SITE-SELECTIVE C-C BOND FORMATION USING CYCLODEXTRIN AS CATALYST

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ABSTRACT. Selective formylation of phenol at the 4-position is achieved by using β-cyclodextrin as catalyst in the reaction of phenol with chloroform in aqueous alkali. The reactions of 1,3-dihydroxybenzene and indol, respectively, in the place of phenol give 2,4-dihydroxybenzaldehyde and indole-3-aldehyde in virtually 100% selectivies and high yields. The reactions of para-substituted phenols, 4-methylphenol and 5,6,7,8-tetrahydro-2-naphthol, instead of phenol, effect the selective dichloromethylation at the para-positions. Selective carboxylation of phenol at the 4-position is achieved in the reaction of phenol with carbon tetrachloride in aqueous alkali by using β-cyclodextrin and copper powder as catalyst.

The reaction of 2,4,6-trimethylphenol and allyl bromide in aqueous alkali using hexa-N-methylformamido-α-cyclodextrin as catalyst yields 4-allyl-2,4,6-trimethyl-2,5-cyclohexadienone in high selectivity.

The structure of the ternary inclusion complex composed of β-cyclodextrin, phenol, and, chloroform or carbon tetrachloride, formed in the reaction mixture, is determined by NMR spectroscopy. The selective catalysis by cyclodextrin was attributed to the regulation of molecular conformation of substrates with respect to dichlorocarbene, to trichloromethyl cation, or to allyl cation in the ternary molecular complex.

1. INTRODUCTION

A site-selective C-C bond formation is important for syntheses of valuable chemicals. Bond cleavage reactions, such as ester hydrolysis and amide hydrolysis, using cyclodextrin (CyD) have been extensively studied. However, there has been only a few reports on C-C bond formation using CyD catalyst [1].

Tabushi et al. [2] reported allylation of 2-methylhydronaphthoquinone with allyl bromide using CyD catalyst. The yield of target compound with allylation at the C_3 position is increased from 12% to 43% by using β-CyD at a molar ratio 5 to 2-methylhydronaphthoquinone.

In the Reimer-Tiemann reaction, a phenol is converted to an

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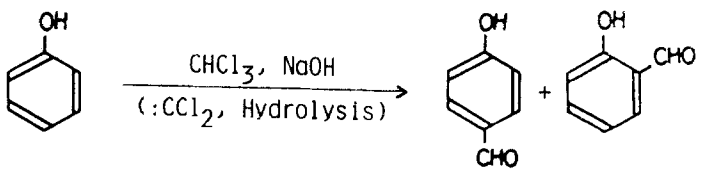
aromatic hydroxylaldehyde by warming with chloroform and aqueous alkali. Ohara and Fukuda [3] carried out the reaction in highly concentrated solution of β-CyD. The selectivity of 4-hydroxybenzaldehyde at a yield of 19% was increased from 49% to 95% by using β-CyD in a molar ratio of 0.75 to phenol.

This paper describes formylation, dichloromethylation, carboxylation of phenol and its derivatives in high yields with high selectivities by use of a small amount of CyD as catalyst. Selective formylation of indole is also reported.

2. FORMYLATION OF PHENOL

In the Reimer-Tiemann reaction, all the chloroform was usually added at the beginning of the reaction.



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The present authors [4] have found the control of the rate of addition of chloroform is very important for the selectivity of para-formylation. The conventional method referrs to "all at once method" and the new method to "dropwise method". The molar ratio of CyD to the total charged chloroform is usually small, e.g. 0.06 - 0.17. Consequently, the molar ratio of CyD to the chloroform present in the reaction mixture is also small for "all at once method", i.e. 0.06 at the initial stage of the reaction. However, the molar ratio is larger than unity for "dropwise method" throughout the reaction time by the dropwise addition of chloroform.

Fig. 1 shows the dependence of the selectivity for para-attack on the molar ratio of β-CyD to phenol.

By the "all at once method", the selectivity for the para-attack decreases remarkably with the decrease in the molar ratio of β-CyD to phenol. Equimolar amount of β-CyD is required for the high selectivity. By the dropwise method, the selectivity for the para-attack is virtually 100% in the wide range of the molar ratio of β-CyD to phenol. The dropwise method requires only a small amount of β-CyD, i.e., 8 mole %, to phenol for 100% selectivity [5].

TABLE I lists the result of the dropwise method. The addition of CyD increases the yield and the selectivity of p-hydroxybenzaldehyde remarkably. β-CyD gives 92% yield with 100% selectivity. In the absence of CyD, the yield and selectivity are much lower, i.e., 25% and 34%, respectively.

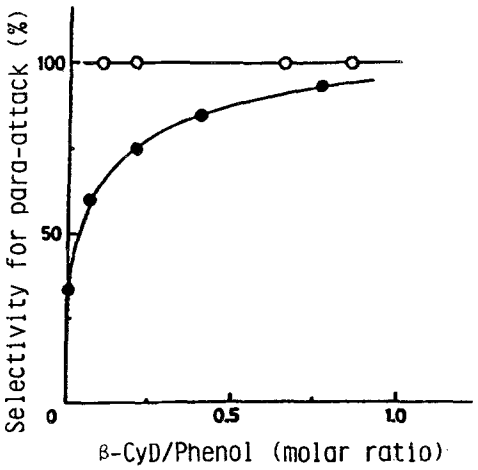

Figure 1. Dependence of the selectivity for para-attack on phenol upon the initial molar ratio of β-CyD to phenol for two reaction methods; (○) dropwise method; (●) "all at once" method. Reaction conditions: phenol 11 mmol, 10% NaOH aq. 50 ml, chloroform 63 mmol, 60°C, 8 h.

TABLE I. FORMYLATION OF PHENOL BY DROPWISE ADDITION OF CHLOROFORM [a]

CyD	Yield (mole%) [b]		Selectivity for para (%)
	para	ortho	
none	18 (25)	35 (49)	34
α-CyD	62 (72)	10 (12)	86
β-CyD	65 (92)	0 (0)	100

a. Reaction conditions: phenol 11 mmol, CyD 7.1 mmol, 10% NaOH aq. 50 ml, chloroform 63 mmol, 60°C, 8 h.
b. The numbers in parentheses are the values calculated in consideration of recovered phenol.

3. DICHLOROMETHYLATION OF 4-METHYLPHENOL

In the absence of CyD, the reaction of para-substituted phenol with chloroform in aqueous alkali gives 4-dichloromethyl-2,5-cyclohexadienone in low yield.

In the presence of β-CyD, the yield and the selectivity are improved to 89% and 97%, respectively, as shown in TABLE II [6].

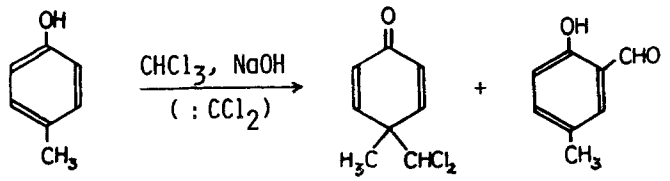

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TABLE II. DICHLOROMETHYLATION OF 4-METHYLPHENOL BY DROPWISE ADDITION OF CHLOROFORM [a]

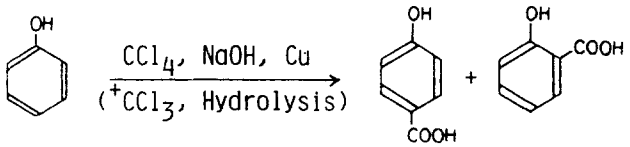
CyD	Yield (mol %)[b] para	ortho	Selectivity for para (%)
none	8(25)	20(63)	29
β-CyD	65(89)	2 (3)	97

a,b. Same as footnotes for TABLE I.

The dependence of the selectivity for para-dichloromethylation on the initial molar ratio of β-CyD to phenol was similar to that for para-formylation of phenol as shown in Fig. 1. The dropwise method required only a small amount of β-CyD, i.e., 10 mol % to 4-methylphenol for 96 % selectivity [5].

4. CARBOXYLATION OF PHENOL

Phenol reacts with carbon tetrachloride in aqueous alkali using copper powder as catalyst, yielding 4-hydroxybenzoic acid and 2-hydroxybenzoic acid.



(3)

In the absence of CyD, the yield of 4-hydroxybenzoic acid is low and the selectivity is small, as shown in TABLE III. α-CyD shows no increase in selectivity, but slightly accelerates the reaction. β-CyD improves the yield and the selectivity to 92 mol % and 99%, respectively. γ-CyD gives a moderate selective catalysis [7].

The selective carboxylation needs a very small amount of β-CyD, i.e. 8 mol % to phenol, or 4 mol % to carbon tetrachloride [8].

TABLE III. CARBOXYLATION OF PHENOL [a]

CyD	Yield (mol %)[b] para	ortho	Selectivity for para (%)
none	8.6(53)	7.1(44)	55
α-CyD	12 (54)	10 (45)	55
β-CyD	59 (92)	0.6(0.9)	99
γ-CyD	12 (58)	4.0(19)	75

a. Reaction conditions: phenol 16 mmol, CyD 1.3 mmol, 20% NaOH aq. 20 ml, copper powder 1.6 mmol, carbon tetrachloride 31 mmol, 80°C, 15 h.
b. Same as footnote for TABLE I.

5. MECHANISM OF SELECTIVE REACTIONS

5.1. Inclusion Complex Formation in the Reaction Mixture

1 in Fig. 2 depicts the structure of the inclusion complex between phenol and β-CyD in 10 wt % aqueous sodium hydroxide solution, determined by ^{1}H-NMR spectroscopy. H3 and H5 are the protons of C_3- and C_5-positions, respectively, of the glucopyranose ring of β-CyD. The phenolate ion penetrates the cavity of β-CyD from the side involving the para carbon atom. The location of the center of the aromatic ring is expressed by Z (Å), the distance from the plane comprised of seven H-3 atoms of β-CyD.

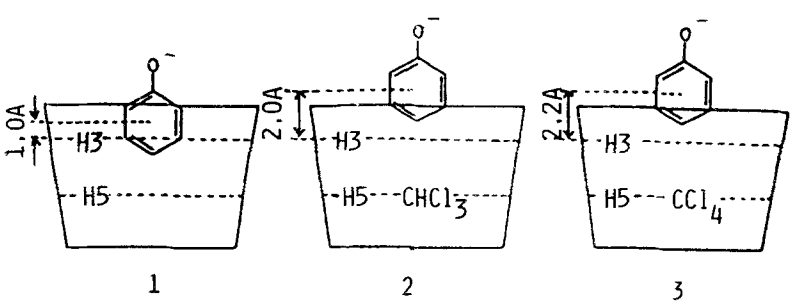


Figure 2. Time-averaged conformation of the binary and ternary inclusion complexes.

TABLE IV. CHEMICAL SHIFT CHANGES Δ_{calc} AND Δ_{obsd} ON INCLUSION COMPLEX FORMATION

System	Z (A)	Protons of β-cyclodextrin	Δ_{calc} [a] (ppm)	Δ_{obsd} [a] (ppm)
Phenol-β-CyD	1.0	H3	+0.14	+0.15
		H5	-0.03	-0.05
Phenol-β-CyD-$CHCl_3$	2.0	H3	+0.07	+0.07
		H5	-0.05	-0.07
Phenol-β-CyD-CCl_4	2.2	H3	+0.06	+0.06
		H5	-0.08	-0.07

a. + and - signs refer the high and low field shifts, respectively.

The distance of the H-3 and H-5 atoms from Z-axis are 4.1 and 3.4 Å, respectively, according to a Corey-Pauling-Koltun molecular model. The chemical shifts of H-3 and H-5 are changed by the shielding effect of the aromatic ring. The shielding effect can be calculated by using Johnson and Bovey shielding map. The chemical shift changes of H-3 and H-5 were observed on addition of phenol to the alkaline solution of CyD. The penetration depth Z can be determined by simultaneous fitting two observed values (Δ_{obsd}) of H-3 and H-5 to the two calculated values (Δ_{calc}), respectively, as shown in TABLE IV, [5, 7].

The penetration depth s of phenolate ion in the cavity are in the following order:

$$\text{Phenol-β-CyD} > \text{Phenol-β-CyD-}CHCl_3 > \text{Phenol-β-CyD-}CCl_4 \qquad (4)$$

Either chloroform or carbon tetrachloride also form the inclusion complexes as shown in Fig. 2. The formation of 2 in Fig. 2 is further confirmed by the fact that the ^1H chemical shift of chloroform is shifted toward lower magnetic field by 0.14 ppm, which is due to the anisotropic shielding effect by the aromatic ring of phenolate ion.

Carbon tetrachloride is too bulky to be included in α-CyD.

5.2. Mechanism of Formylation and Dichloromethylation

The mechanism of the selective catalyses by β-CyD is proposed as depicted in Fig. 3, on the basis of the result of the ^1H-NMR study of the inclusion complexes in the reaction mixtures.

First, a ternary inclusion complex is formed from β-CyD, chloroform, and phenol or its derivative, in which the cavity of β-CyD is largely occupied by chloroform. Phenol or its derivative in its anionic form penetrates shallowly in the cavity from the side involving the para carbon atom, since the inclusion of this apolar side in the apolar cavity is more favorable than the inclusion of the polar side

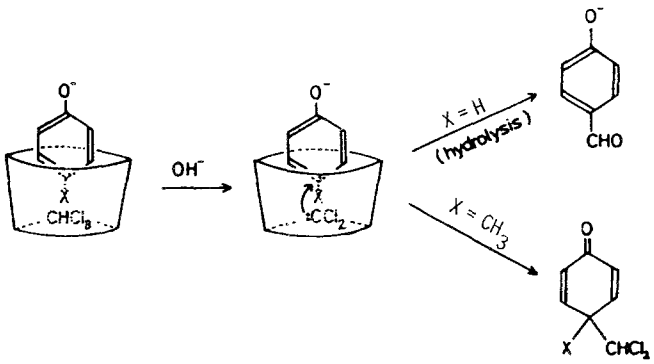


Figure 3. Reaction mechanism of selective formylation and dichloromethylation using β-CyD as catalyst.

involving the phenoxide oxygen atom. Dichlorocarbene, formed in the cavity by the reaction of chloroform with hydroxide ion, should attack overwhelmingly at the para carbon atom of phenol located in close proximity, as shown in Fig. 3. The attack at the ortho carbon atom of phenol is sterically much more unfavorable.

When phenol has a para-substituent, e.g. 4-methylphenol, the addition of dichlorocarbene occurs at para-position, but the subsequent hydrolysis does not take place.

5.3. Mechanism of Carboxylation

Styrene, a powerful quencher for the trichloromethyl radical, showed no measurable effect on the selective carboxylation using β-CyD at the initial molar ratio 0.04 to carbon tetrachloride. Consequently, the selective carboxylation using β-CyD as catalyst probably proceeds with trichloromethyl cations, formed in situ from carbon tetrachloride by the catalysis of copper powder, as the active species.

The mechanism of the selective catalysis by β-CyD is proposed as shown in Fig. 4.

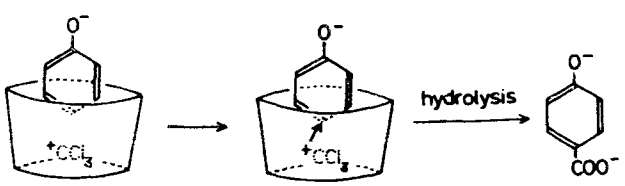
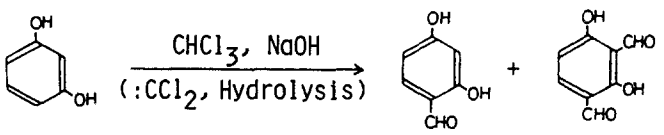


Figure 4. Reaction mechanism of the selective carboxylation using β-CyD as catalyst.

Almost all the trichloromethyl cations should form inclusion complexes with β-CyD prior to the attack at phenols, since the selective carboxylation is achieved at quite a small molar ratio of β-CyD to phenol or carbon tetrachloride. Trichloromethyl cations can be trapped in the cavity of β-CyD immediately after being formed on the surface of copper powder. Alternatively, the trichloromethyl cation can be formed predominantly from the carbon tetrachloride included in the cavity, also with catalysis by copper powder, and thus be trapped in the cavity. There, the electrostatic attraction between the positive charge of the cation and the negative charges of β-CyD is cooperatively functioning with the apolar interaction between the cation and the β-CyD. Then, the trichloromethyl cation should attack overwhelmingly at the para-carbon atom of phenols, which is located in close proximity. 4-Hydroxybenzoic acid is formed by the hydrolyses of the C-Cl bonds in the resulting intermediates.

6. FORMYLATION OF RESORCINOL

Formylation of resorcinol proceeds by using the dropwise method.



(5)

In the absence of CyD, a large amount of 3-formyl-2,4-dihydroxybenzaldehyde is formed and the yield and the selectivity of 2,4-dihydroxybenzaldehyde are low, as shown in TABLE V. In the presence of β-CyD, 2,4-dihydroxybenzaldehyde is produced in 97% yield and 100% selectivity [9].

TABLE V. FORMYLATION OF RESORCINOL [a]

CyD	Yield (mol %)[b]		Selectivity
	para (1)	ortho (2)	for para (%)
none	24 (31)	40 (52)	38
β-CyD	96 (97)	0 (0)	100

a. Reaction conditions: resorcinol 9.1 mmol, β-CyD 7.0 mmol, 10% NaOH aq. 60 ml, Chloroform 62.3 mmol, 60°C, 4 h.
b. Same as footnote for TABLE I.

The reaction mechanism is proposed as depicted in Fig. 5.

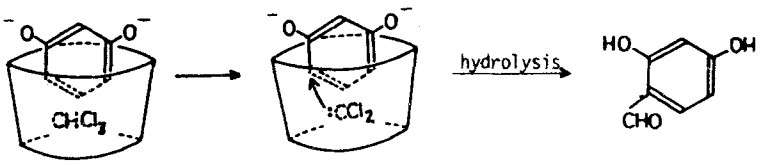
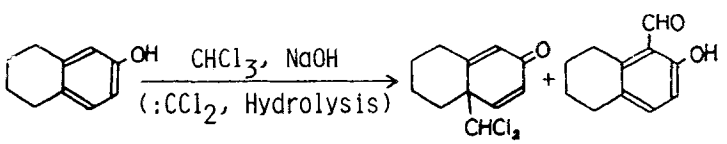


Figure 5. Reaction mechanism for selective formylation of resorcinol using β-CyD as catalyst.

Resorcinol penetrates into β-CyD and the dichlorocarbene in the cavity attacks the para-position to the hydroxyl group easily. This position is also the ortho-position to the other hydroxyl group. A hydroxyl group has a strong orientation effect on the electrophilic substitution reaction to the ortho- and para-positions.

7. DICHLOROMETHYLATION OF TETRAHYDRONAPHTHOL

The dichloromethylation of 5,6,7,8-tetrahydro-2-naphthol proceeds as expressed by eq. 6.



(6)

The results by using the dropwise method are listed in TABLE VI. The presence of α-CyD promotes the dichloromethylation at the para-position. The addition of β-CyD increases the yield and the selectivity to 88% and 100%, respectively, [5].

TABLE VI. DICHLOROMETHYLATION OF 5,6,7,8-TETRAHYDRO-2-NAPHTHOL [a]

CyD	Yield (mol %)[b]		Selectivity
	para	ortho	for para (%)
none	10 (18)	43 (77)	19
α-CyD	38 (81)	3 (6)	93
β-CyD	56 (88)	0 (0)	100

a,b. Same as footnotes for TABLE I.

The proposed reaction mechanism is shown in Fig. 6.

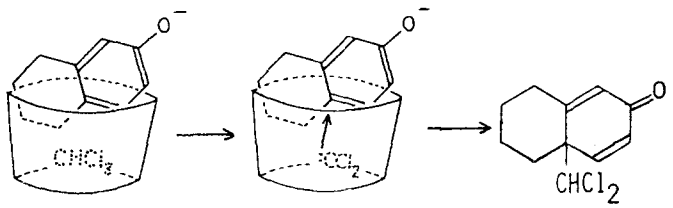
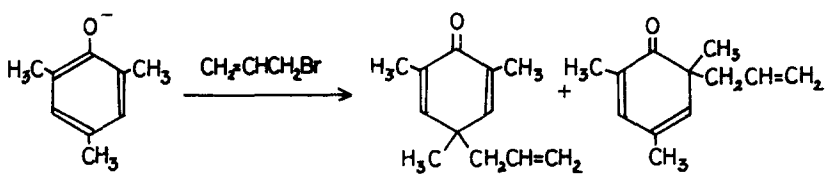


Figure 6. Reaction mechanism for selective formylation of tetrahydronaphthol using β-CyD as catalyst.

8. ALLYLATION OF TRIMETHYLPHENOL

Allylation of 2,4,6-trimethylphenol proceeds in aqueous sodium hydroxide solution by dropping allyl bromide slowly.



(7)

TABLE VII lists the results. In the absence of CyD, the allylation at the ortho position predominantly occurs. α-CyD and β-CyD improve the yield and selectivity of the para allylation [10]. The modification of α-CyD was carried out by N-methyl formamidation of six primary hydroxyl groups of α-CyD. The modified α-CyD gives 4-allyl-2,4,6-trimethyl-2,5-cyclohexadienone in 85% yield with 100% selectivity.

TABLE VII. ALLYLATION OF 2,4,6-TRIMETHYLPHENOL [a]

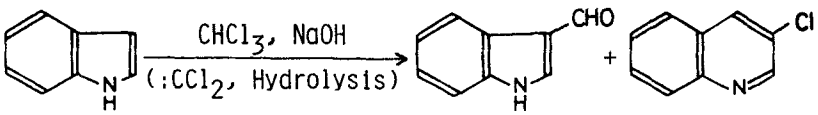
CyD	Yield (mol %) [b]		Selectivity
	para	ortho	for para (%)
none	24	49	33
α-CyD	48	24	65
β-CyD	41	34	55
mod-α-CyD [c]	85	0	100

a. Reaction conditions: trimethylphenol 1.5 mmol, CyD 7.5 mmol, 1% NaOH aq. 50 ml, allylbromide 7.4 mmol, 20°C, 20 h.
b. Same as footnote for TABLE I.
c. Hexa-N-methylformamido-α-cyclodextrin.

The ternary inclusion complex formation of allyl bromide, trimethylphenol and CyD is probably favorable for the modified α-CyD, making para attack of the allyl cation effective.

9. FORMYLATION OF INDOLE

Formylation of Indol proceeds as shown by eq. 8.



(8)

The dropwise method gives the results as listed in TABLE VIII. In the absence of CyD, the formylation gives a considerable amount of 3-chloroquinoline as by-product. In the presence of β-CyD, indole-3-aldehyde is obtained 95% yield and 100% selectivity, [11].

TABLE VIII. FORMYLATION OF INDOLE [a]

CyD	Yield (mol %)[b]		Selectivity
	aldehyde	quinoline	for aldehyde (%)
none	11	7	61
β-CyD	95	0	100

a. Reaction conditions: indole 10.3 mmol, β-CyD 7.0 mmol, 20% NaOH aq. 50 ml, chloroform 37.4 mmol, 60°C, 10 h.
b. Same as footnote for TABLE I.

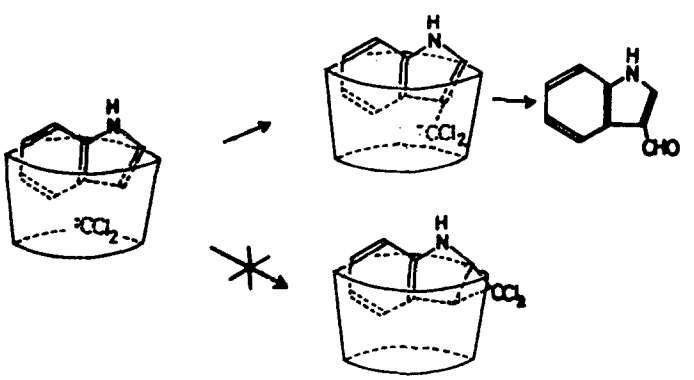


Figure 7. Reaction mechanism for selective formylation of indole using β-CyD as catalyst.

The ternary inclusion complex of indole, β-CyD and dichlorocarbene is probably formed in the reaction mixture as shown in Fig. 7. Dichlorocarbene attacks at 3-position to yield indole-3-aldehyde. In the absence of CyD, dichlorocarbene adds to 2,3-double bond of pyrrole ring. Then, the five-membered ring expands to six-membered ring, resulting in 3-chloroquinoline. β-CyD inhibits sterically the 2,3-double bond addition followed by ring-expansion.

10. CONCLUSION

Formylations of phenol, resorcinol and indole, dichloromethylations of 4-methylphenol and 5,6,7,8-tetrahydro-2-naphthol, carboxylation of phenol, and allylation of 2,4,6-trimethylphenol proceed site-selectively in high yields by using β-cyclodextrin as catalyst. The formation of ternary inclusion complex composed of cyclodextrin, substrate, and dichlorocarbene, trichloromethyl cation or allyl cation in the reaction mixture is an important factor of the site-selective reactions. The cyclodextrin is also effective by limiting the molecular size of the reaction intermediate.

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