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Graphical Abstract

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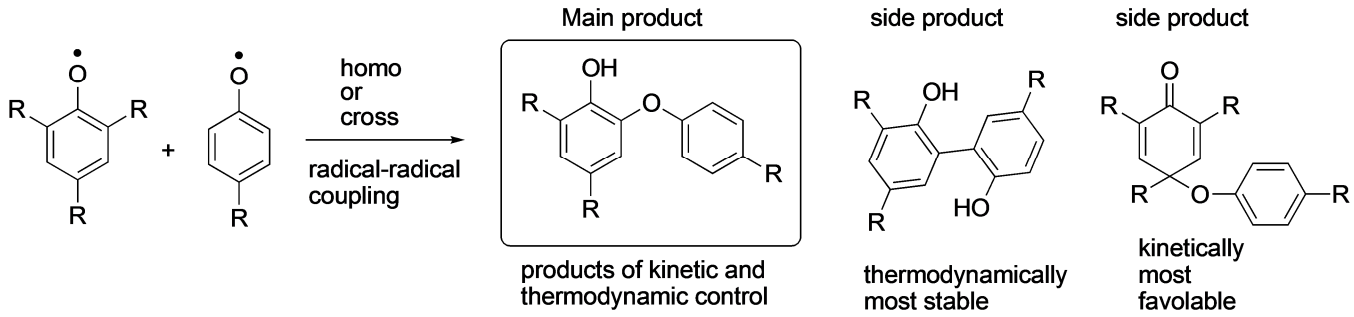

Development of the radical C–O coupling reaction of phenols toward the synthesis of natural products comprising a diaryl ether skeleton

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Abstract

Compounds comprising a diaryl ether skeleton exist among natural phenols. The diaryl ether skeleton is thought to be biosynthesized through the coupling of two or more phenols. It is an important structural feature in medicines and agrochemicals, and it is imperative to develop methods for constructing such skeletons in organic synthesis. However, by the synthesis method through the coupling of phenols, coupling occurs preferentially at the ortho-substituted carbon atom of phenols. In this study, various radical-generating reagents and conditions were investigated with the aim of developing a short-step construction method of the diaryl ether skeleton by the radical homo-coupling of two phenol molecules. In addition, cross-coupling reactions between radicals of 2,4,6-tri-tert-butylphenol and p-substituted phenol were conducted to synthesize eight C (ortho)–O coupling products. Based on the results, a computational chemical approach was employed to verify the cause of C (ortho)–O bond formation.

Keywords: diaryl ether skeleton, phenol, radical, coupling reaction

1. Introduction

Phenols are known to be typical representative compounds found in nature[1]. Some phenols are beneficial even for these simple substances, but the phenol moiety can undergo dimerization, trimerization, or cyclization within the molecule to exhibit interesting biological activity[2,3,4] (Figure 1). In addition, phenols exhibit different activities depending on the coupling position. For example, isomagnolol and magnolol are dimers of allylphenol, but these compounds exhibit different activities. In addition, obovatol, which is

a typical natural phenol comprising a diaryl ether skeleton, exhibits several activities, including antitumor[5], anti-inflammatory[6], and anxiolytic activities[7]. Reactions using peroxidase[8] have been reported with the attempt to obtain these compounds by the homo-coupling of phenols. In these studies, isomagnolol, which is the C (ortho)–O form, is obtained as a side product (5%), in addition to magnolol (21%) as the main product. The dimerization of unprotected phenol by an enzymatic reaction has been reported; however, it is difficult to selectively obtain the diaryl ether skeleton.

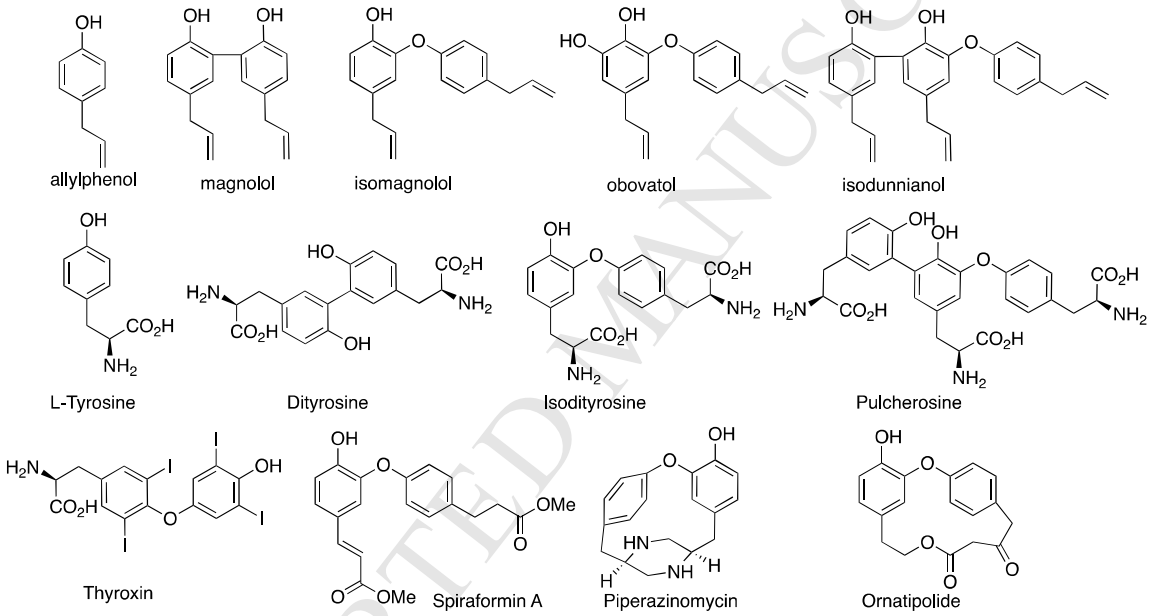
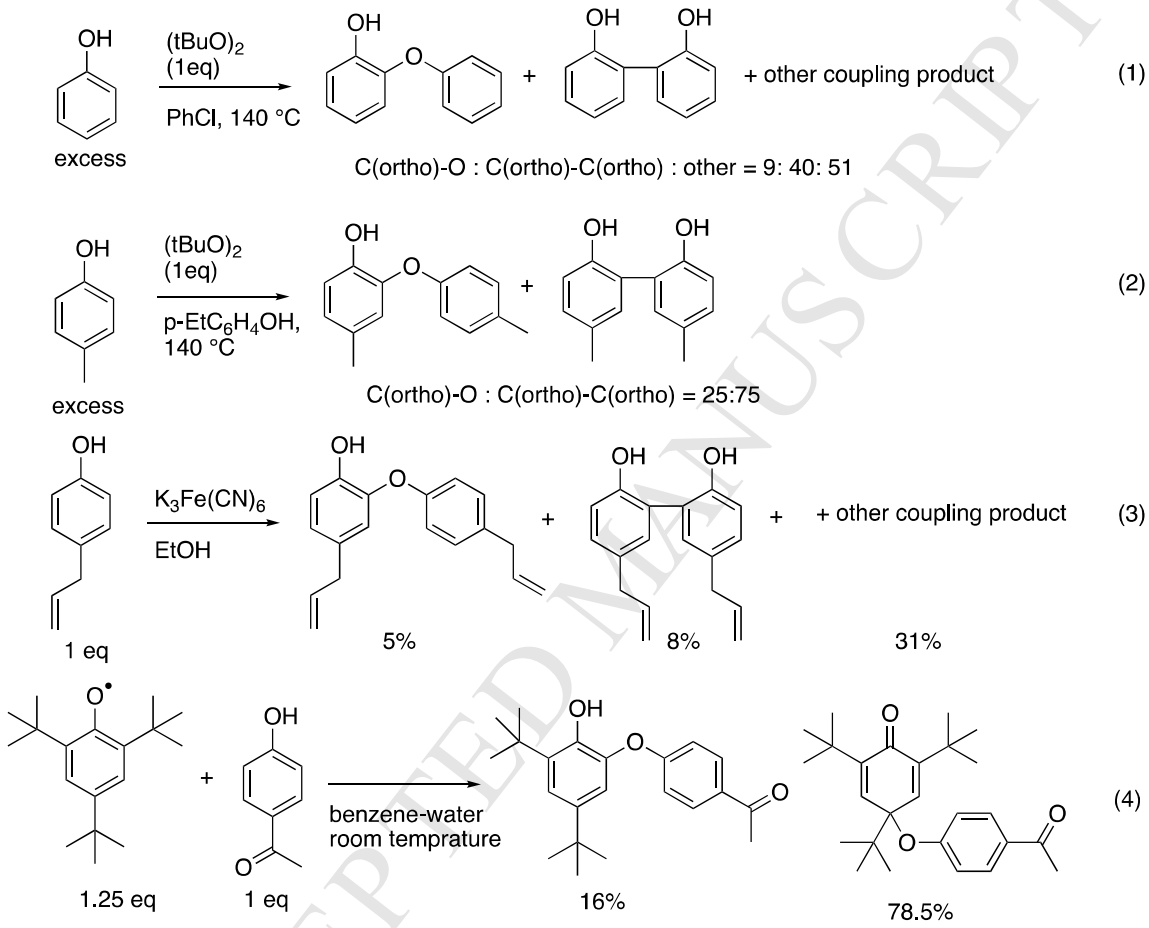


Figure 1. Natural products of related phenols including dimers and trimers.

In synthetic organic chemistry, several examples for the synthesis of symmetrical products have been reported in which C (ortho)–C (ortho) is coupled by a direct homo-coupling reaction[9]. For example, in the radical coupling reaction of 4-allylphenol, a high yield of magnolol is obtained (77%) by using 1,2-dichloro-4,5-dicyano-p-benzoquinone (DDQ), which is a one-electron oxidizing agent, and $AlCl_3$[10]. However, in synthetic organic chemistry, a high-yield synthetic method by the direct or preferential use of asymmetric diaryl ether (C (ortho)–O) has not been reported. Hence, a diaryl ether is synthesized by using a protected phenol and/or a halogenated

phenol by the arylation of a phenol by the Ullmann coupling using Cu[11] and the aromatic nucleophilic substitution reaction (S_NAr)[12].



Scheme 1. Selective examples of the direct synthesis of diaryl ethers by a radical reaction in homo- or cross-coupling.

Statistical studies on the selectivity for homo-coupling reactions using phenol[13] and p-cresol[14, 15] or other substituted phenols[16,17] as substrates using various oxidizing agents and radical initiators have been conducted (Scheme 1 eq1, eq2, eq3). By using allylphenol and $K_3Fe(CN)_6$ as the substrate and the oxidizing agent, respectively, isomagnolol (C (ortho)–O) and magnolol (C (ortho)–C (ortho) are isolated in 8% and 11% yields, respectively, and coupling products at other positions, trimers, and tetramers are obtained[18].

The UV and MW–UV irradiation of 4-*tert*-butylphenol affords C(ortho)–O and C(ortho)–C(ortho) products to be the isomerization products, and their ratio depends on the nature of the solvents and sensitizers used[19], and the C(ortho)–O form (yield 6%) is obtained by the triplet sensitization reaction using acetophenone as the photosensitizer in a hexane solution. The homo-coupling reaction of a para-substituted compound often does not proceed with selectivity, and, depending on the reagent, it is possible to obtain a coupling compounds with dimers, trimers or more with selectivity for different positions.

In the cross-coupling reaction, phenol derivatives and a simple phenol bearing bulky substituents have been reported to be coupled with each other between radicals. A study has reported that a radical of 2,4,6-tri-tert-butylphenol (BHTs) is coupled with the phenol at the para position, affording a quinone form[20] (Scheme 1 eq4). Various studies have been conducted to synthesize a thyroxine derivative (C (para)–O coupling product)[21, 22, 23, 24]. In addition, the coupling reaction between BHTs and para-substituted (electron-withdrawing group) phenol occurs at C (para)–O at low temperature, but o-hydroxydiphenyl ethers are obtained in low yield at high temperatures[25].

Furthermore, the cross-coupling reactions of phenol derivatives have been reported to proceed by oxidation potential differences. A cross-coupling reaction between p-cresol and p-methoxyphenol has been reportedly achieved by the combination of $AlCl_3$ and DDQ[26]. Recently, in a fluoroalcohol solvent (HFIP), cross-coupling with unprotected phenols is achieved by the combined use of an iron catalyst as a one-electron oxidizing agent and a reoxidant, affording an asymmetric biphenol (C (ortho)–C (ortho)) in a high isolated yield of 96%. The cross-coupling of C (ortho)–C (ortho) in the case of unprotected phenols predominantly occurs by the combination of an iron catalyst as a one-electron oxidizing agent and a reoxidant in an HFIP[27]. In addition, oxidative phenol–allen cross-coupling reactions using visible-light redox catalysts have been developed[28]. Moreover, the coupling reaction of substituted phenols has been studied via an electrochemical method[29, 30, 31, 32]. However, even by using these methods, it is difficult for the cross-coupling reactions of phenols to progress by C (ortho)–O.

In the organic synthesis methods for the dimerization of two phenols, C(ortho)–C(ortho) is the predominant product, and a selective synthesis method for the direct homo-coupling reaction of the C(ortho)–O form is not established. In addition, the cross-coupling reaction between different phenols is extremely difficult because of the competition between

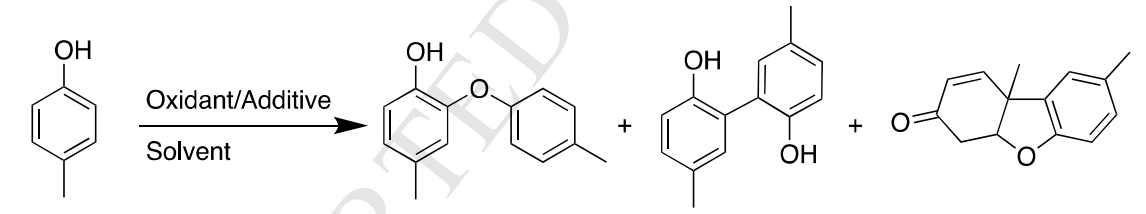
homo-coupling and cross-coupling, in addition to position selectivity. In this study, to realize a short-step synthesis method for obovatol, isodityrosine, and natural phenols comprising various diaryl ether skeletons, the C(ortho)–O coupling and homo- and cross-coupling reactions are discussed. In addition, reaction selectivity factors of C(ortho)–C(ortho), C(para)–O, and C(ortho)–O are clarified by changing the reaction time through the analysis of the byproducts and calculation chemistry.

2. Results

2.1. Model reaction

First, p-cresol with a simple phenol structure was selected as a model substrate, and a homo-coupling reaction was conducted. As the radicalizing reagent of phenol, metal reagents[14, 15] and p-benzoquinone,[26] which are one-electron oxidizing agents, and peroxides,[13, 14, 16] which are radical initiators, are used, and the yield to p-cresol (Table 1). The high-temperature reaction was conducted under pressure in a sealed container to suppress the volatilization of solvents and reagents.

Table 1. Reaction conditions for the dimerization of p-cresol



p-cresol (**1a**) **2a** **3a** Pummerer ketone

Entry	Ox.	Add.	Solv.	Temp. [°C]	Time [h]	Atmo.	Yield [%]* **2a** (C–O)	Yield [%]* **3a** (C–C)	CO:CC
1***	0.1 eq(^{t}BuO)$_2$	-	PhCl	130	24	air	14	29	33:67
2	1 eq (^{t}BuO)$_2$	-	PhCl	130	3	air	10	<1	>95:<5
3	5 eq	-	PhCl	130	3	air	18	<1	>95:<5

4	$(^tBuO)_2$ 5 eq	-	PhCl	130	2	Ar	21	<1	>95:<5
5	$(^tBuO)_2$ 5 eq	Cs_2CO_3	PhCl	130	3	air	<1	22	<5:>95
6	$(^tBuO)_2$ 1 eq	$FeCl_3$	Na_2CO_3	H_2O	r.t.	24	air	0	21
7	0.75 eq DDQ	$AlCl_3$	$MeNO_2$	r.t.	1	N_2	0	21	<5:>95
8	1 eq Ag_2CO_3	-	$MeNO_2$	100	2	air	14	<1	>95:<5
9	1 eq Ag_2CO_3	Cs_2CO_3	$MeNO_2$	100	2	air	3	12	20:80

*Isolated yield. **Concentration of **1a** was 0.02 M. *** Yield was determined from 0.1 eq $(tBuO)_2$

The selectivity for the C (ortho)–O and C (ortho)–C (ortho) forms at the coupling position varied depending on the reaction conditions such as the reagents and equivalent amount used. Notably, by using $(^tBuO)_2$ or Ag_2CO_3, a high selectivity for C (ortho)–O was achieved, unlike in a previously reported study, by fine-tuning the reaction conditions. In comparison to entries 1 and 3, the proportion of the C (ortho)–C (ortho) form was initially high because a low concentration of the radical initiator was used. Different coupling modes for the main products were observed depending on the type and presence of metal. The comparison of entries 3 and 5 with those of entries 8 and 9 revealed that different coupling modes for the main products are observed due to the metal. From the comparison of entries 3 and 4, excess reaction was suppressed under Ar under air, and the yield of the desired compound was slightly improved. The suppression of the side reaction by oxygen is considered to have led to the improved yield. Under any condition, a byproduct having an excessive reaction with a molecular weight greater than that of the coupled product was confirmed. In entries 5, 6, and 9, 9%, 1%, and 8% of the Pummerer's ketone (C (ortho)–C (para) form), corresponding to one of the dimers of the C (ortho)–C (ortho) coupling, were obtained, respectively. With respect to the reaction by $(^tBuO)_2$, studies were conducted with the increase in the temperature, equivalent amount, and concentration, and the extension of

reaction time; however, in both cases, the yield was not observed. In addition, radical initiators other than (^{t}BuO)$_2$ were investigated, but the yield decreased (e.g., AIBN, PINO, and TBHP). Moreover, by using benzoyl peroxide (BPO) as the radical initiator, a product was not obtained because a compound was formed in which p-cresol was coupled with a BPO-derived benzoyloxy radical.

2.2 Time course of the homo-coupling reaction

In the homo-coupling reaction of p-cresol, the change in the product yield over time was investigated. An LC–MS analysis was conducted for estimating the yields obtained at each time (Figure 2). The formation of the C (ortho)–O form has been reported to preferentially occur even in the early stages of the reaction. Furthermore, as the yield of the C (ortho)–O form decreased with the lapse of time, the overreaction to the C (ortho)–O form as homo-coupling was confirmed to progress. In addition, by using Ag_2CO_3 as the oxidant, the reaction was confirmed to not proceed after 30 min. Furthermore, with the increase in the equivalent amount of Ag_2CO_3, the overreaction progressed, and the yield decreased.

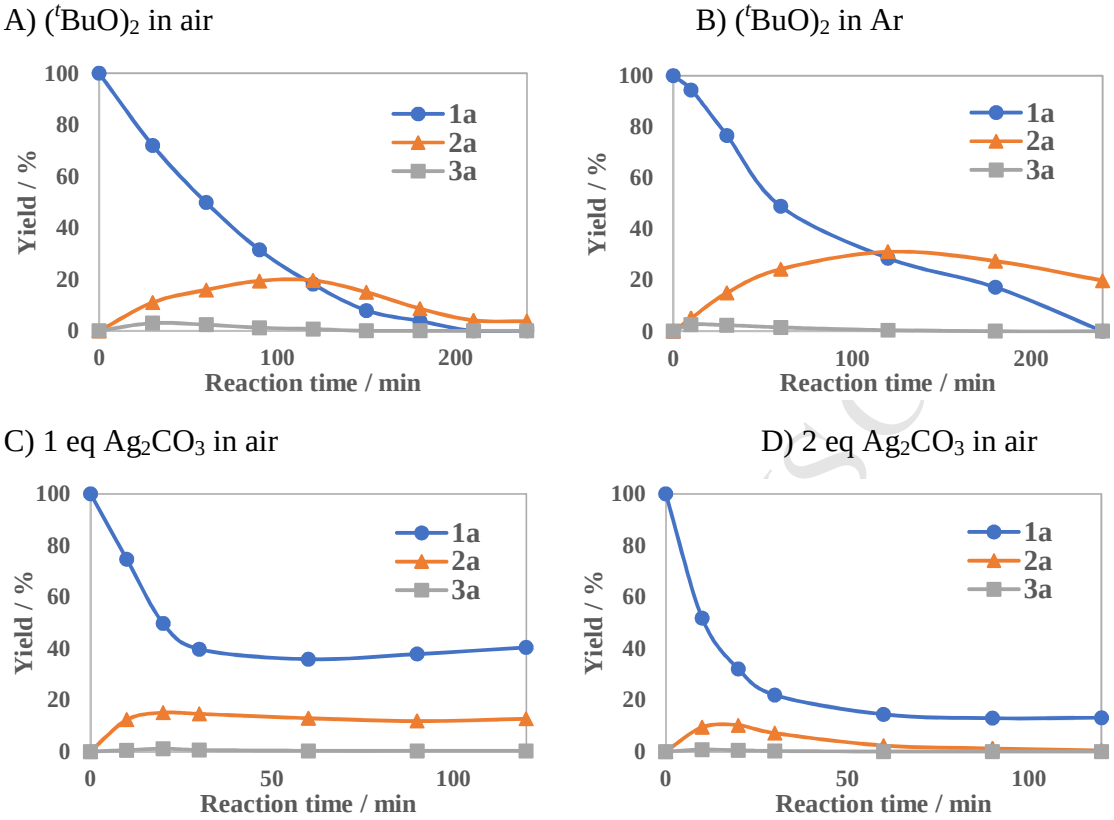


Figure 2. Temporal change in the product yield obtained from the coupling reaction: A) (^{t}BuO)$_2$ in air; B) (^{t}BuO)$_2$ in Ar; C) 1 eq Ag_2CO_3 in air; D) 2 eq Ag_2CO_3 in air. **1a**: *p*-cresol, **2a**: C (ortho)–O coupling compound, **3a**: C (ortho)–C (ortho) coupling compound.

2.3 Identification of the coupling mode by IR analysis

To specify the coupling mode in case of the overreaction, the C (ortho)–O and C (ortho)–C (ortho) byproducts shown in entries 4 and 6 of Table 1 were analyzed by ^{1}H NMR and IR spectroscopy. Each crude product was separated from the product with a larger molecular weight, which was detected by gel permeation chromatography (GPC) at an earlier flow time compared to the dimer and then analyzed. As a complex mixture was obtained, ^{1}H NMR spectra could not be recorded. Figure 3 shows the IR spectrum obtained in each condition.

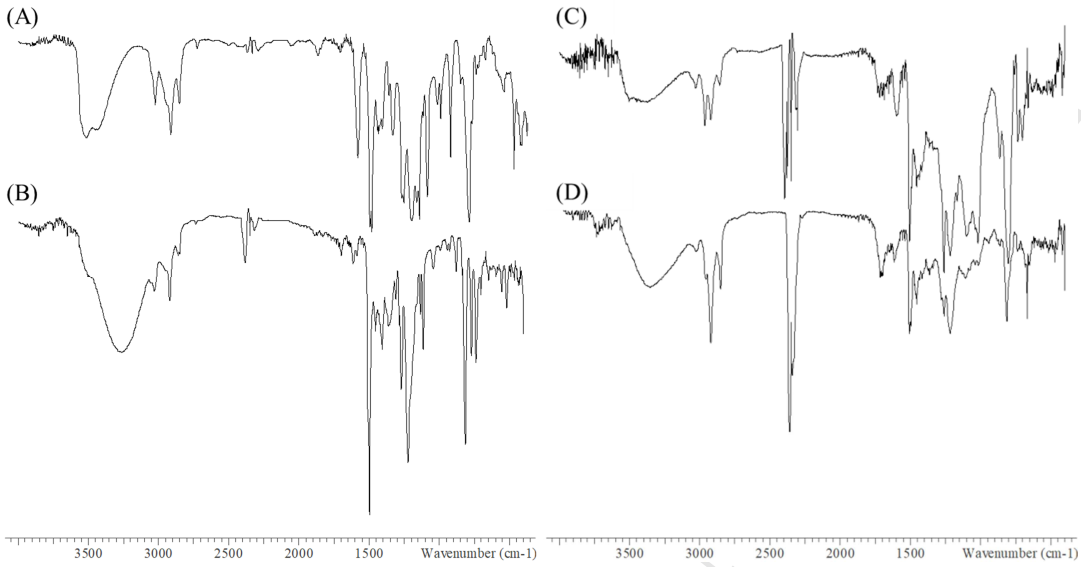


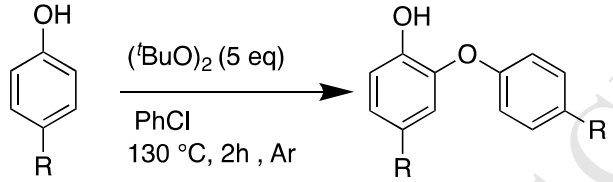
Figure 3. IR spectra of the (A) C (ortho)–O dimer, (B) C (ortho)–C (ortho) dimer, (C) oligomers of **entry 4** in **Table 1**, and (D) Oligomers of **entry 6** in **Table 1**.

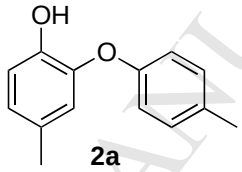
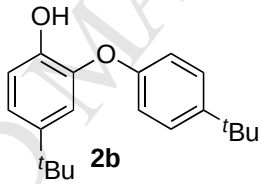
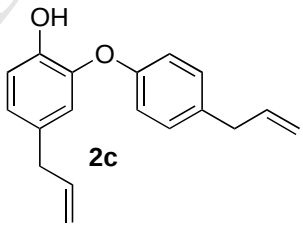
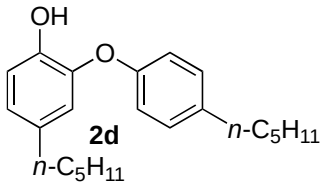
By comparison of the IR spectra of the C (ortho)–O and C (ortho)–C (ortho) forms, sharp peaks for the C (ortho)–O form in the vicinity of 1,600 cm^{-1} were observed, corresponding to the diaryl ether skeleton. By the comparison of the IR spectra of the polymers in entries 4 and 6, the peak in the vicinity of 1,600 cm^{-1} was more prominent in the byproducts of entry 4. From this result, the reaction condition of entry 4 affords a higher C (ortho)–O selectivity compared to that of entry 6 also as the functional group contained in the byproduct. In both cases, a peak corresponding to the carbonyl carbon at ~1,700 cm^{-1} was confirmed. Although the carbonyl carbon was present in trace amounts, phenol was thought to be generated as a side reaction, and quinone oxidized by oxygen in the reaction system was observed.

2.4 Application to various phenols

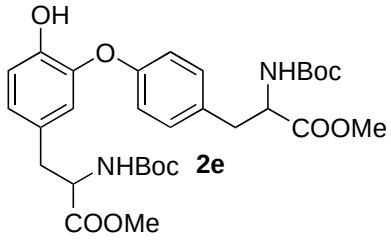
In addition, reaction conditions shown in entry 4 of Table 1 affording a high yield for the C (ortho)–O form were utilized for various phenol coupling reactions. Table 2 summarizes the results.

Table 2. Product yields from the homo-coupling reaction of *p*-substituted phenol.



Entry	R	Structure	Yield [%]
1	Me (a)	 **2a**	21
2	^{t}Bu (b)	 **2b**	7
3	Allyl (c)	 **2c**	11
4	*n*-C_5H_{11} (d)	 **2d**	18

5 $CH_2CH(COOMe)NHBoc$ (e)



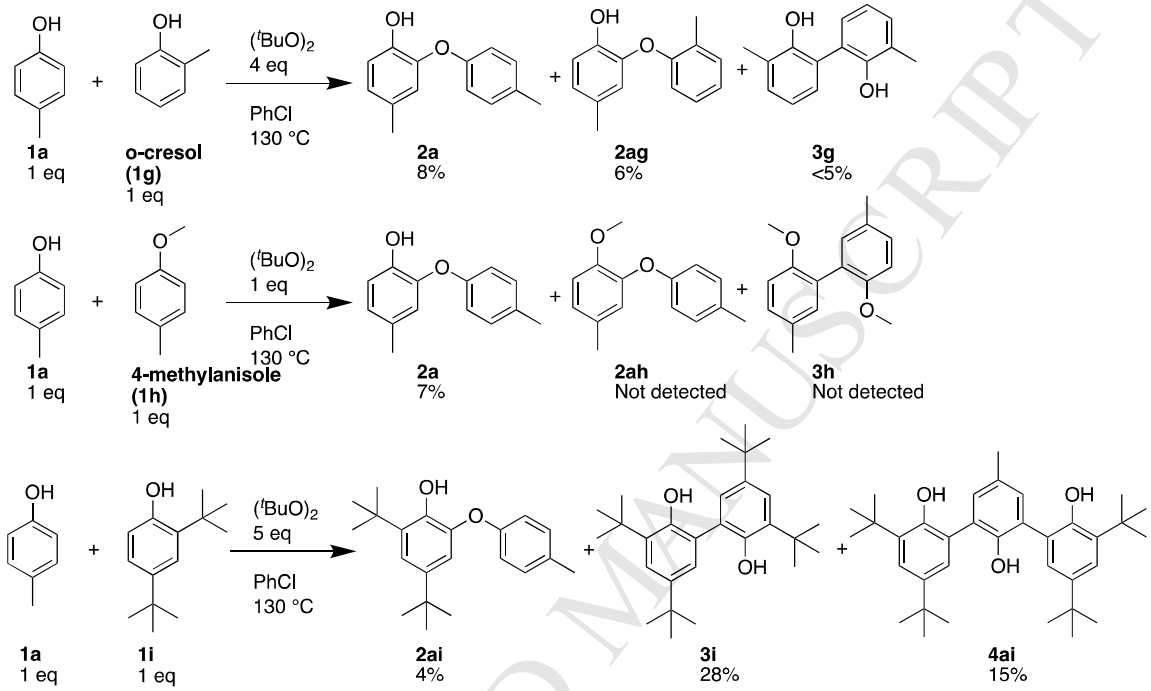
2e 7

By the developed reaction, the C (ortho)–O form of phenol with various substituents including isomagnolol, which is a natural substance, was synthesized. The reaction was confirmed to progress even with substituents other than Me, albeit with decreased product yield. C (ortho)–O was selective for either substrate. Different yields were observed depending on the reaction substrate because the abstraction of the hydrogen atom by $^{t}BuO\cdot$ was more likely to occur with respect to the substituent and/or the side reaction due to higher product reactivity. In addition, the C (ortho)–O coupling reaction possibly progressed to a minimal extent because of steric factors.

2.5. Cross-coupling

$(^{t}BuO)_2$ was used as the radical initiator to investigate the cross-coupling reaction between p-cresol and various phenols. In the cross-coupling reaction between p-cresol (**1a**) and o-cresol (**1g**), homo-coupling and cross-coupling reactions of the respective substrates proceeded, with a low product yield. It is difficult to perform the cross-coupling reaction of compounds with different substitution positions using this approach. In the cross-coupling reaction between *p*-cresol (**1a**) and 4-methylanisole (**1h**), the MS peaks for the cross-coupled compound and the homo-coupled form of anisole were not confirmed even after the LC–MS profile of the crude product was recorded. The formation of **2a**, which is the homo-coupling product of *p*-cresol (**1a**), was confirmed. Unlike using a one-electron oxidizing agent in this method, the coupling of free phenols may be preferential. When the homo-coupling of 4-methylanisole (**1h**) was conducted, a complicated excessive reaction progressed. In the cross-coupling reaction with 2,4-ditert-butylphenol (**1i**), the homo-coupling of **1i** was the main reaction, with the predominant formation of the C (ortho)–C(ortho) form (**3i**). Furthermore, **4ai**, which was a trimer obtained by the C (ortho)–C(ortho) cross-coupling, was obtained in a yield of 15%. In addition, in this

method, the steric factors of the substrate, particularly ortho substituents, affect the selectivity of the C (ortho)–O and C(ortho)–C(ortho) forms.



Scheme 2. Investigation of the cross-coupling reaction between p-cresol and various phenols.

When BHTs, which are known to be extremely stable radicals, as a coupling partner were treated with *p*-cresol, a cross-coupling reaction between *p*-cresol and BHTs progressed, affording **2ai**. Hence, the cross-coupling of BHTs and p-substituted phenols with various substituents was conducted to synthesize the C (ortho)–O form. **Table 3** summarizes the results. In phenol bearing various substituents, the C (ortho)–O form was obtained with a comparatively good yield. Under this reaction condition, the ortho-substituted product was the main product in any case; however, when some phenol was used as the substrate, C (para)–O cross-coupling products were also obtained (**7a**: 2%, **7c**: 2%, and **7e**: 4%).

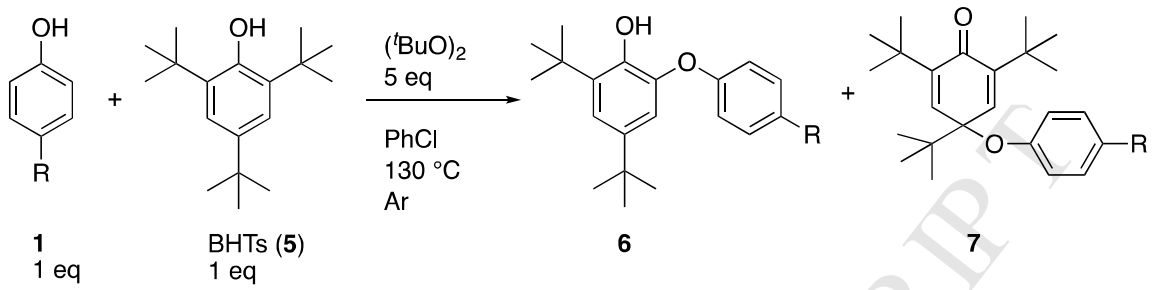
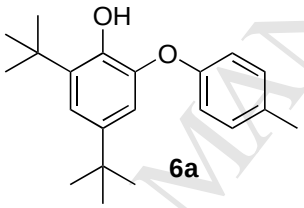
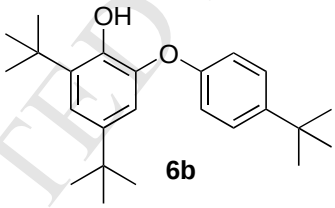
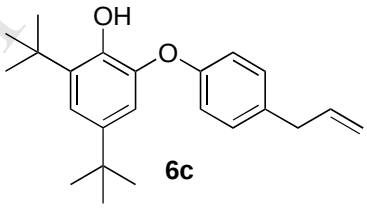
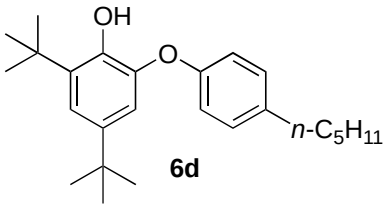
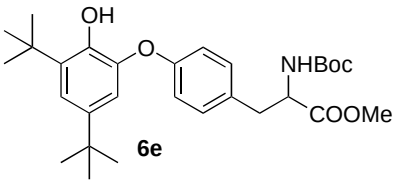
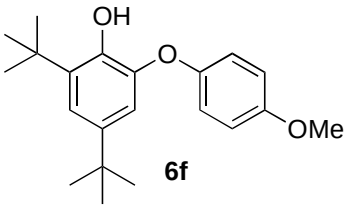
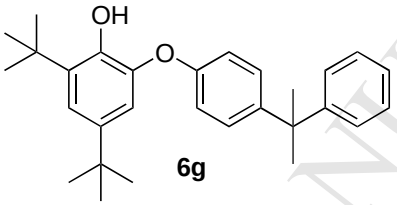


Table 3. Product yield from the cross-coupling reaction of BHTs with *p*-substituted phenols.

Entry	R	Structure	Yield [%]* **6**	Yield [%] **7**
1	Me (a)	 **6a**	40 (57)	2
2**	^{t}Bu (b)	 **6b**	57 (64)	-
3	Allyl (c)	 **6c**	39 (43)	2
4	*n*-C_5H_{11} (d)	 **6d**	43 (55)	-

5	$CH_2CH(COOMe)NHBoc$ (e)	 **6e**	56 (69)	4
6	OMe (f)	 **6f**	16 (16)	-
7	α-Cumyl (g)	 **6g**	23 (18)	-

*Yield within parentheses is based on the recovered starting material. **Reaction time: 6.5 h

2.6. Computational chemistry approach

The theoretical consideration for the selectivity of the homo- and cross-coupling reactions was examined by calculation chemistry. The starting materials, intermediates, and products expected to be involved in the reaction were calculated to examine the changes in the enthalpy, electronic properties of radicals, and bond dissociation energy (BDE) of hydrogen atoms. The initial structure used for input files was generated by a conformational search, which was conducted 2000 times via the MM3 molecular force field calculation using the Medit program[33]. Using this initial structure as an input file, the structure with the (U)B3LYP/6-31G* basis function in Gaussian 09 was optimized[34]. The Winmostar program[35] was employed to visualize each structure. From these results, selectivity factors for the reaction were discussed.

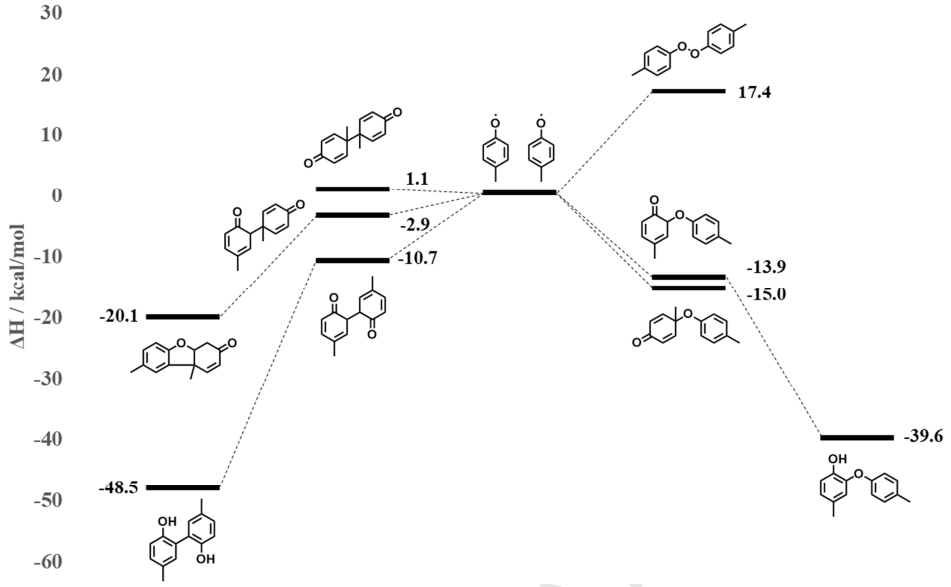
2.6.1. Enthalpy change of the coupling reaction

The coupling of phenols is known to be a reaction occurring between radicals[36, 37]. Additionally, herein, we attempted to couple p-cresol with 4-methylanisole; however, only homo-coupling of p-cresol was observed (Scheme 2). No coupling compound between

4-methylanisole and p-cresol was observed, indicating that the coupling reaction between radials is progressing preferentially, and it is expected that the coupling reaction via this mechanism is different from that via other redox reactions. In this study, using $(^{t}BuO)_2$ as the radical initiator, phenoxy radicals are generated via the hydrogen-atom transfer mechanism (HAT mechanism), and dimerization is expected to occur via the coupling of these radicals.

Figure 4 shows the enthalpy changes of intermediates and coupling products of the C (ortho)–O and C (ortho)–C (ortho) forms. In the cross-coupling reaction, the enthalpy of the product is a value including 1,2-dimethylethene formed by the elimination of the ^{t}Bu group. In the homo-coupling reaction of *p*-cresol, the final product was stable in the C (ortho)–C (ortho) form, but the intermediate was stable in the C (ortho)–O form (Figure 4A). Even for the cross-coupling reaction of BHTs and *p*-cresol, the C (ortho)–O form in the intermediate was stable (Figure 4B). In the case of cross-coupling, there is also selectivity as to which reaction proceeds from which oxygen; however, intermediates were unstable because of steric hindrance for reaction from the oxygen of BHTs. In addition, regarding the C (ortho)–C (ortho) cross-coupled product between BHTs and *p*-cresol, a more unstable intermediate due to the steric bulk of the substituents was observed. It was difficult for the homo-coupling of BHTs to proceed because of steric hindrance. The calculation results revealed that the intermediate is unstable by 21.4 kcal/mol with respect to the BHTs.

A) Homo-coupling of p-cresol



B) Cross-coupling between p-cresol and BHTs

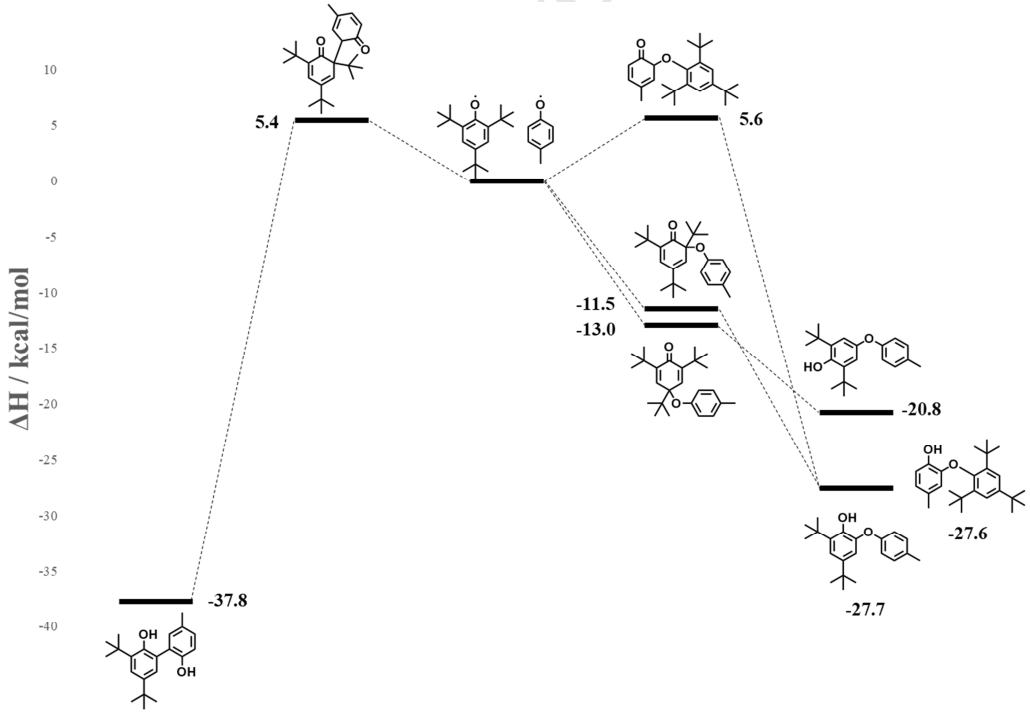


Figure 4. Enthalpy change for the A) homo-coupling reaction of *p*-cresol and B) cross-coupling reaction between *p*-cresol and BHTs.

2.6.2. Electronic properties and bond dissociation energy of phenols

In the radical reaction of phenols, the regioselectivity of the reaction was examined using the spin density[37]. Table 4 summarizes the spin densities of the phenoxy radicals and calculated BDEs of the starting materials and coupling products. BDE is one of the indices reflecting the ease with which a phenol undergoes a reaction. In homo-coupling, the BDEs for the C (ortho)–O forms of the starting material (78.0 kcal/mol) and product (78.0 kcal/mol) were equal, but the C (ortho)–C (ortho) coupling product (**3a**, 73.1 kcal/mol) exhibited a low BDE and underwent facile radical formation. In the cross-coupling reaction, the coupling energy increased in the order of BHTs (**5**, 69.7 kcal/mol), cross-coupling product (**6a**, 76.4 kcal/mol), and *p*-cresol (**1a**, 78.0 kcal/mol).

Table 4 Spin densities of the phenoxy radicals and BDEs of the phenols

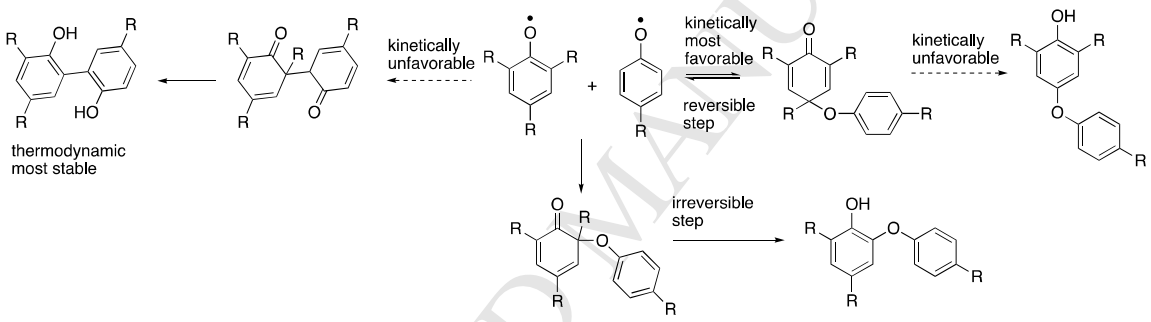
Compound No.	Spin density			BDE [kcal/mol]
	O	*o*-C	*p*-C	
p-cresol (**1a**)	0.43	0.31	0.40	78.0
2a	0.39	0.24	0.35	78.0
3a	0.30	0.16	0.29	73.1
BHTs (**5**)	0.37	0.32	0.40	69.7
6a	0.37	0.22	0.35	76.4

3 **Discussion**

When a para-substituted phenol is treated at high temperature based on the HAT mechanism, coupled products between the phenol oxygen and the ortho-substituted phenol, which are relatively advantageous both thermodynamically and kinetically, are obtained. However, as this selectivity is subtle, with the variation in temperature, presence or absence of a coordination metal, and radical concentration, the selection of a radical generator and control of reaction temperature and time are indispensable. Typically, the coupling reaction at the para position of oxygen and phenol of phenol with a high spin density is more likely to proceed kinetically. Calculation results revealed that the spin density of the alkyl substituent at the para position of the phenol is greater than that at the ortho position. ESR studies also revealed that spin densities for a range of alkyl substituents in the para position of phenols are approximately twice those at the ortho positions[38]. However, under high

temperature, C (para)–O coupling product is thermodynamically unstable and returns to the starting material. However, the final coupling product between the ortho-substituted phenols was the most stable thermodynamically, but it was not favorable kinetically at the stage at which the intermediate cyclohexadienone was obtained.

The selectivity for the cross-coupling reaction between BHTs and *p*-substituted phenols selectively occurred at C (ortho)–O, as was the case with homo-coupling, because of the intermediate stability (Figure 4 B). The coupling reaction of the ortho-substituted type proceeded instead of the para-substituted type, but elimination at the ortho position was easier than that at the para position of the phenol[39] because the ortho-substituted phenol promotes intramolecular elimination.



Scheme 3. Relation between the kinetic selectivity and thermodynamic stability for the coupling of para-substituted phenols

3.1 Cross-coupling using BHTs compared with the homo-coupling of phenol

The cross-coupling reaction of the para-substituted phenol and BHTs proceeded more efficiently than its homo-coupling. This factor was considered from the obtained results. By the comparison of BDEs summarized in Table 4, the BDE of BHTs was significantly less than that of p-cresol, with the preferential generation of BHT radicals. However, in the homo-coupling of BHTs, the intermediate was more unstable than the starting material because of considerable steric hindrance (Figure 4), and the reaction did not proceed. The hydrogen abstraction of *p*-cresol progressed gradually, and radical cross-coupling occurred between phenoxy radicals generated in trace amounts and BHT-derived radicals in large amounts. From the quantitative relation of the radicals in the reaction system, the progress of cross-coupling became dominant.

Cross-coupling using BHTs compared to the homo-coupling of phenol led to higher yield because of the suppression of the overreaction. From Table 4, the BDEs of BHTs were significantly less than that of product **6a**, and the ease of hydrogen abstraction for BHTs was greater than that of **6a**; hence, the overreaction is suppressed in comparison to homo-coupling. BHTs serve as a reagent and a scavenger to suppress excess reaction. Hence, the C (ortho)–O coupling between BHTs and para-substituted phenol progresses selectively, further inhibiting the excess reaction, and the reaction progresses with a relatively good yield. The ^{t}Bu group can be eliminated by the same procedure as that reported previously[40], and 14 novel C (ortho)–O form products can be expected from the product obtained this time.

4 Conclusion

In the homo-coupling reaction of phenols through the formation of radicals using a metal-free peroxide as the initiator, the C (ortho)–O form was predominantly formed on the basis of the kinetic dominance. This reaction represented an example of the selective synthesis of the diaryl ether by the extremely atypical C (ortho)–O coupling of phenol in organic synthesis, although there was room for improvement of the product yield. The cross-coupling reaction of 2,4,6-tri-tert-butylphenol with the para-substituted phenol was conducted to synthesize seven C (ortho)–O forms. The cross-coupling reaction according to this study was proposed to be a synthesis method for the C (ortho)–O compound through reactions between radicals, affording a novel diaryl ether skeleton by using an unprotected phenol.

5 Experimental section

5.1 General

All reactions were monitored by thin-layer chromatography using a Merck 60 F254 precoated silica gel plate (0.25 mm in thickness). ^{1}H and ^{13}C spectra were recorded on BRUKER DRX-300, JEOL ECX-400, and BRUKER DRX-500 instruments. ^{1}H NMR data were reported as chemical shifts (δ ppm), with multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), integration, and assignment.

^{13}C NMR data were also reported as chemical shifts. Liquid chromatography–mass spectrometry (LC–MS) profiles were recorded on Shimadzu LC-2010CHT and Shimadzu LCMS-2020 systems using a Wakopack Navi C18-5 φ 2.0 mm × 150 mm (D) column. Purification by GPC was conducted by using a MULTIPLE PREPARATIVE HPLC LC-FORTE/R (YMC) and transferring the mobile-phase solvent EtOAc to YMC GPC T-2000 (21.2 × 600 mm) and T-4000 columns (21.2 × 600 mm) to 10.0 mL/min. FTIR spectra were recorded on a Nicolet iS10 FTIR spectrometer (KBr pellet method). High-resolution mass spectra were recorded on a Hitachi Nano Frontier LD spectrometer (APCI).

5.2 Chemicals

Reagents purchased from TCI and Wako were used without purification. 4-Allylphenol was synthesized by the method reported by Agharahimi et al.[41]

*5.2.1 Typical procedure for the homo-coupling reaction (**2a**)*

First, p-cresol (**1a**, 96.0 mg, 0.9 mmol, 1 equiv) was added to PhCl (4.5 mL, 0.2 M) in a pressure-resistant vessel, and (^{t}BuO)$_2$ (655.2 mg, 5 equiv) was added dropwise to this solution at room temperature. Second, this solution was bubbled with Ar for 15 min and then heated at 130 ° C in a pressure-resistant vessel. After 2 h, the reaction solution was cooled to room temperature, and the solvent was then removed under reduced pressure. Finally, the crude product was purified by PTLC and GPC to obtain homo-coupled product **2a** (19.9 mg, 21%).

^{1}H NMR ($CDCl_3$) δ 7.15 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 3H), 6.81 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 5.42 (s, 1H), 2.34 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.6, 145.1, 143.8, 133.3, 130.5, 130.3, 124.9, 119.0, 118.3, 115.7, 20.8, 20.8; IR (KBr): 3517 (br m), 2922 (m), 1600 (s), 1513 (s), 1504 (s) cm^{-1}. HRMS (APCI−) m/z calculated for $[C_{14}H_{13}O_2]^-$ 213.09210; found 213.09191.

Compound 2b was prepared using a typical procedure described above using **1b**, affording homo-coupled product **2b** in a 7% yield. The product was confirmed by comparing with the ^{1}H NMR spectrum of a known compound[19].

Compound 2c was prepared using a typical procedure described above using **1c**, affording homo-coupled product **2c** in an 11% yield. The product was confirmed by comparing with the ^{1}H NMR spectrum of a known compound[6].

Compound 2d was prepared using a typical procedure described above using **1d**, affording homo-coupled product **2d** in an 18% yield. ^{1}H NMR ($CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.83 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 5.41 (br s, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.46 (t *J* = 7.8 Hz, 2H), 1.61 (quintet, *J* = 6.9 Hz, 2H), 1.51 (quintet, *J* = 6.9 Hz, 2H), 1.42–1.17 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.9, 145.3, 143.4, 138.2, 135.6, 129.8, 124.4, 118.7, 117.8, 115.8, 35.3, 35.3, 31.6, 31.5, 31.5, 31.4, 22.7, 22.6, 14.2, 14.2; IR (KBr): 3559, 2928, 1599, 1505 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{22}H_{29}O_2]^-$ 325.21730; found 325.21618.

The ***isodityrosine*** **derivative (2e)** was prepared using a typical procedure described above using **1e**, affording homo-coupled product **2e** in a 7% yield.

^{1}H NMR ($CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.80 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 5.49 (s, 1H), 5.04–4.89 (m, 2H), 4.63–4.43 (m, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 3.16–2.85 (m, 4H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.4, 172.3, 155.9, 155.2, 155.1, 146.7, 143.2, 131.4, 130.9, 128.5, 125.9, 119.8, 118.1, 116.3, 80.2, 80.1, 54.6, 54.5, 52.5, 52.4, 37.7, 37.7, 28.4, 28.4; IR (KBr): 3367, 2977, 1713, 1595, 1506 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{30}H_{39}N_2O_{10}]^-$ 587.26102; found 587.26064.

*5.3 Typical procedure for the cross-coupling reaction (**6a**)*

First, 2,4,6-tri-tert-butylphenol (BHTs, 1.0 equiv, 116.2 mg, 0.46 mmol) and *p*-cresol (1 equiv, 50.1 mg, 0.46 mmol) were added to PhCl (2.3 mL, 0.2 M) in a pressure-resistant vessel, and (^{t}BuO)$_2$ (335.6 mg, 2.3 mmol, 5 equiv) was added dropwise to this solution at room temperature. Second, this solution was bubbled with Ar for 15 min and then treated at 130 °C in a pressure-resistant vessel. After 4 h, the reaction solution was cooled to room

temperature, and the solvent was then removed under reduced pressure. Finally, the crude product was purified by PTLC to obtain cross-coupled product **6a** (54.8 mg, 40%). The final product was verified by comparing with the ^{1}H NMR spectrum of a known compound.

Compound 6b was prepared using a typical procedure described above using **1b**, affording cross-coupled product **6b** in a 57% yield. ^{1}H NMR ($CDCl_3$) δ 7.34 (d, *J* = 6.6 Hz, 2H), 7.08 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 6.6 Hz, 2H), 6.84 (d, *J* = 1.8 Hz, 1H), 5.73 (s, 1H), 1.44 (s, 9H), 1.32 (s, 9H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.0, 146.0, 144.1, 142.8, 142.1, 136.2, 126.7, 119.0, 116.8, 114.0, 35.2, 34.6, 34.4, 31.7, 31.6, 29.7; IR (KBr): 3543, 2961, 1593, 1508 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{24}H_{33}O_2]$- 353.24860; found 353.24737.

Compound 6c was prepared using a typical procedure described above using **1c**, affording cross-coupled product **6c** in a 39% yield. ^{1}H NMR ($CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.05–5.88 (m, 1H), 5.73 (s, 1H), 5.15–5.05 (m, 2H), 3.37 (d, *J* = 6.9 Hz, 2H), 1.44 (s, 9H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.6, 143.9, 143.0, 142.2, 137.6, 136.2, 135.0, 130.0, 118.9, 117.7, 116.0, 113.7, 39.6, 35.2, 34.6, 31.7, 29.7; IR (KBr): 3541, 2958, 1592, 1505 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{23}H_{29}O_2]^-$ 337.21730; found 337.21636.

Compound 6d was prepared using a typical procedure described above using **1d**, affording cross-coupled product **6d** in a 43% yield. ^{1}H NMR ($CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 5.75 (s, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.62 (quin, *J* = 7.5 Hz, 2H), 1.44 (s, 9H), 1.39–1.28 (m, 4H), 1.24 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.2, 143.9, 143.1, 142.1, 137.9, 129.7, 128.1, 118.8, 117.6, 113.6, 35.3, 35.2, 34.6, 31.7, 31.6, 31.5, 29.6, 22.7, 14.2; IR (KBr): 3542, 2957, 1731, 1593, 1506 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{25}H_{35}O_2]^-$ 367.26425; found 367.26322.

Compound 6e was prepared using a typical procedure described above using **1e**, affording cross-coupled product **6e** in a 56% yield. ^{1}H NMR ($CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz,

2H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 2.1 Hz, 1H), 5.69 (s, 1H), 5.00 (d, *J* = 8.1 Hz, 1H), 4.64–4.51 (m, 1H), 3.72 (s, 3H), 3.10 (dd, *J* = 13.7 Hz, *J* = 5.7 Hz, 1H), 3.02 (dd, *J* = 14.1 Hz, *J* = 6.0 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.4, 156.5, 155.2, 144.0, 142.7, 142.2, 136.4, 130.8, 130.7, 119.2, 117.6, 114.0, 80.1, 54.6, 52.4, 37.7, 35.2, 34.6, 31.7, 29.6, 28.4; IR (KBr): 3535 (br m), 2957, 1715, 1591, 1506 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{29}H_{40}NO_6]^-$ 498.28611; found 498.28716.

Compound 6f was prepared using a typical procedure described above using **1f**, affording cross-coupled product **6f** in a 16% yield. ^{1}H NMR ($CDCl_3$) δ 7.03 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 2.4 Hz, 1H), 5.82 (s, 1H), 3.81 (s, 3H), 1.44 (s, 9H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.8, 150.4, 144.2, 143.4, 142.0, 136.0, 119.6, 118.3, 115.0, 112.4, 55.8, 35.2, 34.6, 31.7, 29.6; IR (KBr): 3538, 2956, 1592, 1505 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{21}H_{27}O_3]^-$ 327.19657; found 327.19531.

Compound 6g was prepared using a typical procedure described above using **1g**, affording cross-coupled product **6g** in a 23% yield. ^{1}H NMR ($CDCl_3$) δ 7.33–7.21 (m, 5H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 9.3 Hz, 2H), 6.84 (d, *J* = 2.1 Hz, 1H), 5.71 (s, 1H), 1.68 (s, 6H), 1.43 (s, 9H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.2, 150.7, 145.6, 144.0, 142.7, 142.2, 136.3, 128.2, 128.2, 126.9, 125.8, 119.1, 116.8, 114.1, 42.6, 35.2, 34.6, 31.7, 31.0, 29.6; IR (KBr): 3541, 2963, 1592, 1504 cm^{-1}. HRMS (APCI-) m/z calculated for $[C_{29}H_{35}O_2]^-$ 415.26425; found 415.26456.

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Supplementary data

Supplementary data to this article can be found online

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Figure Legends and Schemes

Figure 1. Natural products of related phenols including dimers and trimers.
Figure 2. Temporal change in the product yield obtained from the coupling reaction: A) (^{t}BuO)$_2$ in air; B) (^{t}BuO)$_2$ in Ar; C) 1 eq Ag_2CO_3 in air; D) 2 eq Ag_2CO_3 in air. **1a**: *p*-cresol, **2a**: C (ortho)–O coupling compound, **3a**: C (ortho)–C (ortho) coupling compound.
Figure 3. IR spectra of the (A) C (ortho)–O dimer, (B) C (ortho)–C (ortho) dimer, (C) oligomers of **entry 4** in **Table 1**, and (D) Oligomers of **entry 6** in **Table 1**.
Figure 4. Enthalpy change for the A) homo-coupling reaction of *p*-cresol and B) cross-coupling reaction between *p*-cresol and BHTs.
Scheme 1. Selective examples of the direct synthesis of diaryl ethers by a radical reaction in homo- or cross-coupling.
Scheme 2. Investigation of the cross-coupling reaction between p-cresol and various phenols.
Scheme 3. Relation between the kinetic selectivity and thermodynamic stability for the coupling of para-substituted phenols

2. Results

2.1. Model reaction

First, p-cresol with a simple phenol structure was selected as a model substrate, and a homo-coupling reaction was conducted. As the radicalizing reagent of phenol, metal reagents[14, 15] and p-benzoquinone,[26] which are one-electron oxidizing agents, and peroxides,[13, 14, 16] which are radical initiators, are used, and the yield to p-cresol (Table 1). The high-temperature reaction was conducted under pressure in a sealed container to suppress the volatilization of solvents and reagents.

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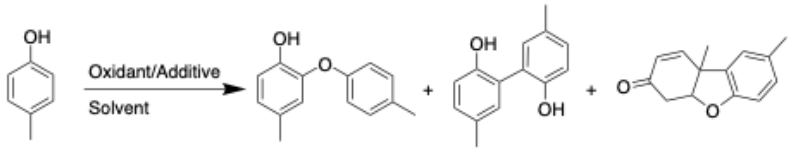
Table 1. Reaction conditions for the dimerization of p-cresol



p-cresol (**1a**) **2a** **3a** Pummerer ketone

Entry	Ox.	Add.	Solv.	Temp. [°C]	Time [h]	Atmo.	Yield [%]* **2a** (C–O)	Yield [%]* **3a** (C–C)	CO:CC
1***	0.1 eq(^{t}BuO)$_2$	-	PhCl	130	24	air	14	29	33:67
2	1 eq (^{t}BuO)$_2$	-	PhCl	130	3	air	10	<1	>95:<5