and reduction product toluene (**16**) were obtained (Table 2-4). Lower conversion of **3** than that of benzhydrol (**1**) was observed under the similar reaction conditions, indicating lower reactivity of **3** than that of **1**. Benzene (**17**) was also obtained in the reaction, which should be generated by thermal decomposition of **8**.[12] Again, the total amount of

Table 2-4. Reaction of benzyl alcohol (**3**) in supercritical water[a)]



3 **8** **16** **17**

Entry	Temperature (°C)	Water density (g mL^{-1})[b)]	Reaction time (min)	Conversion (%)	Product (%)		
					8	**16**	**17**
1	380	0.35	180	9	5	<1	—[c)]
2	400	0.35	180	18	10	2	<1
3	420	0.35	180	26	14	5	1
4	440	0.35	180	40	21	10	8

a) Reaction conditions: 1.09 mmol of **3**, water, under N_2 in the SUS 316 batch type tubular reactor.

b) Value of water density: water (g)/volume of the reactor.

c) Not detected.

the oxidation products **8** and **17** in this reaction is always larger than that of the reduction product **16**.

2-3 Conclusions

The reaction behavior of secondary alcohols, benzhydrol (**1**) and its higher homologue benzoin (**2**), both of which have two benzene subunits, a secondary hydroxyl group, and no hydrogen atom on the β-position of the hydroxyl group in sub-CW and SCW in the absence of any oxidizing reagent or catalyst was demonstrated. Oxidation product benzophenone (**11**) and reduction product diphenylmethane (**12**) were produced in the reaction of **1**. In the absence of water, almost equal amounts of **11** and **12** were obtained, suggesting that disproportionation between two molecules of alcohol **1** occurred thermally. The yields of **11** were always higher than those of **12** in SCW under all conditions examined. Efficient oxidation of **1** was achieved to give 63% of **11** at 460 °C for 180 min in 0.35 g mL^{-1} water density in an SUS 316 reactor. Water played a key role in this reaction. The ratio of **11**:**12** always exceeded unity and rapidly increased with an increase in the water density and temperature. Evolution of hydrogen gas was confirmed in the reaction of **1** in SCW in a quartz tubular reactor. In the reaction of **2**, the total yield of oxidation product **14** and its secondary reaction products **1**, **11**, and **12** was also higher than that of reduction product **15** in the presence of water. The evolution of hydrogen gas, water density dependence of alcohol reaction, and larger amounts of oxidation products than those of reduction products in SCW indicate that the water-catalyzed hydrogen generation mechanism is the most favorable mechanism to explain the reaction behavior of alcohols in SCW.

2-4 Experimental Section

2-4-1 General

^{1}H NMR spectra were obtained on a Varian Unity Inova spectrometer operating 400 MHz. GC-MS analyses were performed on a Shimadzu GCMS-QP 5050. GC analyses were done on a Shimadzu GC-17A gas chromatograph with CBP-5 and/or DB-1 columns. Benzhydrol and benzyl alcohol were purchased from Nacalai Tesque Inc. and benzoin was purchased from Wako Pure Chemical Industries Ltd.

The reagents and reverse osmosis water, into which N_2 gas bubbled for 30 min to remove the dissolved oxygen, were introduced into an SUS 316 batch type tubular reactor (10 mL volume). The reactor was purged with N_2 for 10 min to remove the oxygen in the reactor and sealed with a screw cap, which was equipped with a thermocouple for measuring the inner reactor temperature. The reactor was then put in a molten salt bath, which was kept at an appropriate temperature, and heated for an appropriate time. It took about 20−30 s to raise the inner reactor temperature up to 300−460 °C. After the reaction, the reactor was placed into an ice water bath to quench the reaction. When the reactor was completely cooled down, the screw cap was opened. The reaction mixture was extracted 3 times with ethyl ether. The organic phase was separated and the solvent was evaporated in vacuo to give crude products. The crude products were purified by using silica gel chromatography (Wako C-200, ether and hexane) and GPC (JAI gel 1H and 2H, chloroform), if necessary. The products were identified using ^{1}H NMR and GC-MS by comparing the spectra with those of authentic samples. Conversions of the starting materials and yields of the products were determined using an internal standard method in the GC analysis. Heptadecane and dodecane were used as internal standards.

2-4-2 Reaction of benzhydrol (1) in quartz tubular reactor

To a quartz tubular reactor was introduced benzhydrol (**1**) (50 mg, 0.272 mmol) and water (0.34 mL). The quartz tubular reactor, which had an inner volume of 1 mL, was sealed with a flame under N_2. The sealed quartz reactor was inserted into the SUS 316 reactor, which was filled with 4 mL of water, and then the SUS 316 reactor was closed tightly. The SUS 316 reactor with the small quartz reactor inside was heated at a desired temperature by the method similar to that described above. Evolved gases were identified and quantified with GC.

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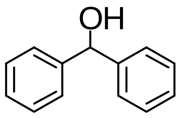
Chapter 3.

Non-Catalytic Oppenauer Oxidation of Alcohols under Solvent-Free Conditions and in Supercritical Water

3-1 Introduction

Recently, solvent-free reaction system has attracted much attention in organic reactions, since it is one of the most sustainable reaction systems.[1,2] Several reactions under solvent-free conditions have been reported, such as DMAP-catalyzed esterification,[3] Pd(0) catalyzed diamination of terminal olefins,[4] asymmetric catalyzed alkyl additions to ketones,[5] and asymmetric hetero-Diels-Alder reaction.[6] On the other hand, SCW has also been applied for some organic reactions as a green reaction medium, due to its quite unique properties as mentioned in chapter 1.

The Oppenauer oxidation is one of the highly selective oxidation methods of alcohols producing the corresponding aldehydes or ketones, which requires metal alkoxide as a catalyst.[7] Very recently, non-catalytic Meerwein-Ponndorf-Velery (MPV) reduction of ketones and aldehydes, which is the opposite reaction of the Oppenauer oxidation of alcohols, has been reported in supercritical alcohols.[8] In these reactions, ketones and aldehydes were reduced to alcohols without any catalyst in excess amounts of supercritical alcohols, such as methanol, 1-propanol, and 2-propanol, which acted as both reaction media and reductants. The very intriguing non-catalytic MPV reduction of aldehydes and ketones in supercritical alcohols indicates that non-catalytic Oppenauer oxidation of alcohols proceeds in the presence of carbonyl compounds as oxidants under the similar reaction conditions. Unfortunately, it would be a problem to expose carbonyl compounds to such high temperature and pressure because of the lability of carbonyl compounds under such drastic conditions. So far, little has been known about the non-catalytic Oppenauer oxidation of alcohols. In this chapter, the author investigates non-catalytic Oppenauer oxidation of alcohols, benzhydrol (**1**) and benzyl alcohol (**3**), by formaldehyde (**4**) as an oxidant and compares the results between under solvent-free conditions and in SCW.



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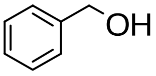

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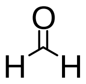


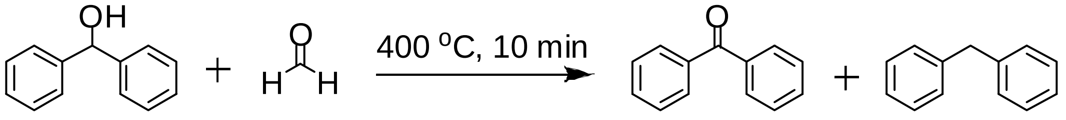
4

3-2 Results and Discussion

3-2-1 Non-catalytic Oppenauer oxidation of benzhydrol (1) under solvent-free conditions and in supercritical water

A secondary alcohol, benzhydrol (**1**), was treated with and without an oxidant, formaldehyde (**4**), under solvent-free conditions (0 g mL^{-1} water density, no water)

Table 3-1. Oxidation of benzhydrol (**1**) with and without formaldehyde (**4**) under solvent-free conditions and in supercritical water[a]



1 **4** **11** **12**

Entry	Mole Ratio of **1**:**4**	Water Density (g mL^{-1})[b]	Conversion of **1** (%)	Yield (%)	
				11	**12**
1	—[c]	0	46	17	19
2	—[c]	0.35	9	2	<1
3	1:1[d]	0	47	27	16
4	1:1	0.35	21	15	<1
5	1:5[d]	0	86	64	13
6	1:5	0.35	36	30	<1

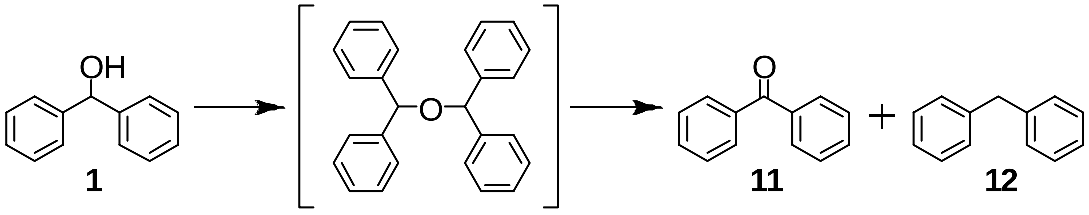
a) Reaction conditions: 0.54 mmol of **1** and different mole equivalent of **4** was treated in SCW (0.35 g mL^{-1} water density) and under solvent-free conditions under N_2 at 400 °C for 10 min in SUS 316 batch type tubular reactor.

b) Value of water density: water (g)/volume of the reactor.

c) No compound **4** was applied in the reaction.

d) 1,3,5-Trioxane (**7**), which affords **4** under the reaction conditions, was used instead of **4**. The mole ratio of **1**:**4** was calculated using the mole ratio of **1**:**7**.

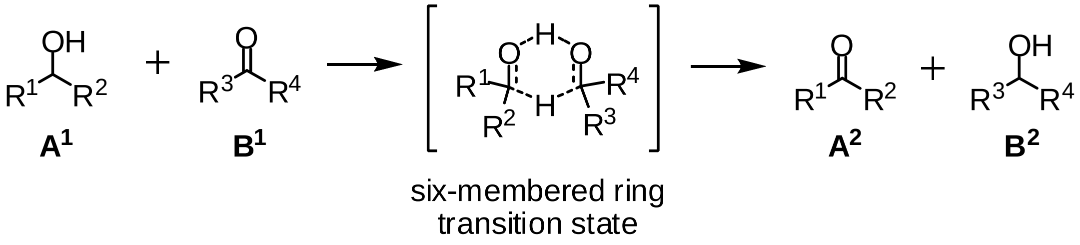
and in SCW (0.35 g mL^{-1} water density) at 400 °C for 10 min in the SUS 316 batch type tubular reactor (Table 3-1). Under solvent-free conditions, almost equal amounts of oxidation product, benzophenone (**11**), and reduction product, diphenylmethane (**12**), were obtained even in the absence of any oxidant (Entry 1), indicating disproportionation between two molecules of **1** took place thermally as mentioned in chapter 2 (Scheme 3-1). However, in the presence of 3.5 mL water, consumption as well as oxidation of **1** was suppressed to afford a very small amount of oxidation product **11** (yield: 2%) with almost no reduction product **12** in SCW (Entry 2). These observations indicate clearly that water suppressed the disproportionation of **1** leading to reduction product **12**. By using an equivalent amount of **4** to **1** as an oxidant, however, oxidation of **1** was accelerated to afford a satisfactory yield of oxidation product **11** (27%) even under the solvent-free conditions. In SCW, although conversion of **1** (21%) and yield of **11** (15%) became lower as compared to those under solvent-free conditions, almost no side reaction product **12** (<1%) was obtained which made the selectivity of oxidation product very high (Entry 4). More oxidant **4** (5 equivalent to **1**) caused more oxidation of **1** (conversions: 86%) to achieve a good yield of oxidation product **11** (yield: 64%),



Scheme 3-1. Proposed disproportionation mechanism.

while a small amount of reduction product **12** (yield: 13%) was still observed under solvent-free conditions (Entry 5). Again, the conversion of **1** (36%) as well as yield of **11** (30%) decreased in SCW with almost no reduction product **12** (<1%) (Entry 6). Water played a crucial role in suppressing the formation of side reaction product **12** for the highly selective Oppenauer oxidation of **1**. In addition, oxidation of **1** was also suppressed in SCW as compared to that under solvent-free conditions. These results can be explained as follows: the proposed six-membered ring transition state consisting of one alcohol molecule and a ketone or aldehyde molecule for the Oppenauer oxidation (Scheme 3-2)[9] should be broken by water in SCW.

In chapter 2, the author discussed non-catalytic oxidation of **1** in SCW. It took as much as 3 h to oxidize alcohol **1** in SCW at a higher temperature 460 °C and 0.35 g mL^{-1} water density to reach 63% yield of oxidation product **11** and 10% yield of reduction product **12**. Here, similar yields of **11** (64%) and **12** (13%) were achieved under the solvent-free conditions (Entry 5). In SCW, although the yield of **11** (30%) were not high enough as compare to that under solvent-free conditions, effective suppression of reduction product **12** led to a very high selectivity for oxidation in a



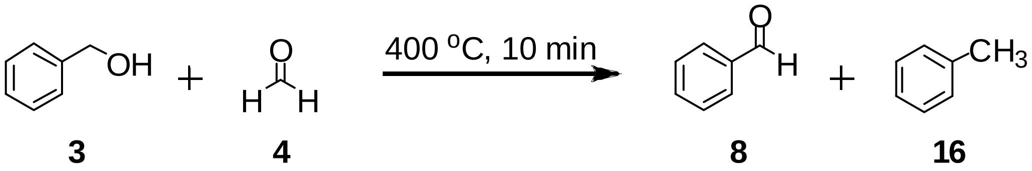
Scheme 3-2. Proposed six-membered ring transitions of non-catalytic Oppenauer oxidation.

very shorter reaction time (10 min) at a lower temperature 400 °C as compared to those in chapter 2 (Entry 6). Judging from these results, it is now very clear that non-catalytic Oppenauer oxidation of alcohols in SCW is a good method for oxidation of alcohols and water is essential for highly selective Oppenauer oxidation of alcohols.

3-2-2 Non-catalytic Oppenauer oxidation of benzyl alcohol (3) under solvent-free conditions and in supercritical water

A primary alcohol, benzyl alcohol (**3**), was treated with and without **4** under solvent-free conditions (0 g mL^{-1} water density) and in SCW (0.35 g mL^{-1} water density) in the SUS 316 batch type tubular reactor at 400 °C for 10 min without any

Table 3-2. Oxidation of benzyl alcohol (**3**) with and without formaldehyde (**4**) under solvent-free conditions and in supercritical water[a)]



Entry	Mole Ratio of **3**:**4**	Water Density (g mL^{-1})[b)]	Conversion of **3** (%)	Yield (%) **8**	Yield (%) **16**
1	—[c)]	0	32	13	9
2	—[c)]	0.35	<1	<1	0
3	1:1[d)]	0	57	41	7
4	1:1	0.35	35	37	<1
5	1:5[d)]	0	94	95	2
6	1:5	0.35	66	66	<1

a) Reaction conditions: 0.926 mmol of **3** and different mole equivalent of **4** were treated in SCW (0.35 g mL^{-1} water density) and under solvent-free conditions under N_2 at 400 °C for 10 min in SUS 316 batch type tubular reactor.

b) Value of water density: water (g)/volume of the reactor.

c) No compound **4** was added in the reaction.

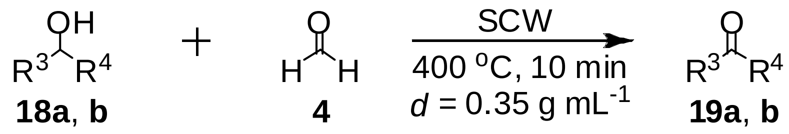
d) 1,3,5-Trioxane (**7**), which affords **4** under the reaction conditions, was used instead of **4**. The mole ratio of **3**:**4** was calculated using the mole ratio of **3**:**7**.

catalyst to know the possibility of non-catalytic Oppenauer oxidation method for oxidation of primary alcohol (Table 3-2). Under solvent-free conditions, reaction of **3** afforded similar amounts of oxidation product **8** (13%) and reduction product **16** (9%, Entry 1). Water suppressed the consumption of **3** (<1%) and almost no product was observed except for a trace amount of oxidation product **8** (<1%) (Entry 2). The yield of oxidation product **8** (41%) was improved more than 3 times by using an equivalent amount of **4** as an oxidant under the solvent-free conditions (Entry 3) as compared to that in the absence of **4** (Entry 1), while a small amount of reduction product **16** (7%) was also observed under solvent-free conditions (Entry 3). On the other hand, oxidation of alcohol **3** was suppressed slightly, but almost no reduction product **16** was observed in SCW (Entry 4) as compared to that under the solvent-free conditions (Entry 3). More oxidant **4** (5 equivalent to **3**) caused not only a higher conversion of **3** but also a higher yield of oxidation product **8** (95%) under the solvent-free conditions, while a small amount of reduction product **8** (2%) was still observed (Entry 5). When water (0.35 g mL^{-1} water density) was introduced in this reaction, oxidation of alcohol **3** was also suppressed slightly to afford **8** in a good yield of 66% in SCW. However, it is quite notable that the side reaction leading to reduction product **16** was almost completely suppressed (<1%) to show quite high oxidation selectivity (Entry 6).

3-2-3 Non-catalytic Oppenauer oxidation of 1-butanol (18a) and 2-butanol (18b) in supercritical water

A simple primary alcohol 1-butanol (**18a**) and a simple secondary alcohol 2-butanol (**18b**) were also treated with and without **4** in SCW under the conditions of 400 °C, 10 min, and 0.35 g mL^{-1} water density (Table 3-3). In the absence of **4**,

Table 3-3. Oxidation of 1-butanol (**18a**) and 2-butanol (**18b**) with and without **4** in supercritical water[a)]



a: $R^3 = CH_3CH_2CH_2$, $R^4 = H$
b: $R^3 = CH_3CH_2$, $R^4 = CH_3$

Entry	Alcohol	Mole Ratio of **18**:**4**	Conversion of **18** (%)	Yield of **19** (%)
1	**18a**	—[b)]	17	—[c)]
2	**18a**	1:5	65	30
3	**18b**	—[b)]	27	—[c)]
4	**18b**	1:5	83	26

a) Reaction conditions: 1.35 mmol of **18a** or **18b** with and without 6.75 mmol of **4** was treated in SCW (0.35 g mL^{-1} water density) or under solvent-free conditions under N_2 at 400 °C for 10 min in the SUS 316 batch type tubular reactor. Value of water density: water (g)/volume of the reactor.

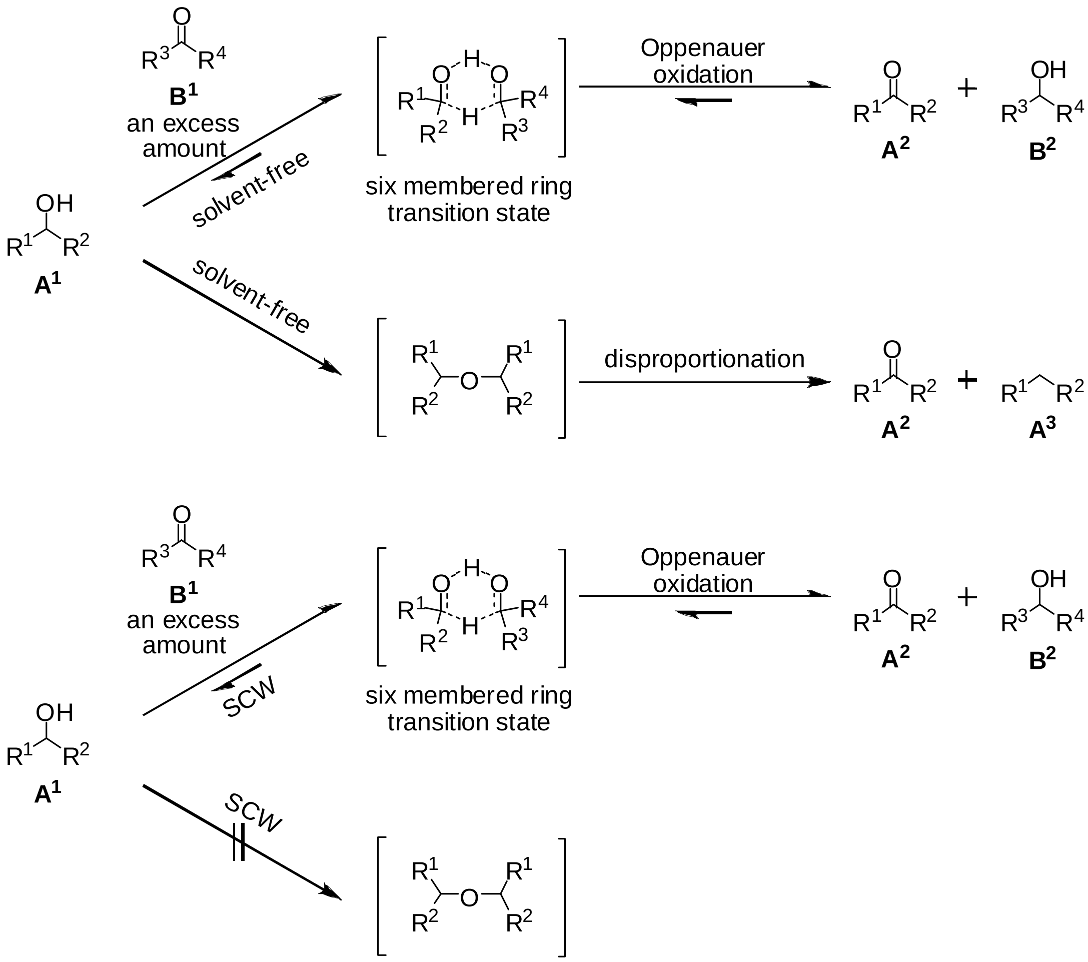
b) No compound **4** was applied in the reaction.

c) No compound **19** was observed.

alcohol **18a** was consumed in 17% conversion, but no oxidation product **19a** was observed (Entry 1). However, in the presence of an excess amount of **4** (5 equivalent to **18a**), the conversion of **18a** (65%) and yield of **19a** (30%) were greatly improved (Entry 2). Similar results to the reaction of **18a** were obtained in the oxidation of alcohol **18b** (Entries 3 and 4). No oxidation product **19b** was observed in the absence of **4**, though 27% alcohol **18b** was consumed (Entry 3). In the presence of an excess amount of **4** (5 equivalent to **18b**), conversion of **18b** (83%) as well as yield of **19b** (26%) increased (Entry 4).

3-2-4 Plausible reaction pathway

Combining the results of the reactions of alcohols, **1** and **3**, with and without **4** as an oxidant under solvent-free conditions and in SCW, the author proposed two plausible reaction pathways. One is the Oppenauer oxidation pathway consisting of a six-membered ring transition state[8] and the other is the disproportionation



Scheme 3-3. Plausible reaction pathways of the oxidation of alcohols under solvent-free conditions (upper) and in supercritical water (lower).

pathway which was mentioned in chapter 2 (Scheme 3-3).

Under solvent-free conditions, Oppenauer reaction, which proceeds via the reaction pathway consisting of a six-membered ring transition state, should be an equilibrium reaction and more oxidant shifts the equilibrium to the direction of formations of $\mathbf{A}^2$ and $\mathbf{B}^2$. Disproprtionation of the ether intermediate also gives the same amounts of oxidation product $\mathbf{A}^2$ and reduction product $\mathbf{A}^3$ as mentioned in chapter 2, simultaneously. However, the ether would not be stable in SCW, since the ether will be hydrolyzed easily to reproduce two molecules of $\mathbf{A}^1$ under such drastic reaction conditions of SCW, which leads to high selectivity of $\mathbf{A}^2$. In addition, SCW also prevents $\mathbf{A}^1$ and $\mathbf{B}^1$ from constructing the six-membered ring Oppenauer oxidation transition state and thus the reaction leading to $\mathbf{A}^2$ is slightly suppressed.

3-3 Conclusions

A new oxidation method of alcohols, non-catalytic Oppenauer oxidation utilizing a carbonyl compound, formaldehyde (**4**), as an oxidant, was successfully applied in the oxidation of alcohols, such as benzhydrol (**1**) and benzyl alcohol (**3**), and simple aliphatic alcohols, such as 1-butanol (**18a**) and 2-butanol (**18b**), in SCW and the results were compared to those under the solvent-free conditions. Water was essential for the highly selective non-catalytic Oppenauer oxidations of alcohols, **1** and **3**, which produced almost pure oxidation products, benzophenone (**11**) and benzaldehyde (**8**), respectively. Under the solvent-free conditions, Oppenauer oxidation and disproportionation of **1** and **3** took place simultaneously to afford oxidation products **11** and **8** in good yields (64% and 95%, respectively) concomitant with small amounts of reduction products **12** (13%) and **16** (2%), respectively, at 400 °C for 10 min. Although yields of oxidation products **11** (30%) and **8** (66%) were lowered as compared to the results under solvent-free conditions, the formations of reduction products **12** (<1%) and **16** (<1%) were almost completely suppressed in SCW under the conditions of 400 °C for 10 min in 0.35g mL^{-1} water density.

3-4 Experimental Section

Benzhydrol, benzyl alcohol, formaldehyde solution, and 1,3,5-trioxane were purchased from Nacalai Tesque Inc., and 1-butanol and 2-butanol were purchased from Wako Pure Chemical Industries Ltd.

Similar procedures were applied as mentioned in chapter 2.

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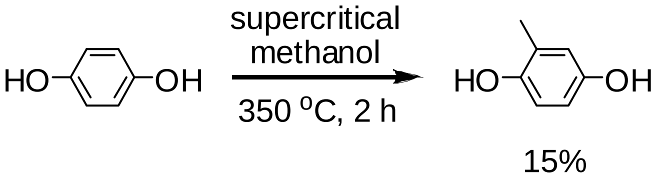
9 The six-membered ring transition state has been proposed in the non-catalytic MPV reduction, which is the opposite reaction of Oppenauer oxidation.[8]

Chapter 4.

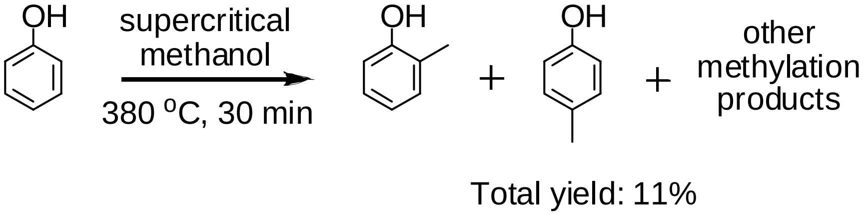
A Simple Permethylation Method of Catechol Derivatives in Subcritical and Supercritical Water

4-1 Introduction

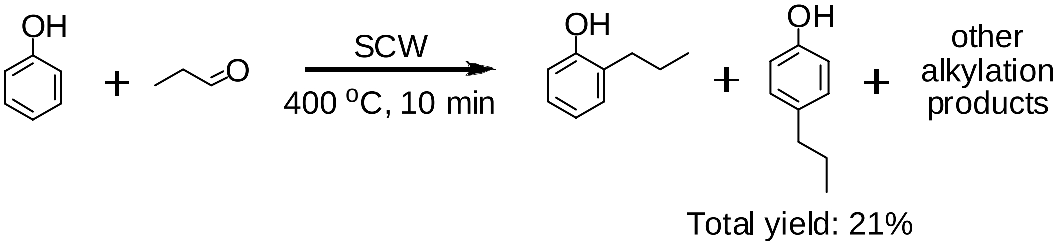
Alkylation of catechol derivatives is an important process in organic synthesis, since many alkyl catechol derivatives are important industrial intermediates.[1] A typical alkylation method of catechol derivatives is the Friedel-Crafts process using strong acid catalysts, such as protic acids (HF and H_3PO_4), Lewis acids ($AlCl_3$ and BF_3), and solid acids (metal oxides and zeolites).[2] Among them, methylation is one of the most important processes, because methyl catechol derivatives, such as 3-methylcatechol, 4-methylcatechol, and 2,3,5-trimethylhydroquinone, are widely applied in the syntheses of agricultural chemicals and pharmaceuticals as intermediates.[1] In the methylation of catechol derivatives, permethylation is a relatively difficult process. In order to produce the permethylated catechol, several steps are required generally even in the presence of catalyst.[3] Little has been reported on non-catalytic permethylation of catechol derivatives. Recently, non-catalytic methylation of hydroquinone in supercritical methanol, has been reported, while only a mono-methylation product, 2-methylhydroquinone (15%), was obtained even in the presence of an excess amount of methanol at 350 °C in 2 h (Scheme 4-1).[4] In addition, non-catalytic methylation of phenol derivatives in supercritical methanol (Scheme 4-2)[5] and non-catalytic alkylation of phenol using propionaldehyde in SCW have been reported (Scheme 4-3).[6] In these two reactions, the alkylation of phenol using aldehyde in SCW takes a shorter reaction time (10 min) and affords a higher total yield of alkylation products (21%) than the methylation of phenol in supercritical methanol (11% in 30 min),[4] suggesting mathylation using formaldehyde in SCW is more effective than that using



Scheme 4-1. Non-catalytic methylation of hydroquinone in supercritical methanol.



Scheme 4-2. Non-catalytic methylation of phenol in supercritical methanol.



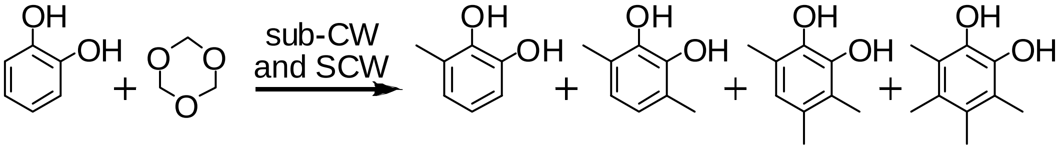
Scheme 4-3. Non-catalytic alkylation of phenol with propoinaldehyde in supercritical water.

supercritical methanol. In this chapter, the author investigates non-catalytic permethylation of catechol derivatives with 1,3,5-trioxane (**7**)[7] in sub-CW and SCW.

4-2 Results and Discussions

4-2-1 Non-catalytic permethylation of catechol (5) and 4-methylcatechol (6) in subcritical and supercritical water

As a preliminary experiment, catechol (**5**) was treated with an excess amount of 1,3,5-trioxane (**7**) (3.3 equivalent to **5**) in sub-CW and SCW without any catalyst in the SUS 316 batch type tubular reactor (Scheme 4-4). Compound **5** was consumed completely and permethylation product 3,4,5,6-tetramethylcatechol (**23**, 5%) was obtained as an almost sole product with a trace amount of 3,4,6-trimethylcatechol (**22**, <1%) at a lower temperature of 350 °C for 10 min in 3.5 mL water. At a higher temperature of 400 °C, a slightly smaller amount of permethylation product **23** (3%) concomitant with 3,6-dimethylcatechol (**21**, <1%) and **22** (3%) was also obtained under the conditions of 10 min and 0.35 g mL^{-1} water density. In the absence of water, **23** was not obtained at all but **20** (3%), **21** (3%), and **22** (2%) were obtained under the conditions of 400 °C and 10 min.[8] Thus, permethylation of catechol (**5**) was performed in sub-CW and SCW without any



5 **7** **20** **21** **22** **23**

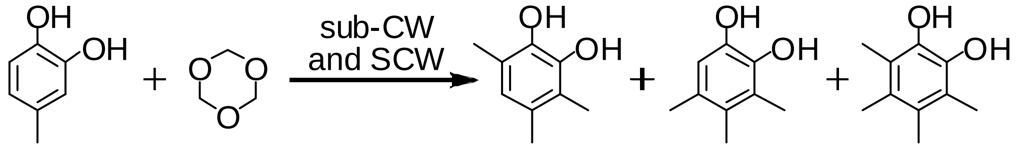
Scheme 4-4. Reaction of catechol (**5**) and 1,3,5-trioxane (**7**) in subcritical and supercritical water.

catalyst, while the yield of permethylation product was not satisfactory. The low yield of the permethylation product **23** in this reaction could be ascribed to the low stability of **5**, which hinders the author from knowing the potential of the non-catalytic permethylation of catechol derivatives in sub-CW and SCW. Other substrates with higher stability should be considered.

A catechol derivative, 4-methylcatechol (**6**), which has higher stability than **5**, was selected as another candidate to investigate the non-catalytic permethylation of catechols. When **6** was treated with an excess amount of **7** (3.3 equivalent to **6**) in sub-CW and SCW, dimethylation products **22** and 4,5,6-trimethylcatechol (**24**) and permethylation product **23** were obtained, as expected (Table 4-1).[9] Temperature dependence was examined under the conditions of fixed reaction time (10 min) and fixed water density (0.35 g mL^{-1}). At a lower temperature (300 °C), only permethylation product **23** was obtained in a very low yield (3%) with complete consumption of **6** (Entry 1). With an increase of the reaction temperature, the yield of permethylation product **23** as well as **22** and **24** increased (Entries 2–4) and the highest yield of **23** (13%) was achieved at 400 °C (Entry 4). Concerning the reaction time, longer reaction time improved the yield of **23** as well as the yields of **22** and **24** and the yields of products saturated in 10 min under the conditions of 380 °C and 0.35 g mL^{-1} water density (Entries 5, 3, and 6). Permethylation product **23** was obtained under all the conditions in sub-CW and SCW (Entries 1–6).

Water effect in the permethylation of **6** was investigated by varying the water density at 400 °C for 10 min. In the absence of water, reaction afforded **22** mainly with very small amounts of **24** and permethylation product **23** (Entry 7). With an increase of water density, however, the yield of permethylation product **23** increased (Entries 7, 8, and 3), and then the yield of **23** saturated at 0.35 g mL^{-1} water density (Entries 3 and 9). In addition, water densities did not influence the yield of **22**. Thus, water accelerated methylation of **6** to produce permethylation product **23**.

Table 4-1. Reaction of 4-methylcatechol (**6**) and 1,3,5-trioxane (**7**) in subcritical and supercritical water.[a]



6 **7** **22** **24** **23**

Entry	Temperature (°C)	Time (min)	Water Density (g mL^{-1})[b]	Conversion of **6** (%)	Yield (%)		
					22	**24**	**23**
1	300	10	0.35[c]	100	0	0	3
2	350	10	0.35[c]	100	<1	0	9
3[d]	380	10	0.35	100	5	1	11
4[d]	400	10	0.35	100	10	2	13
5[d]	380	1	0.35	100	2	0	3
6[d]	380	30	0.35	100	6	2	12
7[d]	400	10	0	100	9	2	2
8[d]	400	10	0.2	100	10	2	7
9[d]	400	10	0.4	100	9	2	12

a) Reaction conditions: 0.81 mmol of **6**, 2.45 mmol of **7**, and water, under N_2 in SUS 316 tubular reactor.

b) Value of water density: water (g)/volume of the reactor

c) The value of water density of subcritical water is an average, because the reaction medium was not homogeneous under subcritical conditions.

d) Quite small amounts of 3,5-dimethylcatechol, 3,4-dimethylcatechol, and 4,5-dimethylcatechol were also observed in this reaction under the reaction conditions.

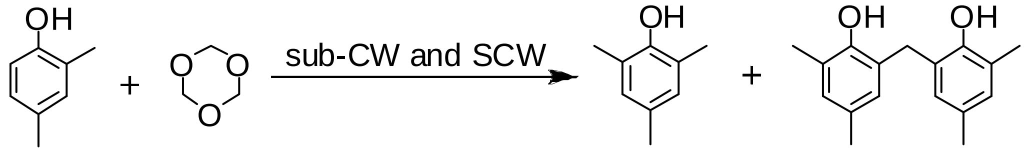
In order to compare the methylation ability using **7** to that using methanol in SCW, compound **6** was treated with an excess amount of methanol (10 equivalent to **6**) instead of **7** in sub-CW (3.5 mL of water at 350 °C for 10 min) and in SCW (0.35 g mL^{-1} water density at 400 °C for 10 min). As results, conversions of **6** were less than 1% and no product was obtained in both reactions. It is clear that permethylation of catechol derivatives by **7** is better than that by methanol both in sub-CW and SCW. As a conclusion, the yield of permethylation product **23** was not excellent, while the utilization of a formaldehyde equivalent as a source of methyl groups in sub-CW and SCW is quite a simple and easy method for permethylation of catechol derivatives.

4-2-2 Reaction pathway investigation

4-2-2-1 *Ortho*-methylation of 2,4-xylenol (25) and *para*-methylation of 2,6-xylenol (26) in subcritical and supercritical water

Methylation reaction pathways of catechol derivatives were investigated by treating phenol derivatives, 2,4-xylenol (**25**) and 2,6-xylenol (**26**), with an excess amount of **7** (3.3 equivalent to **25** or **26**) in sub-CW and SCW, since they have only

Table 4-2. Reaction of 2,4-xylenol (**25**) and 1,3,5-trioxane (**7**) in subcritical and supercritical water.$^{a)}$



25 **7** **27** **28**

Entry	Temperature (°C)	Time (min)	Water Density (g mL^{-1})$^{b)}$	Conversion of **25** (%)	Yield (%)	
					27	**28**
1	300	10	0.35$^{c)}$	>99	5	20
2	400	10	0.35	88	31	1
3	420	10	0.35	86	30	0
4	400	0$^{d)}$	0.35	58	2	31
5	400	1	0.35	86	10	26
6	400	20	0.35	91	30	0
7	400	10	0	57	17	2
8	400	10	0.45	93	32	0

a) Reaction conditions: 0.82 mmol of **25**, 2.48 mmol of **7**, and water, under N_2 in SUS 316 tubular reactor.

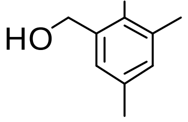
b) Value of water density: water (g)/volume of the reactor.

c) The value of water density of subcritical water is an average, because the reaction medium was not homogeneous under subcritical conditions.

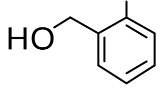
d) As soon as the temperature reached 400 °C, the reaction was quenched by rapid cooling of the reactor in ice-water.

one *ortho*- or *para*-position of hydroxyl group to be substituted on benzene ring.

In the reaction of **25** (Table 4-2), almost complete consumption of **25** was observed, while a small amount of methylation product, 2,4,6-trimethylphenol (**27**) and a considerable amount of bisphenol derivative, 6,6’-methylenebis(2,4-dimethyl -phenol) (**28**), were obtained at a lower temperature 300 ˚C (Entry 1). With an increase of temperature, conversion of **25** and yield of **28** became lower, while the yield of methylation product **27** increased and then saturated at a higher temperature 400 °C (Entries 2 and 3). Concerning the reaction time, prolonged reaction time improved the conversion of **25** as well as yield of methylation product **27** and suppressed the formation of side reaction product **28** (Entries 4, 5, 2, and 6). These results indicate that decomposition of **28** affords **27** and **25** at high temperatures in longer reaction times. In addition, a new product 2-(hydroxymethyl)-4,6-dimethylphenol (**29**) was obtained at very beginning of the reaction (Entry 4), which should be a precursor of **27**. Actually, when salicylalchol (**30**), a homologue of **29**, was treated in SCW instead of **29** under the conditions of 400 ˚C, 10 min, and 0.35 g mL^{-1} water density, reduction of **30** took place to produce *ortho*-methylphenol and phenol in 4 and 14% yields, respectively, as expected,



29

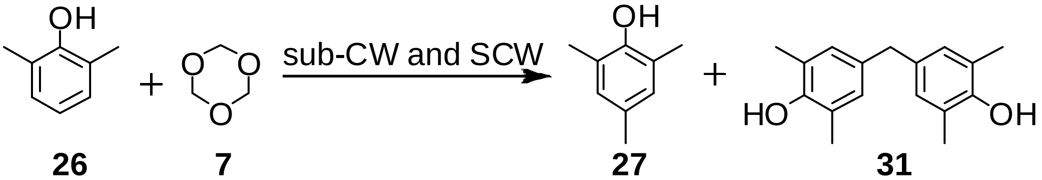


30

indicating that compound **29** is a precursor of **27** in SCW. On the other hand, water effect was examined by changing the water density at 400 °C for 10 min. In the absence of water, *ortho*-methylation of **25** occurred and a small amount of **27** with a very small amount of **28** was obtained (Entry 7). With an increase of water density, the yield of methylation product **27** increased and saturated in 0.35 g mL^{-1} water density (Entries 7, 2, and 8). The *ortho*-methylation proceeded even without water, though water promoted the *ortho*-methylation.

Next, in the reaction of **26**, *para*-methylation proceeded and methylation product **27** and a bisphenol derivative, 4,4'-dihydroxy-3,3',5,5'-tetramethyldiphenylmethane (**31**), were obtained (Table 4-3). Higher temperatures (Entries 1 and 2) and longer reaction times (Entries 3, 2, 4, and 5) improved the yield of **27** and suppressed the consumption of **26** as well as the formation of **30**. These results indicate that **30** decomposes to same amounts of **26** and **27** under the reaction conditions. Actually, when compound **31** was treated in SCW under the conditions of 420 °C, 30 min, and 0.35 g mL^{-1} water density, **31** was not recovered and similar amounts of **26** (yield: 37%) and **27** (yield: 26%) were obtained, which indicates that compound **31** is a precursor of the methylation product **27** at a high temperature such as 420 °C. Water effect was also examined in this reaction. Water played a key role for the formation of *para*-methylation product **27** (Entries 6, 7, 2, and 8). In the absence of water, almost no *para*-methylation product **27** was obtained. Water promoted the *para*-methylation of **26** to afford *para*-methylation product **27** (Entries 6, 7, 2, and 8).

Table 4-3. Reaction of 2,6-xylenol (**26**) and 1,3,5-trioxane (**7**) in subcritical and supercritical water.a)



Entry	Temperature (°C)	Time (min)	Water Density (g mL^{-1})b)	Conversion of **26** (%)	Yield (%)	
					27	**31**
1	350	10	0.35c)	69	7	18
2	420	10	0.35	52	12	4
3	420	1	0.35	44	4	12
4	420	30	0.35	43	10	0
5	420	60	0.35	45	13	0
6	420	10	0	28	<1	0
7	420	10	0.1	27	2	0
8	420	10	0.4	47	11	1

a) Reaction conditions: 0.82 mmol of **26**, 2.48 mmol of **7**, and water, under N_2 in SUS 316 tubular reactor.

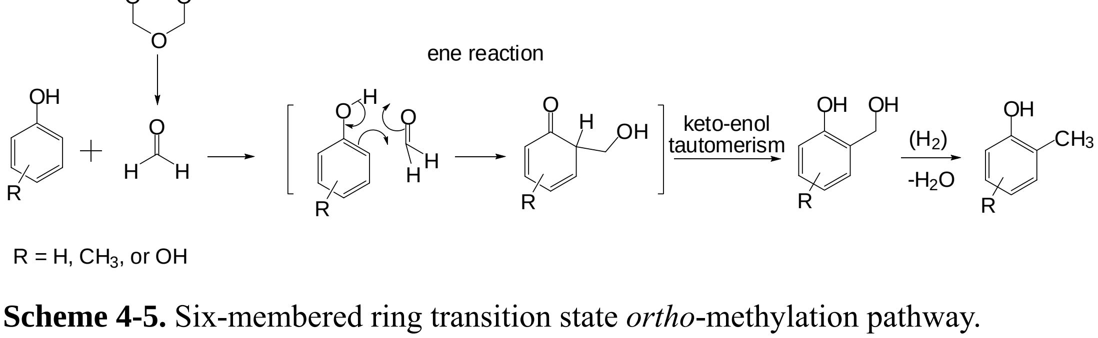
b) Value of water density: water (g)/volume of the reactor.

c) The value of water density of subcritical water is an average, because the reaction medium was not homogeneous under subcritical conditions.

4-2-2-2 Plausible reaction pathways of methylation of phenol derivatives

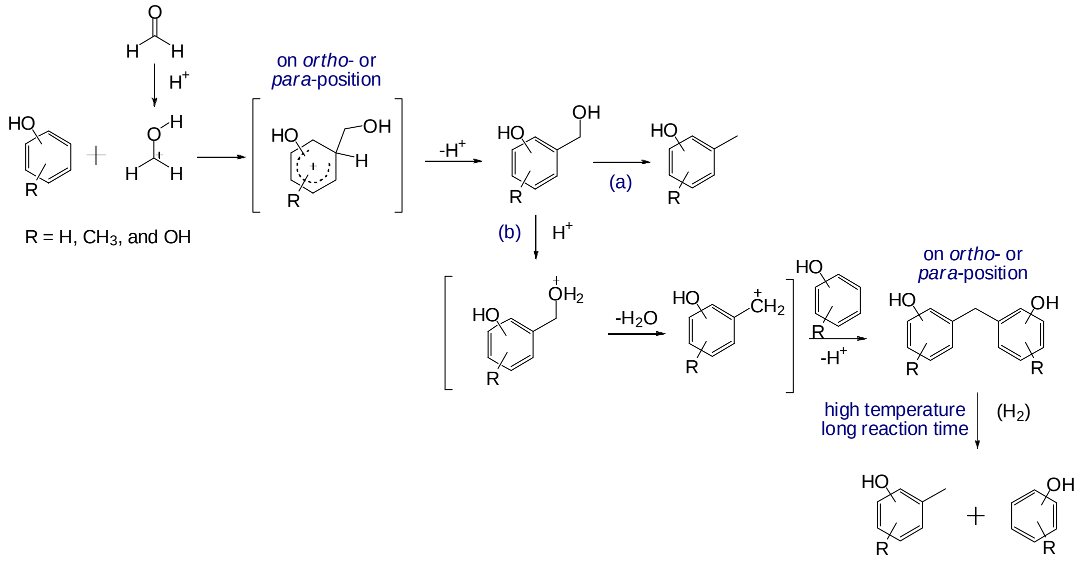
The fact that *ortho*-methylation of phenol derivatives is more favorable than *para*-methylation in the absence of water indicates that *ortho*-methylation of phenol derivatives proceeds via the proposed six-members ring transition state (Scheme 4-5).[10] In this reaction pathway, an ene reaction of phenol derivative and formaldehyde, which is generated from **7**,[7] followed by keto-enol tautomerism leads to *ortho*-hydromethylation of phenol derivertives. Reduction of the *ortho*-hydromethylphenol would afford *ortho*-methylation products.

On the other hand, the facts that water promotes *ortho*-methylation and is a trigger for the *para*-methylation of phenol derivatives indicate that another water supported H^+ catalyzed methylation occurs in sub-CW and SCW (Scheme 4-6). In this reaction pathway, formaldehyde and H^+ produce a hydroxymethyl cation. Both *ortho*- and *para*-electrofilic substitutions by the cation would be plausible. *Ortho*- and *para*-methylphenol derivatives are afforded via pathway (a). At the same time, the hydroxymethylphenol with H^+ also forms the *ortho*- or *para*-hydroxymethylphenol cations via pathway (b). After the dehydration, the



Scheme 4-5. Six-membered ring transition state *ortho*-methylation pathway.

resulting methylphenol cations attack on the *ortho*- or *para*-position of hydroxyl group of another phenol derivative to afford bisphenol derivatives in sub-CW or SCW. At high temperature, the bisphenol derivatives decompose to same amounts of methylation product and starting material.



Scheme 4-6. Plausible reaction pathway of methylation of phenol derivatives in subcritical and supercritical water.

4-3 Conclusions

Non-catalytic permethylation of catechol (**5**) and 4-methylcatechol (**6**) was successfully performed by use of 1,3,5-trioxane (**7**) in sub-CW and SCW. The formation of permethylation product, 3,4,5,6-tetramethylcatechol (**23**), was observed in both reactions of **5** and **6** and almost only permethylation product **23** was obtained in these two reactions at 350 °C for 10 min in 3.5 mL water in the SUS 316 batch type tubular reactor. Reaction temperature-dependence and time-dependence were observed in the reaction of **6**. Higher temperature and longer reaction time caused higher yield of permethylation product 3,4,5,6-tetramethylcatechol (**23**) as well as higher yields of other methylation products, 3,4,6-trimethylcatechol (**24**) and 3,4,5-trimethylcatechol (**22**). Water density dependence of the permethylation of **6** was observed. In the absence of water, only a small amount of permethylation product **23** (4%) was obtained at 380 °C for 10 min. However, water improved the formation of permethylation product **23** in 11% and 13% yields at 380 and 400 °C, respectively, under the conditions of 10 min, and 0.35 g mL^{-1} water density. Reaction pathways of methyaltion of catechol derivatives were investigated by using methylation of phenol derivatives, 2,4-xylenol (**25**) and 2,6-xylenol (**26**), which made the methylation simple. Two proposed reaction pathways, six-membered ring transition state *ortho*-methylation and H^+ catalyzed *ortho*- and *para*-methylation of phenol derivatives, would be favorable for the permethylation of catechol derivatives.

4-4 Experimental Section

4-4-1 General

Catechol, 4-methylcatechol, and 1,3,5-trioxane were purchased from Nacalai Tesque Inc., and 2,4-xylenol, 2,6-xylenol, and salicylalchol were purchased from Wako Pure Chemical Industries Ltd.

Similar general experimental methods were applied as mentioned in chapter 2.

4-4-2 NMR and GCMS analysis

3,4,6-Trimethylcatehcol (22): ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.50 (s, 1H), 5.10 (s, 1H), 4.75 (s, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.82, 139.43, 128.81, 122.86, 120.40, 120.09, 19.36, 15.21, 11.65. MS (EI) *m/z* 152 (M$^+$).

3,4,5,6-Tetramethylcatechol (23): ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.94 (s, 2H), 2.16 (s, 6H), 2.13 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.57, 127.09, 119.82, 15.78, 12.26. MS (EI) *m/z* 166 (M$^+$).

3,4,5-trimethylcatehcol (24): ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.53 (s, 1H), 5.00 (s, 1H), 4.88 (s, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 140.27, 139.94, 127.95, 123.17, 121.78, 113.95, 20.10, 15.19, 12.19. MS (EI) *m/z* 152 (M$^+$).

6,6'-Methylenebis(2,4-dimethyl-phenol) (28): ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.93 (s, 2H), 6.79 (s, 2H), 6.05 (s, 2H), 3.84 (s, 2H), 2.22 (s, 6H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.04, 130.28, 130.19, 129.03, 126.40, 124.06, 31.39, 20.71, 16.25. MS (EI) *m/z* 256 (M$^+$).

2-(Hydroxymethyl)-4,6-dimethylphenol (29): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.17 (s, 1H), 6.90 (s, 1H), 6.67 (s, 1H), 4.80 (d, J = 5.2, 2H), 2.22 (s, 6H), 2.17 (t, J = 5.6, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 151.94, 131.37, 128.68, 125.81, 125.10, 123.73, 64.84, 20.31, 15.54. MS (EI) *m/z* 152 (M$^+$).

4,4'-Dihydroxy-3,3',5,5'-tetramethyldiphenylmethane (31): ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.77 (s, 4H), 4.45 (s, 2H), 3.68 (s, 2H), 2.18 (s, 12H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 150.32, 133.39, 128.84, 122.84, 40.26, 15.92. MS (EI) *m/z*

256 (M^+).

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7 1,3,5-Trioxane (**7**) was selected instead of formaldehyde water solution as a reagent to avoid the potential influence of methanol which was added to the solution as a stabilizer.

8 Other methylation products, 4-methylcatechol (**6**), 3,5-dimethylcatechol, 3,4-dimethylcatechol, and 3,4,5-trimethylcatechol, were also observed in the reaction of catechol (**5**) with 1,3,5-trioxane (**7**) under the reaction conditions, while the yields of these methylation products were very low (<1%).

9 Several other methylation products such as 3,5-dimethylcatechol, 3,4-dimethylcatechol, and 4,5-dimethylcatechol were also observed in the reaction of 4-methylcatechol (**6**) with 1,3,5-trioxane (**7**) under the reaction conditions, while the yields of these methylation products were very low (<1%).

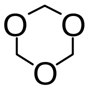
10 T. Sato, G. Sekiguchi, T. Adschiri, R. L. Smith Jr., and K. Arai, *Green Chemistry*, **2002**, *4*, 449.

Chapter 5.

Subcritical Water Assisted Clean Cross-Aldol Reactions

5-1 Introduction

Recently, much attention has been paid to organic reactions under the solvent-free conditions in organic synthesis, because solvent-free system is one of the most sustainable reaction systems.[1] Several methods, such as mechanical mixing, grinding, milling, sonication, and super-vibration, have been applied to accelerate the reactions under solvent-free conditions.[2] Heating is also suitable to accelerate the reactions, though the considerable decomposition of not only starting materials but also reaction products sometimes occurs due to its high temperature.[3] On the other hand, water is one of the quite limited media, which can be utilized under the extreme conditions, such as high-temperature (for example: >250 °C), high-pressure, and oxidative atmosphere, without decomposition. Recently, SCW (>374 °C, >22.1 MPa) has been applied for a green reaction system as a reaction medium. Several quite unique reactions have been performed in SCW, which have been mentioned in chapter 1. However, considerable decomposition of substrates and products also occurred in SCW, due to the high temperature. Meanwhile, sub-CW has a lower temperature (200–374 °C) than SCW. If sub-CW is adopted in the organic reactions as a solvent instead of SCW, it is easily anticipated to suppress the decomposition of organic compounds, because of its lower temperature than that of SCW. In this chapter, the author investigates the sub-CW assisted clean cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**)[4] in the presence of an inorganic additive, ZnCl$_2$.[5]



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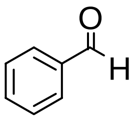

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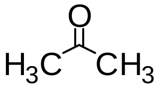

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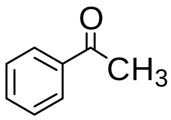

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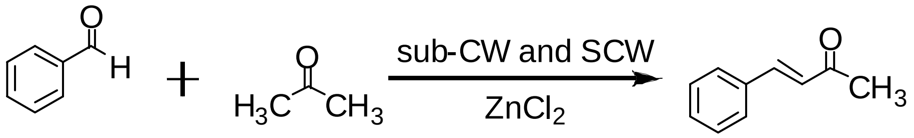
5-2 Results and Discussion

5-2-1 Clean cross-aldol reaction of benzaldehyde (8) and acetone (9)

A mixture of benzaldehyde (**8**) and an excess amount of acetone (**9**) (4 equivalent to **8**) was treated with and without $ZnCl_2$ under the conditions of various reaction temperatures for 20 min in the SUS 316 batch type tubular reactor (Table 1). When compound **8** and **9** were heated at a low temperature of 100 °C in the absence of $ZnCl_2$ under the solvent-free conditions, a small amount of **8** was consumed, while no desired cross-aldol reaction product benzalacetone (**32**) was obtained at all (Entry 1). However, a small amount of **32** (6%) was obtained in the presence of $ZnCl_2$ even under the solvent-free conditions (Entry 2). Conversion of **8** (18%) as well as yield of **32** (0%) was suppressed slightly in 3.5 mL of water on the contrary (Entry 3). With an increase of reaction temperature, more consumption of compound **8** concomitant with very small amounts of **32** were observed under the solvent-free conditions in the absence of $ZnCl_2$ (Entries 4 and 7), suggesting the activation energy of the reaction without $ZnCl_2$ is quite high. Complete consumption of **8** without any product was observed in the presence of an equal amount of $ZnCl_2$ to **8** under the solvent-free conditions (Entries 5 and 8).[6] In the presence of water, compound **8** was consumed (27%) even without $ZnCl_2$, while the yield of **32** was very low (<1%) (Entry 9). However, the presence of water changed the nature of reaction to a greater extent in the presence of $ZnCl_2$. Water retarded the loss of **8** and accelerated the formation of **32** in the presence of $ZnCl_2$ at higher temperatures (Entries 5 and 6; 8 and 12). Additionally, yield of **32** was improved in accordance with the increase of reaction temperature until 250 °C (23%, Entry 12),

Table 5-1. Reaction of **8** and **9** in subcritical water under various conditions[a)]



8 **9** **32**

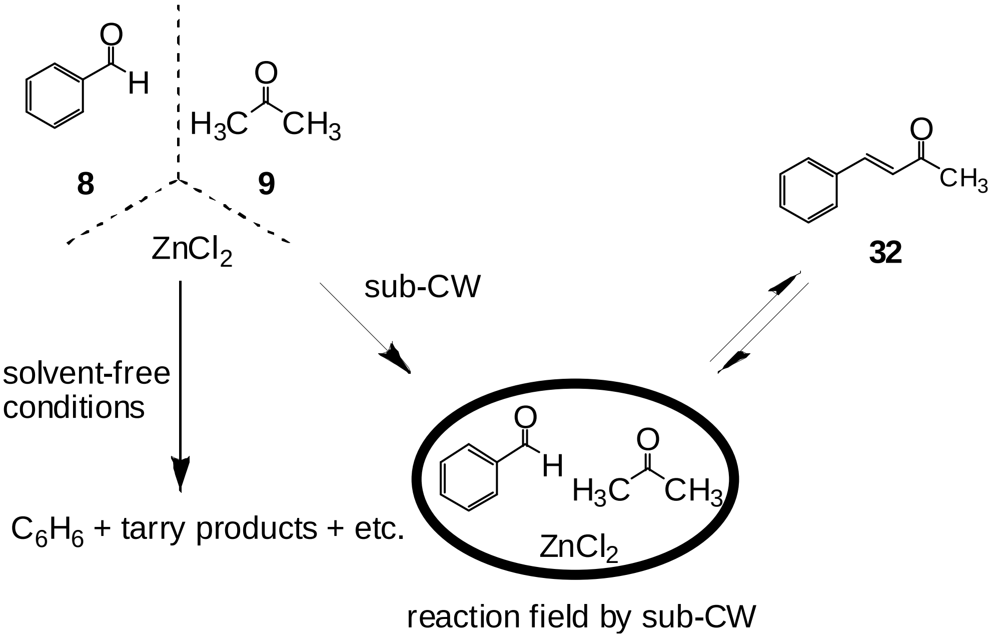
Entry	Temperature (°C)	Time (min)	Water (mL)	Mole Ratio of $ZnCl_2$/**8**	Conversion of **8** (%)	Yield of **32** (%)
1	100	20	0	0	9	0
2	100	20	0	1	25	6
3	100	20	3.5	1	18	0
4	200	20	0	0	18	4
5	200	20	0	1	96	0
6	200	20	3.5	1	32	7
7	250	20	0	0	31	5
8	250	20	0	1	99	0
9	250	20	3.5	0	27	<1
10	250	20	0.5	1	52	11
11	250	20	1.5	1	47	21
12	250	20	3.5	1	42	23
13	250	5	3.5	1	27	9
14	250	10	3.5	1	31	12
15	250	15	3.5	1	37	17
16	250	30	3.5	1	44	24
17	300	20	3.5	1	45	15
18	350	20	3.5	1	52	5
19	380	20	3.5	1	61	3

a) Reaction conditions: 0.94 mmol of **8**, 3.76 mmol of **9**, under N_2 in the SUS 316 batch type tubular reactor.

and then it became lower (Entries 17–19). These results indicate that sub-CW prevents **8** from decomposing and assists the reaction providing **32** at higher temperatures of 200 and 250 °C. Higher conversions of **8** (45, 52, and 61%) and lower yields of **32** (15, 5, and 3%) were achieved at much elevated temperatures (300, 350, and 380 °C), respectively (Entries 17, 18, and 19, respectively). These observations can be explained by supposing the decomposition of **8** and/or **32** and the retro-aldol reaction of **32** reproducing **8** under such high temperature of SCW. Actually, when compound **8** was treated in 3.5 mL water at 250 °C for 20 min in the presence of an equal amount of $ZnCl_2$ to **8**, 14% of **8** was consumed. Under solvent-free conditions, however, compound **8** was relatively unstable and 61% of **8** was consumed at 250 °C for 20 min in the presence of $ZnCl_2$. In the case of **32**, complete consumption of **32** was observed at 250 °C for 20 min in the presence of $ZnCl_2$ under solvent-free conditions, while no formation of retro-aldol product **8** was observed. Under similar conditions in sub-CW, only 29% of **32** reacted to afford 21% yield of **8**.[7] Again, these results indicate that water play a very important role in protecting both **8** and **32** from the decomposition. Decreasing conversion of **8** and increasing yield of **32** were observed with an increase in water amount at a fixed temperature (250 °C) in a fixed reaction time (20 min) (Entries 8, 10, 11, and 12), indicating that water played a crucial role in suppressing decomposition of **8** and/or **32** and assisting the cross-aldol reaction of **8** and **9** to a larger extent at this temperature.

Next, reaction time dependence was investigated under the conditions of a fixed temperature (250 °C) and a fixed amount of water (3.5 mL) in the presence of an equal amount of $ZnCl_2$ to **8** (Entries 13–15, 12, and 16). With an increase of reaction time, both conversion of **8** and yield of **32** increased, though the reaction was almost saturated at around 20 min (Entries 12 and 16) to reach 24% of **32**. In a related study, Savage et al reported a similar non-catalytic reaction in sub-CW, but it needed much longer reaction time of 5 h to reach similar 24% yield of **32**.[8] Our reaction time, 20 min, is sufficiently shorter than that of the reported non-catalytic reaction in simple sub-CW to reach almost same yield (23%). Additionally, Nolen et al investigated a similar non-catalytic Claisen–Schmidt condensation of benzaldehyde with 2-butanone in sub-CW, and the required reaction time was as much as 30 h.[9] Thus, we successfully showed a utilization of sub-CW in a reaction containing both organic and inorganic reagents at once by use of a quite common cross-aldol reaction.

Considering all experimental data, a plausible reaction scheme (Scheme 5-1) is proposed: The possibility of meeting three components of liquid **8** (bp: 179 °C), vapor **9** (bp: 56.5 °C), and solid $ZnCl_2$ (bp: 732 °C) at once should be very lower under solvent-free conditions at a low temperature such as 100 °C because of the heterogeneous reaction system. Increasing reaction temperature such as over 250 °C can slightly improve situation, while the inorganic compound $ZnCl_2$ is still solid, which would lead to decomposition of **8** due to the high-temperature involved affording benzene and CO, and to produce the tarry products with Lewis acid, $ZnCl_2$. Sub-CW shows moderate polarity at such temperature ($\varepsilon_r = 27.1$ at 250 °C, 5 MPa), which is similar to that of ambient methanol ($\varepsilon_r = 32.7$ at 20 °C, 0.1 MPa).[10] Then, sub-CW would dissolve these components including organic compounds **8** and **9** and inorganic $ZnCl_2$ to serve a more “homogeneous-like” reaction field. Of course, water should not be the only reaction medium, which has the ability of serving the reaction field to dissolve inorganic and organic substances at once. However, water can be one of the most stable materials to tolerate such vigorous conditions of high-temperature and high-pressure. Furthermore, water has the advantage that can be also used as a reaction medium even in the quite oxidative atmosphere, where usual organic solvents are easily oxidized.[11]

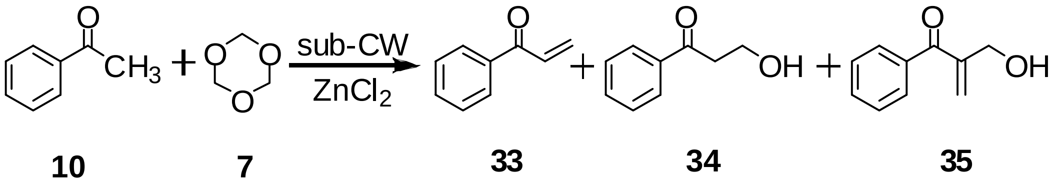


Scheme 5-1. Plausible reaction scheme of the reaction of **8** and **9** with $ZnCl_2$ under solvent-free conditions and in subcritical water.

5-2-2 Clean cross-aldol reaction of acetophenone (10) and 1,3,5-trioxane (7)

In order to clarify the possibility of the sub-CW assisted clean cross-aldol reactions, other substrates, which provide more stable products than **32**, are investigated. Another cross-aldol reaction of acetophenone (**10**) with 1,3,4-trioxane (**7**) was selected, which afforded 1-phenylprop-2-en-1-one (**33**), 3-hydroxy-1-phenylpropan-1-one (**34**), and 2-hydroxymethyl-1-phenylprop-2-en-1-one (**35**) to evaluate whether sub-CW suppresses the decomposition of substrates and accelerates the formations of the products or not.[12] A quite similar tendency to the reaction between **8** and **9** was observed in the reaction between **10** and **7** (Table 2). In the absence of water and $ZnCl_2$, small consumption of **10** with no product was observed at 100, 200, and 250 °C (Entries 1, 4, and 9). Conversion of **10** was greatly improved in the presence of $ZnCl_2$ at 100 °C under the solvent-free conditions, while no product was obtained (Entry 2). At higher temperatures 200 and 250 °C, compound **10** was completely consumed in the presence of an equal amount of $ZnCl_2$ to **10** under the solvent-free conditions without any product (Entries 5 and 10). Again, 3.5 mL water decelerated the consumption of **10** dramatically (Entries 3, 6, and 8) as compared to those of the solvent-free reactions (Entries 2, 5, and 10). Additionally, sub-CW assisted the cross-aldol reaction of **10** and **7** at 250 °C in the presence of an equal amount of $ZnCl_2$ to **10**. Water amount effect was also observed in the cross-aldol reaction of **10** and **7**. In the absence of water, almost complete consumption of **10** was observed, however, no product was obtained except for a trace amount of **33** at 250 °C for 5 min in the presence of an equal amount of $ZnCl_2$ to **10** (Entry 10). With increasing water amounts, conversion of **10** decreased and total yields of **33**, **34**, and **35** increased (Entries 10, 11, 8, and 12), which also indicates that water promotes the

Table 5-2. Reaction of **10** and **7** in subcritical water under various conditions[a)]



Entry	Temperature (°C)	Time (min)	Water (mL)	Mole Ratio of $ZnCl_2$/**10**	Conversion of **10** (%)	Yields (%)			
						33	**34**	**35**	Total[b)]
1	100	5	0	0	7	0	0	0	0
2	100	5	0	1	50	0	0	0	0
3	100	5	3.5	1	6	0	0	0	0
4	200	5	0	0	9	0	0	0	0
5	200	5	0	1	99	0	0	0	0
6	200	5	3.5	1	31	9	14	<1	24
7	250	1	3.5	1	51	25	16	2	43
8	250	5	3.5	1	81	27	13	19	59
9	250	5	0	0	11	0	0	0	0
10	250	5	0	1	99	<1	0	0	<1
11	250	5	1.5	1	90	19	7	25	51
12	250	5	4.5	1	79	29	17	17	63

a) Reaction conditions: 0.8 mmol of **10**, 1.1 mmol of **7**, under N_2 in an SUS 316 batch type tubular reactor.

b) Total yield of **33**, **34**, and **35**.

cross-aldol reaction under the reaction conditions. Prolonged reaction time caused a higher total yield of cross-aldol reaction products (Entries 7 and 8). A very short reaction time (1 min) is enough to produce **33**–**35** in a satisfactory total yield (43%, Entry 7) in the presence of $ZnCl_2$. A good total yield was obtained in 5 min (59%, Entry 8).

5-3 Conclusions

Sub-CW assisted clean cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of $ZnCl_2$ were successfully performed in sub-CW. Under solvent-free conditions, substrates **8** and **10** were completely consumed with (almost) no product in the presence of $ZnCl_2$, while sub-CW suppressed the decomposition of substrates **8** and **10** and assisted the cross-aldol reactions efficiently to afford satisfactory yield of **32** (23%) and total yield of **33**, **34**, and **35** (63%) in fairly short reaction times 20 min and 1–5 min in the presence of an equivalent of $ZnCl_2$, respectively. Sub-CW assisted quite a common cross-aldol reaction to suppress loss of organic materials under such high-temperature conditions. Thus, sub-CW can be used as a reaction medium containing both organic and inorganic materials under drastic conditions such as high-temperature and high-pressure. A new aspect of sub-CW application was shown by use of cross-aldol reactions containing both organic and inorganic materials as an example.

5-4 Experimental Section

5-4-1 General

Benzaldehyde, acetone, acetophenone, and 1,3,5-trixoane were purchased from Nacalai Tesque Inc., and $ZnCl_2$, $ZnSO_4$, $CuSO_4$, $AlCl_3$, and LiCl were purchased from Wako Pure Chemical Industries Ltd.

Similar procedure was applied as mentioned in chapter 2.

5-4-2 NMR and GCMS analysis

1-Phenylprop-2-en-1-one (33): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.96 (m, 2H), 7.58 (tt, J = 7.6, 1.2 Hz, 1H), 7.46-7.50 (m, 2H), 7.16 (dd, J = 17.2, 10.4 Hz, 1H), 6.44 (dd, J = 17.2, 2 Hz, 1H), 5.93 (dd, J = 10.4, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.50, 133.23, 132.62, 130.44, 128.93, 128.86, 191.32. MS: *m/z* 132 (M^+).

3-Hydroxy-1-phenylpropan-1-one (34): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.97 (m, 2H), 7.58 (tt, J = 7.6, 1.2 Hz, 1H), 7.44-7.49 (m, 2H), 4.03 (t, J = 5.2 Hz, 2H), 3.22 (t, J = 4.8 Hz, 2H), 2.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.73, 136.87, 133.76, 128.92, 128.29, 58.29, 40.63. MS: *m/z* 150 (M^+).

2-Hydroxymethyl-1-phenylprop-2- en-1-one (35): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J = 8.0, 0.8 Hz, 2H), 7.55 (tt, J = 7.2, 1.6 Hz, 1H), 7.43 (t, J = 7.2 Hz, 2 H), 6.14 (s, 1H), 5.80 (s, 1H), 4.49 (d, J = 4.8 Hz, 2H), 2.52 (t, J = 6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.28, 146.43, 137.56, 132.79, 129.67, 128.57, 127.72, 63.46. MS: *m/z* 162 (M^+).

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4 1,3,5-Trioxane (**7**) was selected instead of formaldehyde water solution as a reagent to avoid the potential influence of methanol, which was added to the solution as a stabilizer.

5 Inorganic additives such as $ZnCl_2$, $ZnSO_4$, $CuSO_4$, $AlCl_3$, HCl (0.05 mol L^{-1}), LiCl, and NaOH (0.01 mol L^{-1}) were applied for crossed aldol reactions of **8** with **9** and **10** with **7** in sub-CW at 250 °C for 20 min (reaction of **8** and **9**) and 5 min (reaction of **10** and **7**) in 3.5 mL water. Among these additives, $ZnCl_2$ was the most effective.

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6 Formation of gaseous and/or tarry products was observed in the reactions of **8**/**9** and **10**/**7** with and without $ZnCl_2$. Much amount of tarry product was obtained especially under the solvent-free conditions at high temperatures (250–380 °C). In the reactions at high temperatures, this kind of decomposition of organic compounds is well known especially in the presence of acids. The decomposition of organic compounds has been reported: a) Y. Shibasaki , T. Kamimori , J. Kadokawa , B. Hatano, and H. Tagaya, *Polym. Degrad. Stab.* **2004**, *83*, 481. b) K. Park and H. Tomiyasu, *Chem. Commun.* **2003**, 694. c) I.-G. Lee, M.-S. Kim, and S.-K. Ihm, *Ind. Eng. Chem. Res.* **2002**, *41*, 1182. d) M. A. Grela and A. J. Colussi, *J. Phys. Chem.* **1986**, *90*, 434. e) D. F. Debenham and A. J. Owen, *J. Chem. Soc. B*, **1966**, 675.

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Chapter 6.

Conclusions

This thesis deals with studies on organic transformations in sub-CW and SCW. Quite unique four organic transformations, such as non-catalytic oxidation of secondary alcohols in SCW, non-catalytic Oppenauer oxidation of alcohols in SCW, non-catalytic permethylation of catechol derivatives in sub-CW and SCW, and sub-CW assisted clean cross-aldol reactions, were investigated. The results obtained through the researches are summarized and concluded as follows:

First, the author focused on the investigations of the reaction behavior of two secondary alcohols, benzhydrol (**1**) and its higher homologue benzoin (**2**), in sub-CW and SCW in the absence of any oxidant or catalyst, since both of alcohol **1** and **2** have two benzene subunits, a secondary hydroxyl group, and no hydrogen atom on the β-position of the hydroxyl group, to avoid dehydration in sub-CW and SCW. In the reaction of **1**, oxidation product, benzophenone (**11**), as well as reduction product, diphenylmethane (**12**), was produced. Higher reaction temperature and longer reaction time caused higher yields of oxidation product **11** and reduction product **12**. Water played a key role for the product distributions in this reaction. In the absence of water, almost same amounts of **11** and **12** were obtained, suggesting that disproportionation between two molecules of alcohol **1** occurred thermally. However, in the presence of water, the higher yields of oxidation product **11** than those of reduction product **12** were always achieved under all conditions examined. The most efficient oxidation of **1** was obtained at

460 °C for 180 min in 0.35 g mL^{-1} water density in an SUS 316 reactor to give oxidation product **11** in 63% yield. The ratio of **11**:**12** always exceeded unity and rapidly increased with an increase in the water density and temperature. Evolution of hydrogen gas was confirmed in the reaction of **1** in a quartz tubular reactor. In the reaction of **2**, the total yield of oxidation product **14** and its secondary reaction products **1**, **11**, and **12** was also always higher than that of reduction product **15** in the presence of water. Water also played a crucial role in the reaction of **2**. The facts of hydrogen gas evolution, water density dependence of alcohol reaction, and more oxidation products than reduction products in SCW indicate that the water-catalyzed hydrogen generation mechanism is favorable to explain the oxidation behavior of alcohols in SCW.

Second, the author concentrated on the investigation of the non-catalytic Oppenauer oxidation of alcohols, such as benzhydrol (**1**) and benzyl alcohol (**3**), utilizing formaldehyde (**4**) as an oxidant in SCW and the results were compared to the oxidation under solvent-free conditions. Water was found to be very important to the clean Oppenauer oxidation of alcohols affording almost only oxidation product in both these two reactions. Under the solvent-free conditions, Oppenauer oxidation as well as disproportionation took place simultaneously in both reactions of **1** and **3** to produce oxidation products, benzophenone (**11**, 64%) and benzaldehyde (**8**, 95%) in very good yields, along with small amounts of reduction products, diphenylmethane (**12**, 13%) and toluene (**16**, 2%), respectively, at 400 °C within a very short reaction time (10 min) in the SUS 316 batch type tubular reactor. Although lower yields of oxidation products **11** (30%) and **8** (66%) were obtained, the formations of reduction products, **12** (<1%) and **16** (<1%), were almost completely suppressed in SCW under the conditions of 400 °C, 10 min, and 0.35 g mL^{-1} water density. A plausible reaction pathway (six-membered ring transition state of non-catalytic Oppenauer oxidation) for the non-catalytic Oppenauer oxidation of alcohols was discussed.

Third, non-catalytic permethylation of catechol (**5**) and 4-methylcatechol (**6**) was performed with 1,3,5-trioxane (**7**) in sub-CW and SCW without any catalyst. The formation of permethylation product, 3,4,5,6-tetramethylcatechol (**23**), was obtained in both reactions of **5** and **6**, and almost only permethylation product **23** was obtained in these two reactions at 350 °C for 10 min in 3.5 mL water in the SUS 316 batch type tubular reactor. Reaction temperature-dependence and time-dependence were observed in the reaction of **6**. Higher temperature and longer reaction time caused higher yield of permethylation product 3,4,5,6-tetramethylcatechol (**23**) as well as higher yields of other methylation products, 3,4,6-trimethylcatechol (**24**) and 3,4,5-trimethylcatechol (**22**). Water accelerated permethylation of **6**. In the absence of water, only a small amount of permethylation product **23** (4%) was obtained at 380 °C for 10 min. However, water improved the formation of permethylation product **23** in 11% and 13% yields at 380 and 400 °C, respectively, under the conditions of 10 min and 0.35 g mL^{-1} water density. Reaction pathways of methyaltion of catechol derivatives were investigated by using methylation of phenol derivatives, 2,4-xylenol (**25**) and 2,6-xylenol (**26**), which made the methylation simple. Two proposed reaction pathways, six-membered ring transition state *ortho*-methylation and H^+ catalyzed *ortho*- and *para*-methylation of phenol derivatives, would be favorable for the permethylation of catechol derivatives.

Finally, the author investigated sub-CW assisted clean cross-aldol reaction using the reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of an inorganic additive, $ZnCl_2$. Clean cross-aldol reactions of **8**/**9** and **10**/**7** with $ZnCl_2$ were performed in sub-CW in the SUS 316 batch type tubular reactor with less waste of reagents and/or products as compared to the cases under solvent-free conditions. In the absence of water, almost complete consumption of **8** (conversion: >99%) and **10** (conversion: >99%) was obtained, while no product was observed at 250 °C for 20 and 5 min respectively. In the presence of water, however, water successfully suppressed the consumption of **8** (conversion: 42%) and **10** (conversion: 81%) and assisted the cross-aldol reactions to afford a satisfactory yield of cross-aldol reaction product benzalacetone (**32**, 23%) in the reaction of **7** and a satisfactory total yield (63%) of 1-phenylprop-2-en-1-one (**33**), 3-hydroxy-1-phenylpropan-1-one (**34**), and 2-hydroxymethyl-1-phenylprop-2-en-1-one (**35**), in the reaction of **10** with $ZnCl_2$ under the conditions of 250 °C and 3.5 mL water within short reaction times (1–20 min). Sub-CW assisted quite a common cross-aldol reaction to suppress loss of organic materials under such high-temperature conditions. Thus, sub-CW can be used as a reaction medium containing both organic and inorganic materials under drastic conditions, such as high-temperature and high-pressure.

The advantages of sub-CW and SCW in organic transformations as reaction media were proved through several organic reactions, such as non-catalytic oxidation behavior of secondary alcohols, benzhydrol (**1**) and benzoin (**2**), in SCW, non-catalytic Oppenauer oxidation of alcohols, **1** and benzyl alcohol (**3**), in SCW, non-catalytic permethylation of catechol derivatives, catechol (**5**) and 4-methylcatechol (**6**), in sub-CW and SCW, and sub-CW assisted clean cross-aldol reactions of benzaldehyde (**8**) with acetone (**9**) and acetophenone (**10**) with 1,3,5-trioxane (**7**) in the presence of an inorganic additive, $ZnCl_2$.

The organic transformations utilizing sub-CW and SCW demonstrate that sub-CW and SCW are very good alternative reaction systems as green and sustainable media.

List of Publications and Presentations

Publications

1. **Reaction Behavior of Secondary Alcohols in Supercritical Water**

   Pengyu Wang, Hiroyuki Kojima, Kazuya Kobiro, Koichi Nakahara, Toshihiko Arita, and Okitsugu Kajimoto, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1828-1832.

2. **Subcritical Water Assisted Clean Cross-Aldol Reactions**

   Pengyu Wang and Kazuya Kobiro, submitted.

3. **Non-catalytic Oppenauer Oxidations of Alcohols under Solvent-Free Conditions and in Supercritical Water**

   Pengyu Wang, Xuetang Shi, Koichi Kataoka, Yasuhide Maeda, and Kazuya Kobiro, in preparation.

Presentations

1. **Application of Subcritical Water for Synthetic Reactions Containing Both Organic and Inorganic Reagents**

   Pengyu Wang and Kazuya Kobiro，日本化学会第 88 春季年会，東京，**2008**, 1J1-36.

2. **Organic Transformations in Sub- and Super-critical Water**

   Daigo Nishimura, Pengyu Wang, and Kazuya Kobiro, 1st International Symposium on Aqua Science, Water Resource and Innovation Development of Countryside, Sakawa, Kochi, Japan, **2007**, P-13.

3. **Reaction of Benzyl Alcohol Derivatives in Supercritical Water**

   Pengyu Wang and Kazuya Kobiro, 3rd International Conference on Green and Sustainable Chemistry, Delft, the Netherlands, **2007**, P180.

4. **8-Membered-ring Transition States of Water Assisted Reactions in Sub- and Super-critical Water**

   Kazuya Kobiro and Pengyu Wang, IUPAC 3rd International Symposium on Novel Materials and Synthesis & 17th International Symposium on Fine Chemistry and Functional Polymers, Shanghai, China, **2007**, IL-118.

5. **Reaction Behavior of Secondary Alcohols in Supercritical Water**

   Pengyu Wang and Kazuya Kobiro, 日本化学会第 88 春季年会，大阪，**2007**, 3PB-052.

6. **Reaction Behavior of Oxygen-containing Organic Compounds in Sub- and Super-critical Water**

   Kazuya Kobiro and Pengyu Wang, 1st International IUPAC Conference on Green-Sustainable Chemistry, Dresden, Germany, **2006**, I.4-016.

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