# Ammonium Salt Catalyzed Highly Practical *Ortho*-Selective Mono-Halogenation and Phenylselenation of Phenols: Scope and Applications

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# Ammonium Salt Catalyzed Highly Practical *Ortho*-Selective Mono-Halogenation and Phenylselenation of Phenols: Scope and Applications

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ABSTRACT: An *ortho*-selective ammonium chloride salt-catalyzed direct C-H mono-halogenation of phenols and 1,1′-bi-2-naphthol (BINOL) with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the chlorinating agent has been developed. The catalyst loading was low (down to 0.01 mol%) and the reaction conditions were very mild. A wide range of substrates including BINOLs were compatible with this catalytic protocol. Chlorinated BINOLs are useful synthons for the synthesis of a wide range of unsymmetrical 3-aryl BINOLs that are not easily accessible. In addition, the same catalytic system can facilitate the *ortho*-selective selenylation of phenols.

KEYWORDS**:** ammonium salt, BINOL, halogenation, orgnaocatalysis, phenol, mechanism, selenylation

## 1. INTRODUCTION

Halogenated phenols, naphthols, and their derivatives (e.g. BINOLs) are widely found in numerous natural products,[1-4] pharmaceuticals,[5-7] bioactive compounds and fine chemicals.[8-12] They are also frequently employed as the key precursors in various chemical transformations.[13-15] In the fields of agrochemical and drug discovery, chlorinated compounds are frequently employed to enhance the biological properties.[11-12] Moreover, halogenated BINOLs (e.g. 3,3'-dihalogenated BINOLs) are very useful ligand precursors.[16-19]

Direct C-H halogenation of phenols using electrophilic halogen source is a common method to prepare halogenated phenols. However, treatment of phenols with halogen sources usually give a mixture of polyhalogenated products with *para*-halogenated products preferentially obtained due to their inherent selectivity resulted from the electronic property and steric demand.[20-25] Despite the fact that *ortho*-halogenated phenols and BINOLs are privileged building blocks, direct C-H halogenations to generate the *ortho*-selective halogenated products remain highly challenging; harsh conditions and multi-step chemical operations are often required. [26-27] Thus, the development of a mild, efficient and regioselective method to access *ortho*-halogenated phenols has received continuous attention from the synthetic community.

Among the existing methods, *ortho*-metalation (e.g. lithiation) is a prominent strategy for the preparation of *ortho*-halogenated phenols. However, this strategy often suffers from harsh reaction conditions and narrow substrate scope.[28-29] Transition metal-catalyzed directed C-H halogenations emerged as highly atom- and step-economic methods for C-X (X= Cl, Br, I) bonds formation and significant progress was demonstrated by the examples of *ortho*-selective halogenation of aniline.[30-32] However, the application of these strategies in the *ortho*-halogenation of phenols and BINOLs remain underexploited. Research efforts on using non-

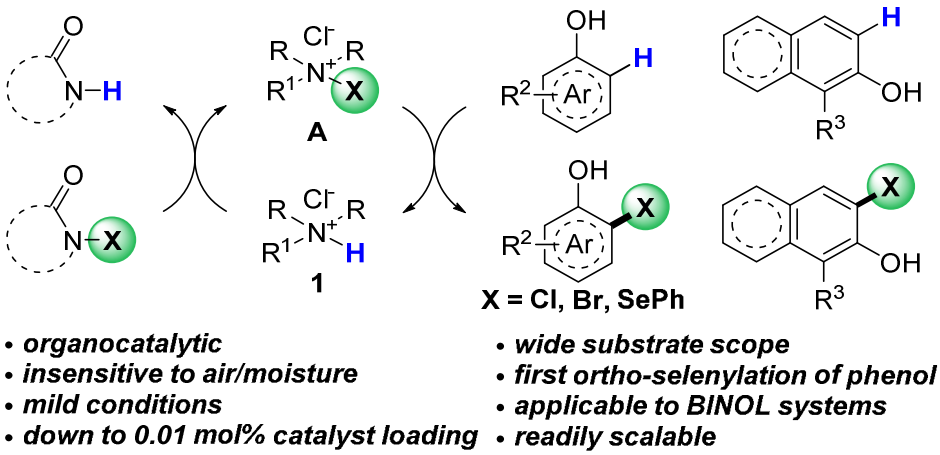
metal promotors/catalysts in the *ortho*-selective halogenation of phenols are also sporadic. Fujisaki reported the pioneer work on an amine-catalyzed *ortho*-bromination of 2-substituted phenols with *N*-bromosuccinimide (NBS) as the stoichiometric halogen source.[33] Later, Sheldon[34] and Snider[35] independently disclosed that the *ortho*-chlorination of a few phenols could be achieved using amines as the catalysts and $SO_2Cl_2$ as the halogen source at elevated temperature. Recently, seminal study has shown that the use of 10 mol% of Nagasawa's bis-thiourea catalyst could promote the chlorination through dual activation of both the phenol and *N*-chlorosuccinimide (NCS) to yield the corresponding *ortho*-halogenated compounds in moderate-to-good regioselectivity.[36] Although some advancements have been achieved in this area, drawbacks including the use of strongly acidic reagent and relatively expensive catalyst, and limited substrate scope hampered their synthetic applications and large-scale production.

Consequently, the development of a sophisticated catalytic protocol aiming at high efficiency, selectivity, and practicality together with wide substrate scope of the *ortho*-halogenation is highly desired. Herein, we are pleased to describe a mild and highly practical catalytic protocol for *ortho*-selective halogenation of phenols and naphthols. Ammonium chloride salts were used as catalysts that are inexpensive and easy to handle. This method can be applied to prepare valuable BINOL ligands at large scale. In addition, the protocol was applied to the first case of organocatalytic *ortho*-selective selenylation of phenols (Scheme 1).

## 2. RESULTS AND DISCUSSION

### 2.1 Reaction optimization

It has been reported that ammonium salts **1**, which can easily be prepared from inexpensive amines and hydrochloric acid, are extremely effective for highly regioselective *ortho*-chlorination of anilines and the in situ generated halogenating agent **A** is believed to be the active



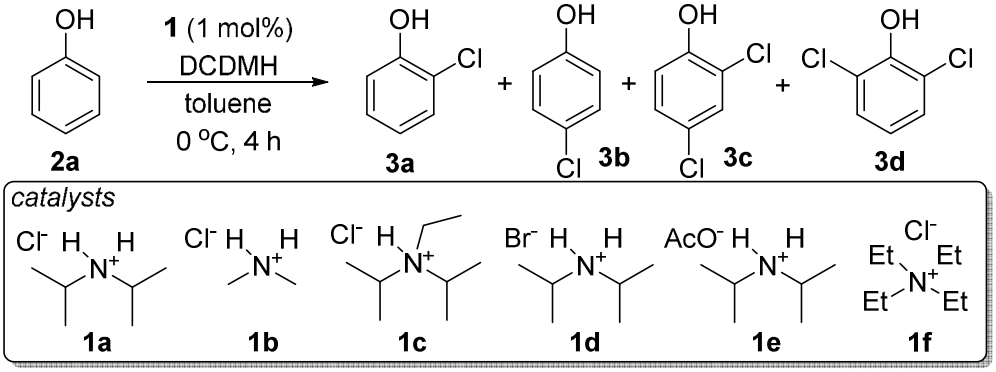

**Scheme 1.** Organocatalytic *ortho*-selective halogenation of phenols and BINOLs

species.[37] We anticipated that phenols or BINOLs, which have acidic protons, could interact with the species **A** and direct the C-H mono-halogenation at the *ortho*-position (Scheme 1). It is worth-mentioning that as compared with anilines, halogenation of phenols is non-trivial since halogenating agents can oxidize phenol compounds readily.[38]

Phenol (**2a**) was chosen as the model substrate and the reaction was conducted at 0 $^{o}$C. Toluene and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) were used as the solvent and the halogenation source, respectively. The reaction was sluggish in the absence of catalyst (Table 1, entries 1 and 2). Nonetheless, we are delighted to realize that the desired *ortho*-chlorinated product **3a** was obtained in 97% isolated yield by employing 1 mol% of ammonium salt catalyst **1a** (entry 3). Notably, only negligible amount of chlorinated isomers was detected. The less bulky ammonium salt **1b** gave slightly lower *ortho*-selectivity (entry 4). Ammonium salt **1c** that is derived from Hünig's base still gave appreciable *ortho*-selectivity although the reaction was relatively sluggish (entry 5). Poorer *ortho*-selectivity was observed when employing the ammonium salt with a bromide (**1d**) or an acetate (**1e**) counter anion, suggesting that the chloride anion in **1a** might play an important role in dictating the site-selectivity (entries 6 and 7). While

the tetraalkylammonium salt **1f** could promote the chlorination of phenol (**2a**), *p*-chlorophenol (**3b**) was found to be the major product (entry 8). Since no observable catalyst degradation was noticed during the reaction, we attempted to lower the catalyst loading of **1a** and studied the efficiency of the *ortho*-chlorination of **2a**. It was found that the reaction could still proceed smoothly at a 0.05 mol% catalyst loading to give **3a** in 96% yield, although a relatively longer reaction time (16 h) was found to be necessary to give reasonably high conversion (entry 9). To our delight, 90% of **3a** could still be obtained when just 0.01 mol % of **1a** was applied (entry 10). The relatively low reaction rate could be compensated by increasing the reaction temperature from 0 to 25 $^{o}$C but a slight decrease in the *ortho*-selectivity was observed (entry 11). We have also conducted the reaction using *i*$Pr_2NH$ instead of **1a** and poor *ortho*/*para*-selectivity was observed, which further highlighted the crucial role of ammonium salt in this catalytic protocol (entry 12). Thus, the conditions in Table 1, entry 3 were then chosen for the exploration of scope indicated in the following sections.

**Table 1.** Catalyst Optimization[a]




| entry | Catalyst (loading) | yield of **3a** (%)[b] | ratio (**2a**/**3a**/**3b**/**3c**/**3d**)[c] |
|---|---|---|---|
| 1 | - | trace | >99/0/0/0/0 |
| 2[d] | - | <5 | >95/5/0/0/0 |

| | | | |
|---|---|---|---|
| 3 | **1a** (1 mol%) | 97 | 0/98/0/1/1 |
| 4 | **1b** (1 mol%) | 89 | 0/93/4/0/1 |
| 5 | **1c** (1 mol%) | 63 | 5/65/9/21/1 |
| 6 | **1d** (1 mol%) | 86 | 1/90/4/1/1 |
| 7 | **1e** (1 mol%) | 63 | 16/74/9/0/1 |
| 8 | **1f** (1 mol%) | 25 | 2/30/65/3/0 |
| 9[e] | **1a** (0.05 mol%) | 96 | 2/>95/3/0/0 |
| 10[d] | **1a** (0.01 mol%) | 90 | 5/91/4/0/0 |
| 11[f] | **1a** (0.01 mol%) | 95 | 0/94/2/2/2 |
| 12 | *i*$Pr_2$NH (10 mol%) | 62 | 23/65/22/0/0 |

[a] Reactions were carried out with phenol (**2a**) (0.2 mmol), catalyst **1** (1 mol%), and DCDMH (0.2 mmol) in toluene (3 mL) in the absence of light at 0 $^{o}$C. [b] Isolated yield of **3a**. [c] The ratios were determined by GC/MS analysis. [d] The reaction time was 24 h. [e] The reaction time was 16 h. [f] The reaction was conducted at 25 $^{o}$C for 6 h. DCDMH = 1,3-dichloro-5,5-dimethylhydantoin.

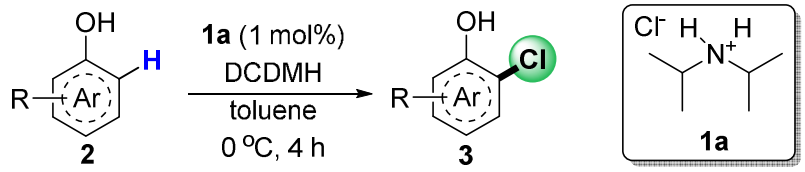
### 2.2 Exploration of the *ortho*-chlorination scope

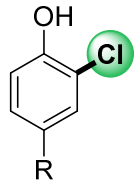
We then examined the generality of catalyst **1a** in this transformation and the results are summarized in Table 2. In general, high site-selectivity at the *ortho*-position of phenol was observed. A series of *para*-substituted phenols **2b–2h** bearing either electron-withdrawing or electron-donating groups were well tolerated, providing the desired mono-chlorinated products **3b–3h** in excellent yields. For the *meta*-substituted phenolic substrates **2i–2k**, chlorination proceeded smoothly at the sterically less hindered C(6) position to give **3i–3k** with high site-selectivity. On the other hand, for the *meta*-substituted substrates with substituents including ester, ketone, aldehyde and boronic ester (**2l–2p**), the *ortho*-chlorination happened selectively at the sterically more congested C(2) position, furnishing the mono-chlorinated products **3l–3p** in good isolated yields. These phenomena could be attributed to the syngeneic directing effect (potentially through hydrogen bonding) of the OH and the *meta*-substituted functional groups

(see Section 2.8). The chlorination of the sterically hindered *ortho*-substituted substrates **2q–2w** worked equally well to furnish the corresponding *ortho*-chlorinated compounds **3q–3w** in good-to-excellent yields. 3,5- and 3,6-disubstitued substrates **2x–2z** also were also compatible with this methodology.

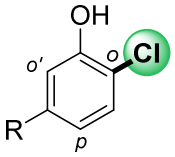
Under the optimized reaction conditions, **3aa** could also be obtained smoothly when using the naphthyl substrates **2aa**. Resorcinol (**2ac**) could also readily undergo double *ortho*-chlorination to yield **3ac**. This method was found to be applicable to the late-stage modification of estrone derivative **2ad** to give the *ortho*-selective chlorination products **3ad** in 68% yield. The practicalities of this catalytic protocol were demonstrated by the gram-scale reactions with **2g**, **2l**, **2u**, and **2y** as the substrates and excellent product yields of **3g**, **3l**, **3u**, and **3y** were still obtained.

**Table 2.** Substrate scope of the *ortho*-chlorination of phenols [a]

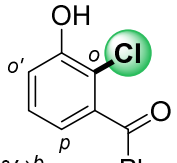


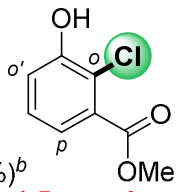

**3a**, R = H (97%)
**3b**, R = Et (89%)
**3c**, R = Ph (96%)
**3d**, R = F (91%)
**3e**, R = Cl (93%)
**3f**, R = Br (91%)
**3g**, R = I (96%, ***1.2 g scale***)
**3h**, R = C(O)Me (92%)[b]



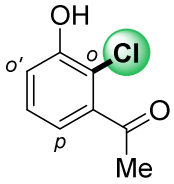

**3i**, R = F (80%); *o-Cl:o'-Cl:p-Cl (>50:1:0)*[e]
**3j**, R = Cl (59%)[c]; *o-Cl:o'-Cl:p-Cl (11:4:1)*[e]
**3k**, R = Br (57%)[c]; *o-Cl:o'-Cl:p-Cl (13:7:1)*[e]



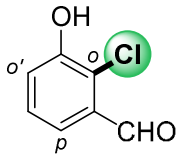

**3m** (71%)[b] *o-Cl:o'-Cl:p-Cl (13:1:0)*[e]



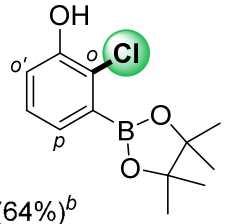

**3l** (89%)[b] (85% @ ***1.5 g scale***) *o-Cl:o'-Cl:p-Cl (32:1:0)*[e]



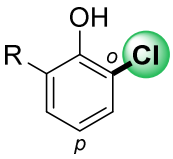

**3n** (86%)[b] *o-Cl:o'-Cl:p-Cl (25:1:0)*[e]



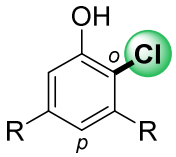

**3o** (93%)[b] *o-Cl:o'-Cl:p-Cl (20:1:0)*[e]



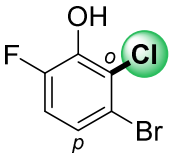

**3p** (64%)[b] *o-Cl:o'-Cl:p-Cl (15:1:0)*[e]



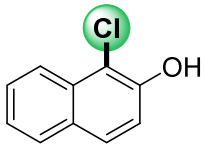

**3q**, R = F (91%); *o-Cl:p-Cl (32:1)*[e]
**3r**, R = Cl (78%)[b]; *o-Cl:p-Cl (19:1)*[e]
**3s**, R = Br (80%)[b]; *o-Cl:p-Cl (>50:1)*[e]
**3t**, R = I (75%)[b]; *o-Cl:p-Cl (>50:1)*[e]
**3u**, R = Ph (97%); *o-Cl:p-Cl (>50:1)*[e] (***2 g scale***)
**3v**, R = 2-Cl-$C_6H_4$ (97%); *o-Cl:p-Cl (>50:1)*[e]
**3w**, R = *t*Bu (90%); *o-Cl:p-Cl (19:1)*[e]



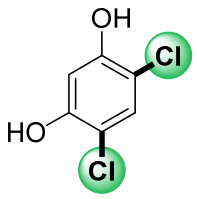

**3x**, R = Me (86%); *o-Cl:p-Cl (15:1)*[e]
**3y**, R = Br (90%); *o-Cl:p-Cl (30:1)*[e] (***1.3 g scale***)



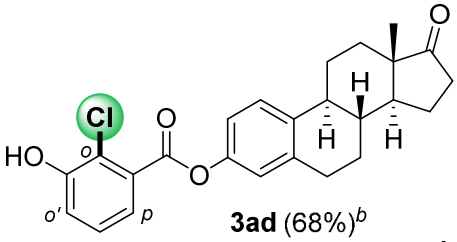

**3z** (94%)[b] *o-Cl:p-Cl (26:1)*[e]




**3aa** (96%)



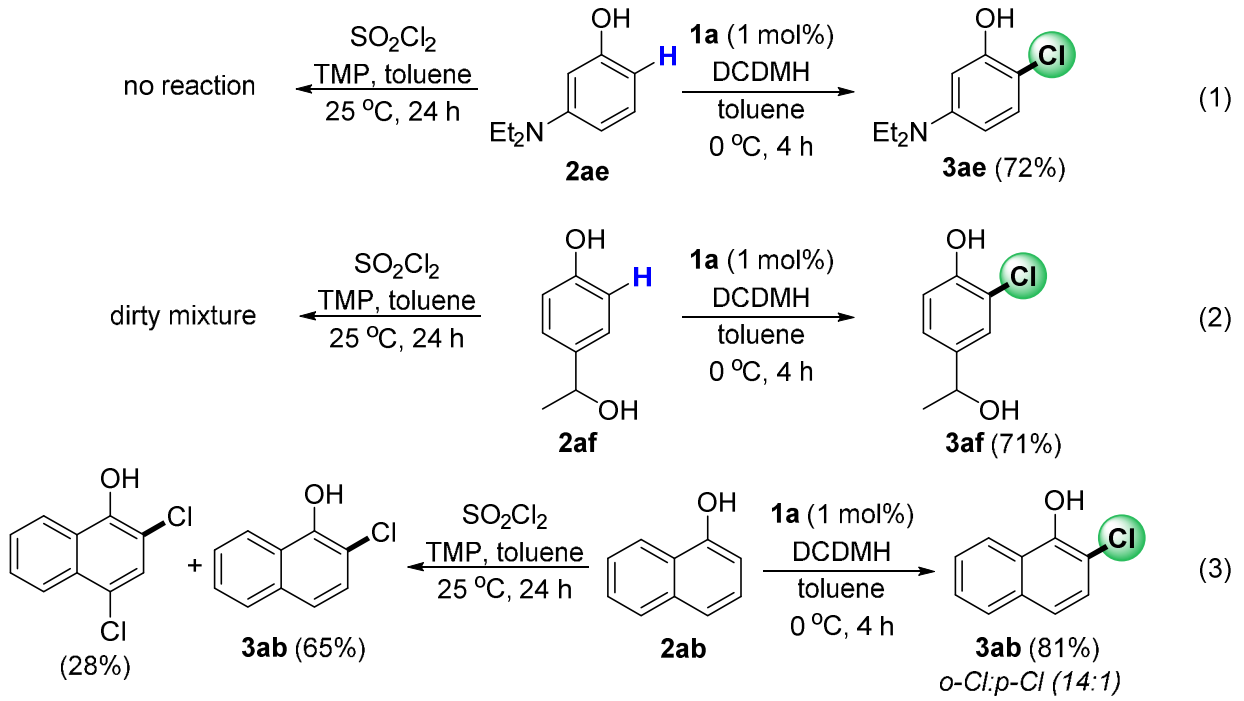

**3ac** (74%)[b,d]




**3ad** (68%)[b] *o-Cl:o'-Cl:p-Cl (8:1:0)*[e,f]

[a] Reactions were carried out with substrate **2** (0.1 mmol), catalyst **1a** (1 mol%, 0.001 mmol), and DCDMH (0.1 mmol) in toluene (2 mL) in the absence of light at 0 °C. The yields were isolated yields (average of two trials) of the pure *o*-chlorinated products. [b] 5 mmol% catalyst **1a** was used. [c] The yield was determined based on the TBS ether derivative. [d] 0.2 mmol of DCDMH was used. [e] The ratio was measured on the crude sample by GC/MS with internal standard. [f] Some starting material was recovered.

Further experimentations revealed that achieving *ortho*-chlorination of phenol or naphthol with high regioselectivity and functional group compatibility is not a trivial task using literature methods. For instance, phenol **2ae** that contains an amine functionality returned sluggish reaction when the classical 2,2,6,6-tetramethylpiperidine (TMP)/$SO_2Cl_2$ protocol was employed.[34-35] On the other hand, the newly developed ammonium salt catalyst system gave the *ortho*-chlorinated product **3ae** smoothly (Scheme 2, eq 1). In addition, ammonium salt **1a** could effectively catalyze the *ortho*-chlorination of **2af** that bears an unprotected hydroxyl group, giving **3af** in 71% isolated yield. In contrast, sluggish reaction together with dirty mixture was observed when applying the TMP/$SO_2Cl_2$ protocol[34-35] to the substrate **2af** (Scheme 2, eq 2). Mono-chlorination of naphthol **2ab** at the *ortho*-position is also not straightforward in which multi-chlorinated products were obtained when employing the TMP/$SO_2Cl_2$ protocol[34-35] (Scheme 2, eq 3), but the mono-chloronaphthol **3ab** could be obtained in high selectivity using our approach. We speculate that the undesirable outcomes using the TMP/$SO_2Cl_2$ protocol could be attributed to the presence of HCl that could protonate the substrates.

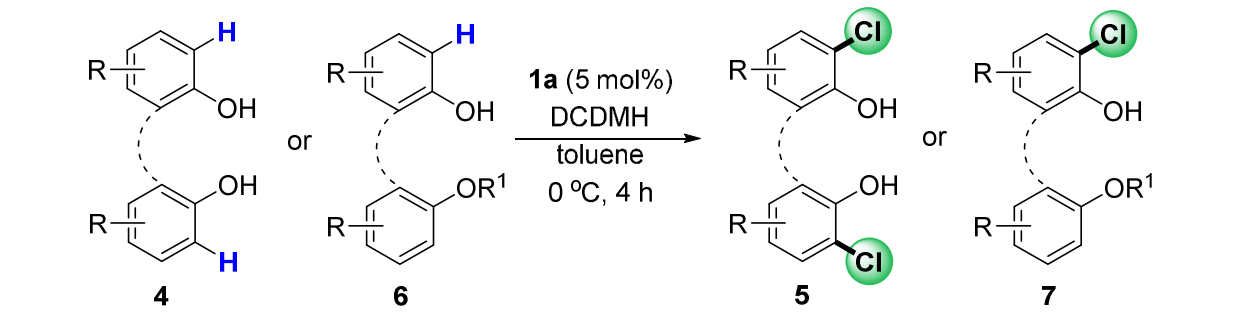


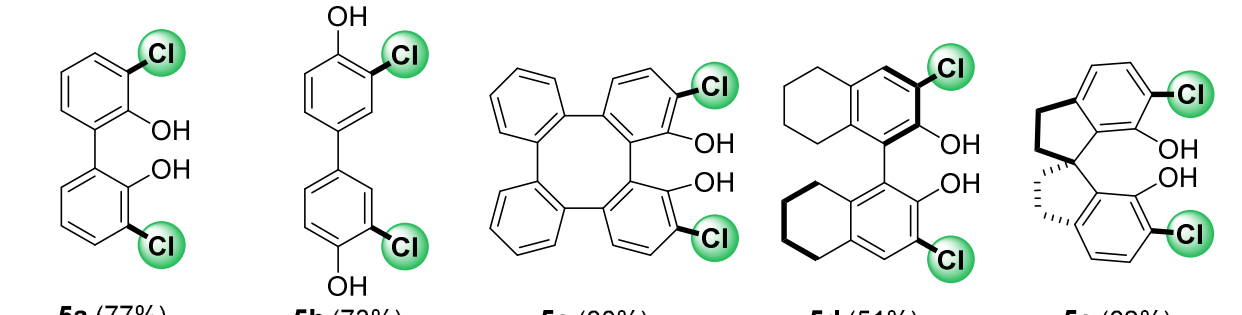

**Scheme 2.** *Ortho*-chlorination of **2ab**, **2ae** and **2af**

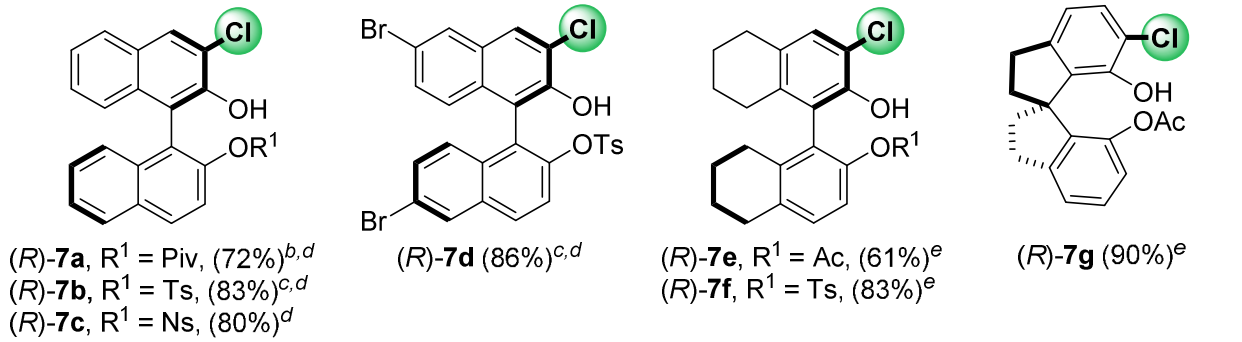
Interestingly, double *ortho*-chlorination of the biphenols **4a**–**4b**, tetraphenylene **4c**[39] and rigid biaryl **4d**–**4e** proceeded readily to provide the corresponding bis-*ortho*-chlorinated products **5a**–**5e** (Table 3). These are very useful intermediates for the preparation of biphenol derivatives,[40-42] which is an important class of ligands that have been extensively applied in various metal-catalyzed asymmetric reactions.[43-46] Particularly, **5d** has been proven to be an exceptionally potent ligand than its bromine derivative in the enantioselective alkene metathesis;[47] the literature procedure for the preparation of **5d** from the corresponding biphenol **4d** is tedious (through the classical approach MOM-protection→lithiation→deprotection sequence). On the other hand, **5d** could be prepared from the direct *ortho*-chlorination of **4d** in a single chemical operation using the ammonium salt catalytic system. The potential application of the *ortho*-chlorination catalytic protocol appears to be quite broad not only with regard to the synthesis of symmetrical *ortho*-chlorinated biphenol derivatives, but also in terms of the preparation of

unsymmetrical mono-chlorinated BINOLs and biphenols with high *ortho*-selectivity. To our delight, chlorination at the *ortho*-position of the naphthol and phenol moieties in **6a**–**6g** proceeded smoothly, giving the corresponding mono-chlorinated products **7a**–**7g** in good isolated yields (Table 3). However, a mixture of chlorinated product was obtained when simple BINOL was used as the substrate.

**Table 3.** O*rtho*-chlorination of biphenols **4** and unsymmetrical BINOLs **6**[a]



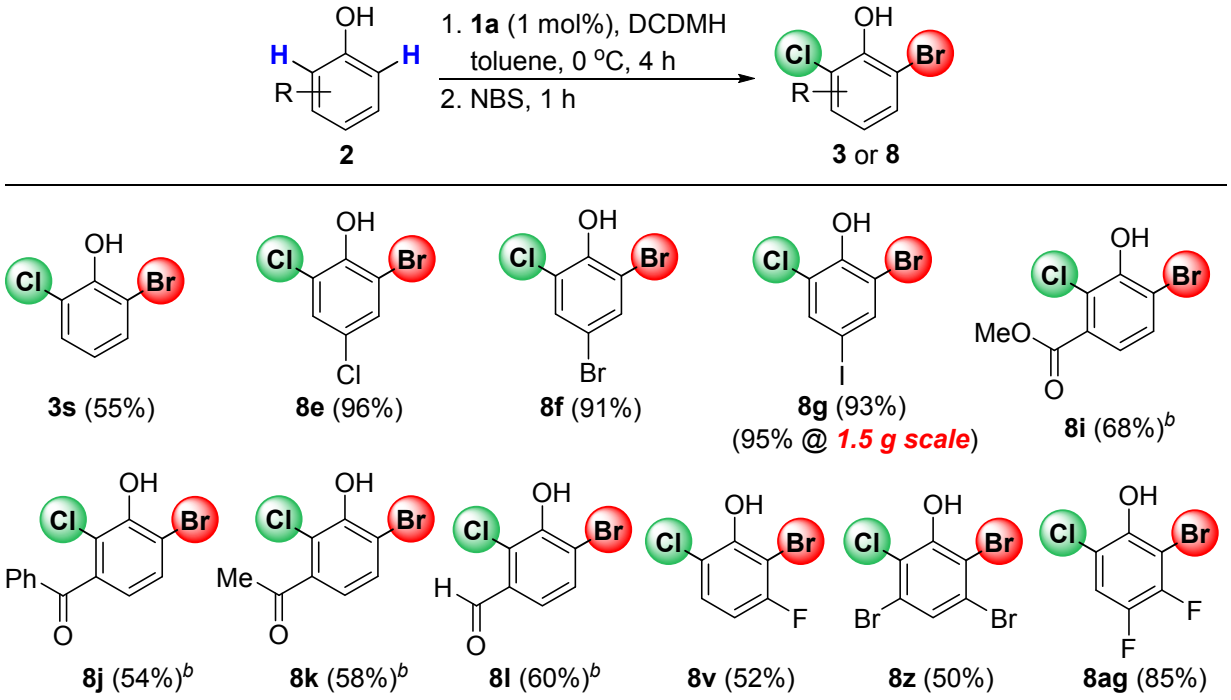




[a] Reactions were carried out with substrate (0.1 mmol), catalyst **1a** (1 mol%, 0.001 mmol), and DCDMH (0.2 mmol) in toluene (2 mL) in the absence of light at 0 °C. The yields were isolated yields (average of two trials). [b] 20 mol% catalyst **1a** was used. [c] 10 mol% catalyst **1a** was used. [d] The reaction was carried out at 25 °C. [e] 1 mol % catalyst **1a** was used.

### 2.3 One-pot sequential *ortho*-halogenation

Despite our success in demonstrating the excellent performance of the ammonium chloride salt **1a** in catalyzing the mono-chlorination of phenols and BINOLs with high *ortho*-selectivity, we sought to explore the versatility of this catalytic halogenation protocol in the one-pot synthesis of 2-chloro-6-bromophenols **8** *via* a sequential *ortho*-selective chlorination and bromination (Table 4). In this process, the phenol substrates **2** were subjected to the standard **1a**-catalyzed *ortho*-chlorination conditions followed by the addition of the other halogen source *N*-bromosuccinimide (NBS). Other than simple phenol, this one-pot chemical operation was applied to the halogenations of a variety of *meta*-and *para*-substituted phenols and the corresponding bis-*ortho*-halogenated phenols **8** were obtained smoothly in all these cases. Again, the reaction was found to be readily scalable through the gram-scale trail in the formation of compound **8g**. These multi-halogenated compounds are attractive building blocks in the synthesis of bioactive compounds and functional materials.[48-50]

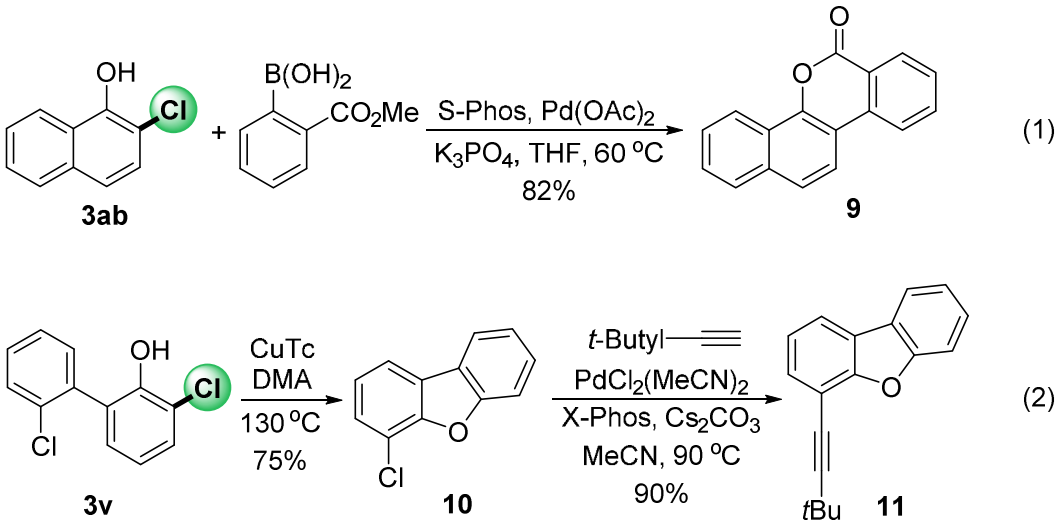
**Table 4.** Substrate scope of the sequential one-pot *ortho*-halogenation[a]




[a] Reactions were carried out with phenol substrate **2** (0.1 mmol), catalyst **1a** (1 mol%, 0.001 mmol), and DCDMH (0.1 mmol) in toluene (2 mL) in the absence of light at 0 °C for 4 h. NBS (0.1 mmol) was then added followed by additional 1 h stirring. The yields were isolated yields (average of two trials) after the two-step reaction. [b] 5 mol% **1a** was used.

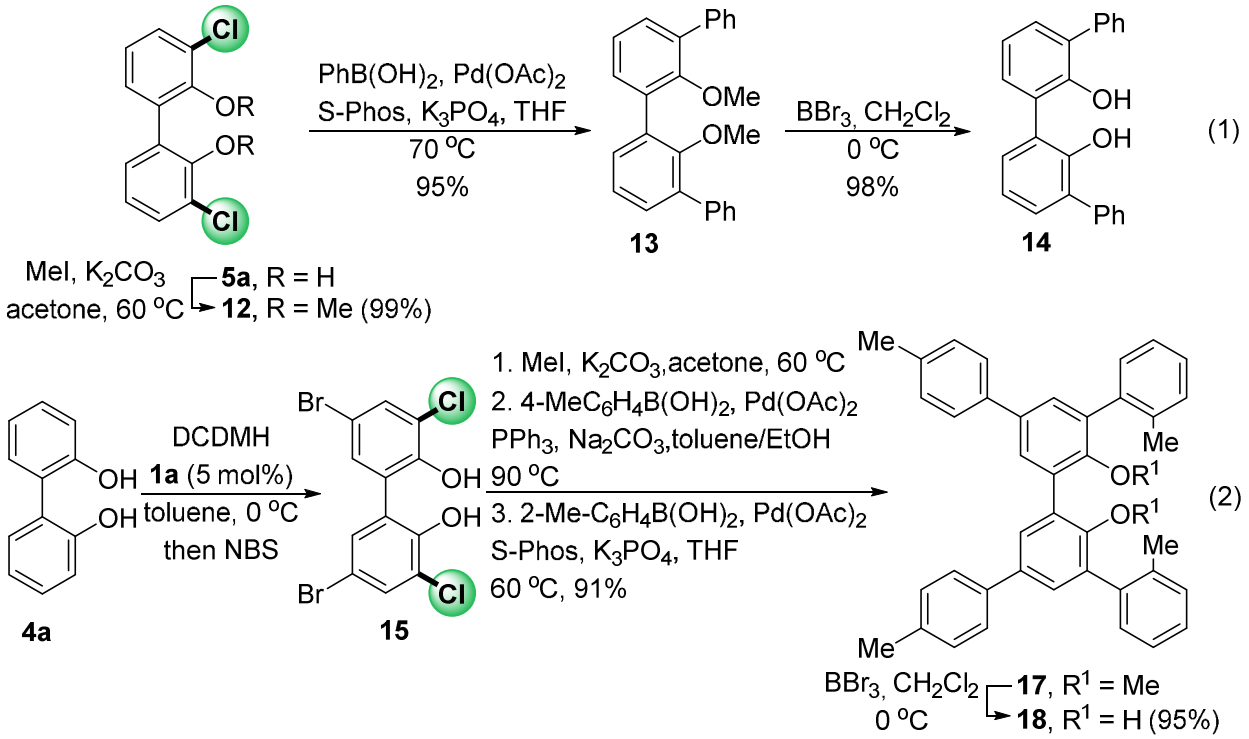
### 2.4 Utilities of the *ortho*-chlorinated phenols and BINOLs

The *ortho*-chlorinated phenols and naphthols are very useful building blocks for the synthesis of functional molecules. For example, *o*-chloronaphthol **3ab** could readily undergo Suzuki-Miyaura cross-coupling/intramolecular transesterification to provide lactone **9** in 82% yield in which the lactone skeleton **9** widely exists in natural products and has been used as the starting material for the preparation of axially chiral biaryl compounds (Scheme 3, eq 1).[51-52] In addition, chlorophenol **3v** could undergo selective intramolecular coupling to form benxofuran **10** in 75% yield.[53-54] Subsequent cross-coupling of **10** with *t*-butylacetylene gave the functionalized benxofuran **11**, which is an important constitutional unit of organic light-emitting diode materials (Scheme 3, eq 2).[55]



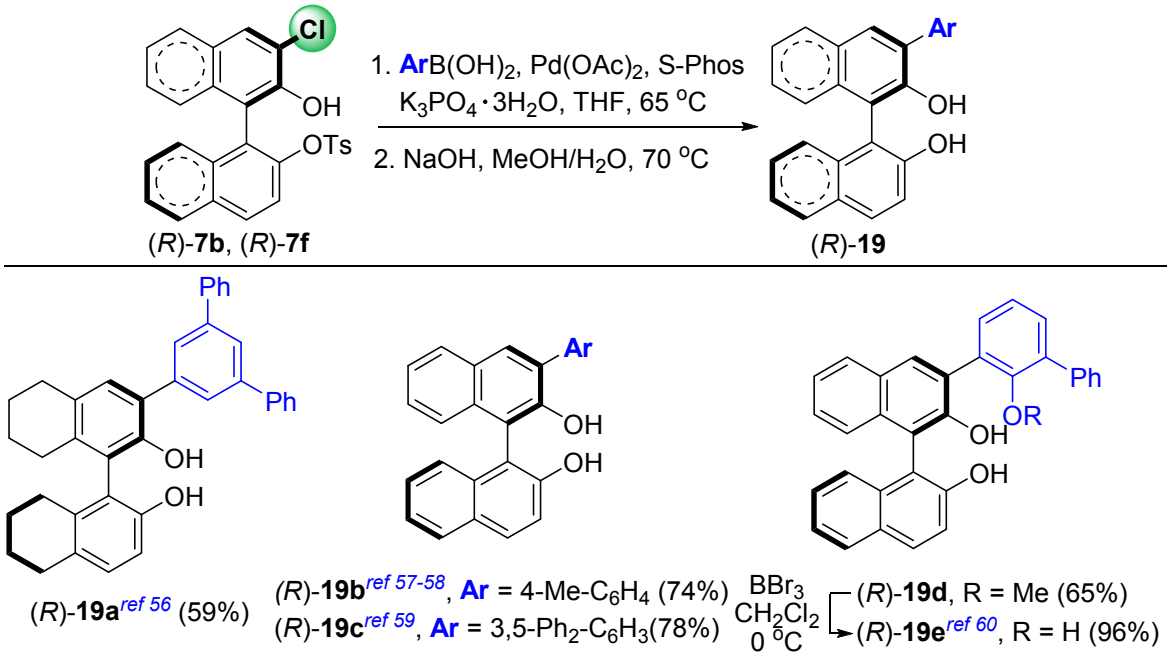

**Scheme 3.** Preparation of functional polycyclic compounds from the *ortho*-chlorinated naphthol **3ab** and phenol **3v**

Another key application of these products is the preparation of ligands. For instance, **5a** is an excellent starting material to prepare biphenol ligands **14** in which this type of ligand has been extensively applied in various metal-catalyzed asymmetric reactions and exhibits much better enantioselectivity than binaphthol in some cases (Scheme 4, eq 1).[43-46] However, the limited structure diversity, partly due to the impractical synthetic sequence, often hinders their applications. Indeed, the functionalization of common biphenol ligands was mainly introduced with the same groups at 3,3'- and 5,5′-positions through lithiation/halogen exchange. Nevertheless, biphenol **15** could readily be obtained by a simple *ortho*-chlorination/*para*-bromination of **4a**. The structure of **15** was confirmed unambiguously by an X-ray crystallographic study. Compound **15** contains two halogen handles with different reactivity towards cross-coupling reaction (Scheme 4, eq 1). A sequential cross-coupling reaction of **15** (after methylation) with different boronic acids could give rise to biphenol ligand **18**. This method provides an easy access to the highly functionalized biphenol ligands.[56-61]



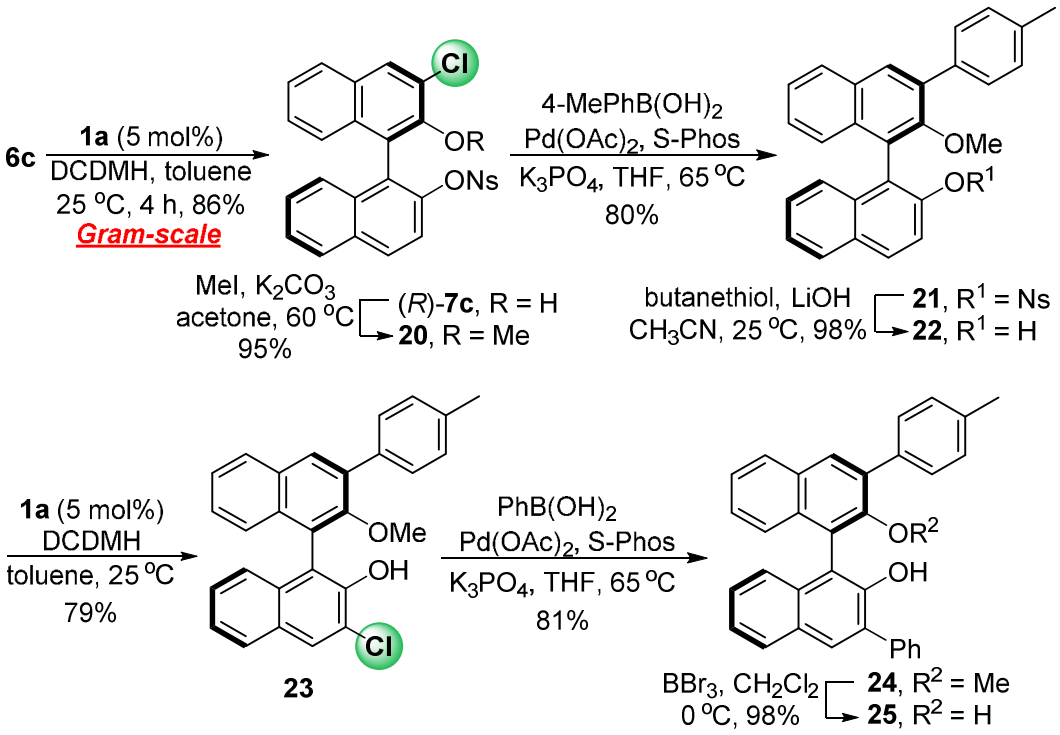

**Scheme 4.** Preparation of biphenol ligands

Other than the preparation of biphenol ligands, the ammonium salt catalytic protocol could be applied to the preparation of chiral unsymmetrical BINOLs and biphenols in which these ligands were found to have superior performance in some challenging reactions.[16-19] For example, it has been demonstrated that the unsymmetrical mono-substituted chiral ligands BINOL (*R*)-**19** have superior performance in some asymmetric reactions as compared with the corresponding symmetrical 3,3′-aryl BINOLs.[56-61] Starting from the *ortho*-halogenated compounds (*R*)-**7b** and (*R*)-**7f**, coupling reactions using different boronic acids followed by hydrolysis under basic condition gave a series of chiral ligands (*R*)-**19** (Scheme 5). Typically, the synthesis of these type of special ligands involves the use of very moisture sensitive organolithium or Grignard reagents at very low temperature, which is tedious and non-trivial for large-scale production.[54-59] On the other hand, the present catalytic protocol is operationally simply with high synthetic convenience.




**Scheme 5.** Preparation of mono-substituted BINOL ligands **19**

In addition, this method could offer an easy access to the unsymmetrical di-substituted 3,3'-aryl BINOLs. For instance, the 3-aryl substituted compound **21** could be efficiently prepared by the palladium catalyzed cross-coupling reaction of the methylated compound **20** (prepared from the *ortho*-chlorination of **6c** in gram-scale) with 4-methylphenyl boronic acid (Scheme 6). After removal of the nosyl group in **21** to give **22**, the naphthol moiety in **22** could undergo the *ortho*-selective chlorination to give **23** in 79% yield. Subsequent cross-coupling reaction and demethylation furnished the unsymmetrical 3,3'-aryl BINOL **25**. Again, this synthetic avenue is readily scalable since the key starting material (*R*)-**7c** could be prepared in gram-scale using the ammonium salt catalytic protocol.

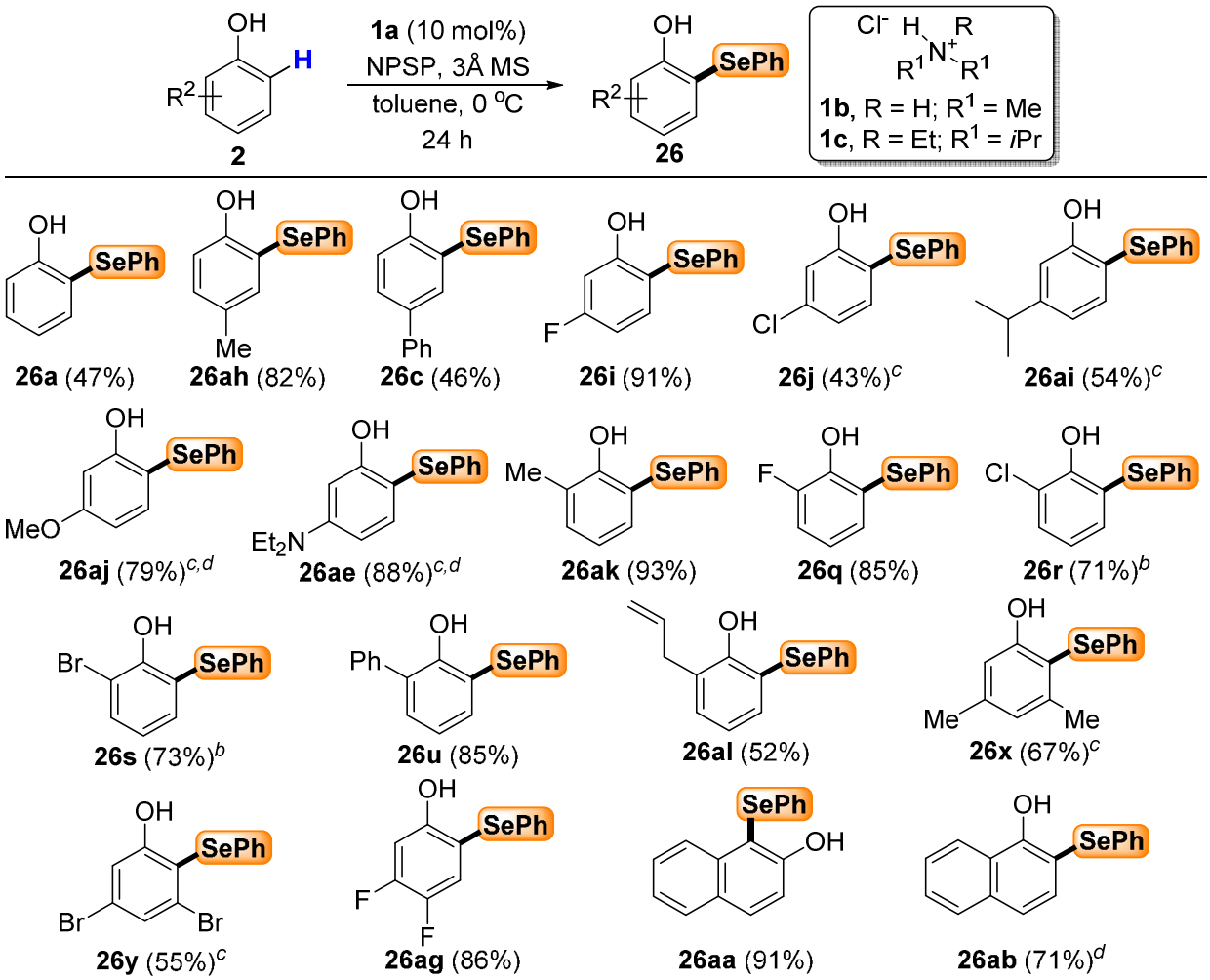



**Scheme 6.** Preparation of unsymmetrical BINOL ligands

### 2.5 Exploration of the *ortho*-selenylation scope

Further evaluation of the ammonium chloride salt showed that catalyst **1a** could catalyze the direct C-H *ortho*-selenylation of phenols with *N*-(phenylseleno)phthalimide (NPSP) as the electrophile. As shown in Table 5, phenols with diverse functionalities were proved compatible under this catalytic protocol and could react smoothly with the selenium reagent NPSP to furnish the corresponding *ortho*-selenylated phenols **26**. Interestingly, allyl-substituted substrate **2al**, which is known to readily undergo selenoetherification,[62] was well-tolerated under this reaction to generate the *ortho*-selenylated product **26al**. For the substrates that have relatively lower reactivity, the less sterically hindered ammonium salt catalyst **1b** was required to ensure a reasonable rate of selenylation, furnishing **26r** and **26s** in good yields. In the case of the *meta*-substituted phenol substrates, monoselenylation could be achieved in moderate-to-excellent yields (**26j**, **26ai**, **26aj**, **26ae**) with ammonium salt catalyst **1c**. The selenylation of naphthols was

**Table 5.** Substrate scope of the *ortho*-selenylation[a]



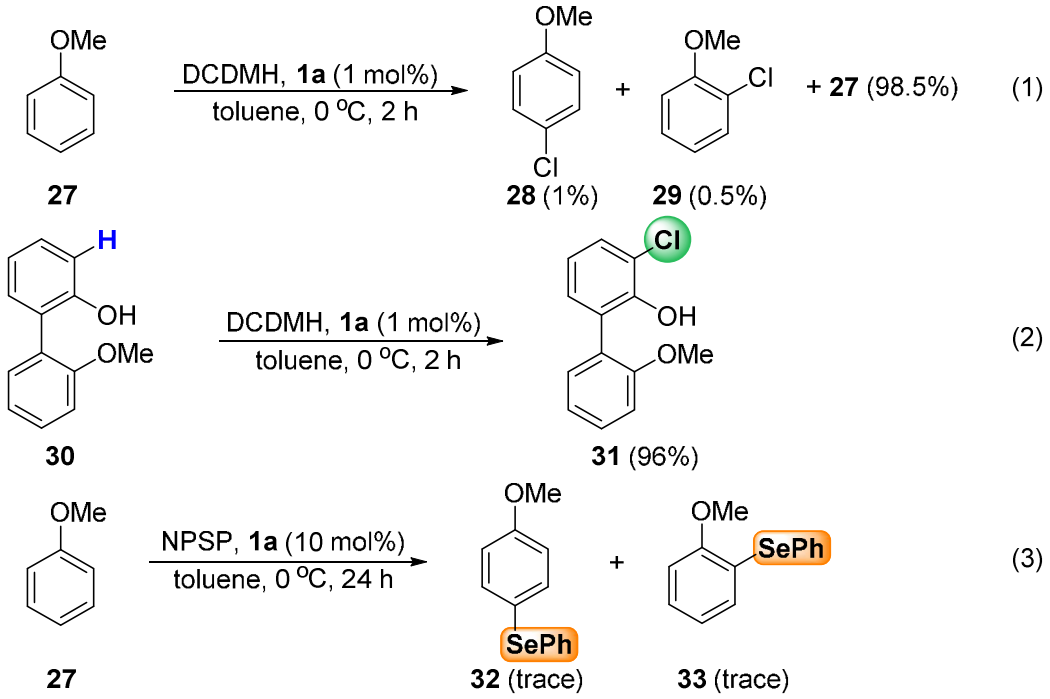

[a] Reactions were carried out with phenol substrate (0.1 mmol), catalyst **1a** (10 mol%, 0.01 mmol), NPSP (0.2 mmol) and 3Å MS (10 mg) in toluene (2 mL) in the absence of light at 0 °C. The yields were isolated yields (average of two trials). [b] **1b** was used as the catalyst. [c] **1c** was used as the catalyst. [d] The reactions were conducted at –10 °C.

also explored, delivering the corresponding *ortho*-selective mono-selenylated compounds in good yields (**26aa-26ab**). It is worth-mentioning that aryl selenides are the scaffolds of many bioactive compounds.[63-64] Although transition metal-catalyzed *ortho*-selective selenylation of arenes could be achieved with specific directing groups,[65-66] using phenol as a substrate remains unknown, potentially due to the unfavorable high-strain C-H activation process. On the other

hand, this report represents the first report of organocatalytic *ortho*-selective selenylation of phenols.

### 2.6 Structural Requirement of Substrate

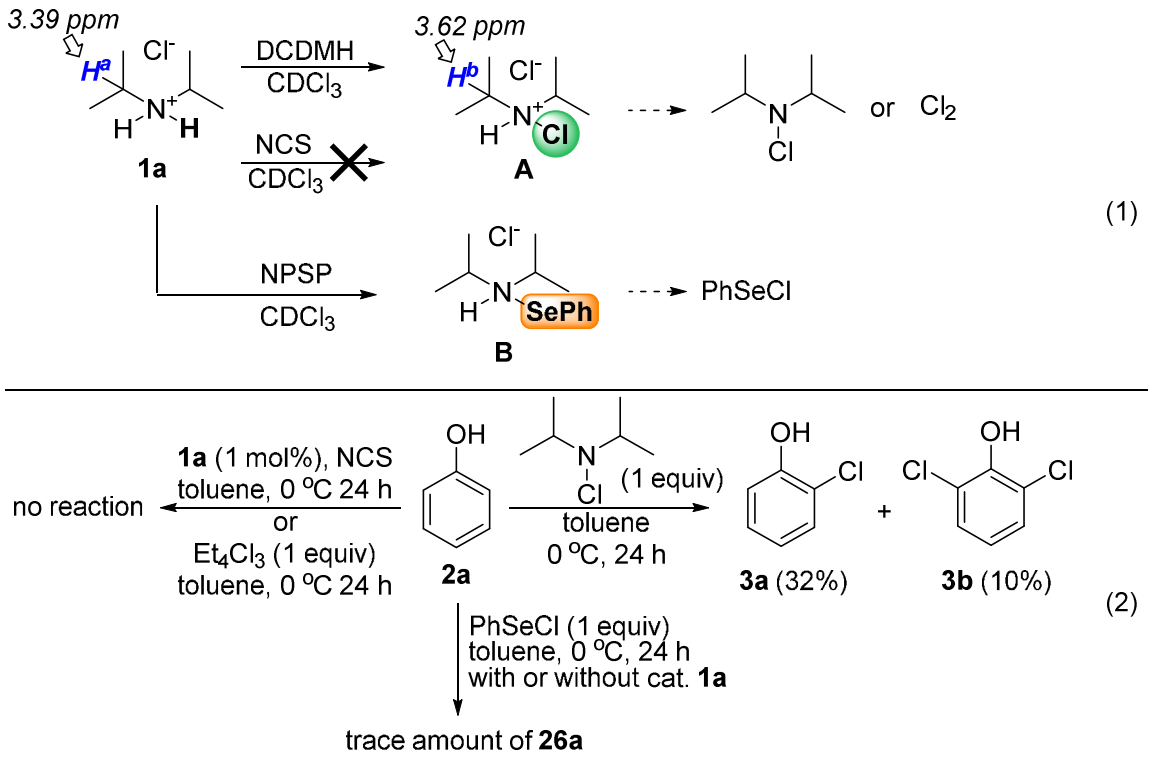
Instead of phenol (**2a**), anisole (**27**) was used as the substrate. Sluggish reaction was observed and poor site-selectivity with *p*-chloroanisole (**28**) as the major product was realized (Scheme 7, eq 1). A similar reaction was performed using **30** as the substrate. Mono-chlorinated product at the *ortho*-position of the phenol moiety in **30** was obtained exclusively, giving **31** in 96% yield (Scheme 7, eq 2). Although methoxy group has a strong electron-donating effect that enables aromatic halogenation,[67] the strong preference of chlorination at the phenol moiety in **30** suggests that the OH group might provide a strong directing effect in the reaction. These results suggest that the hydroxyl handle in phenol might play a crucial role in the ammonium salt catalyzed *ortho*-chlorination, potentially through the hydrogen-bond interaction with the active species. Poor reactivity of the selenylation were also observed when anisole (**27**) was used as the substrate (Scheme 7, eq 3).




**Scheme 7.** Examination of anisole-containing substrates

### 2.7 Active Species in The Catalytic Cycle

It was noticed that both secondary amine-derived ammonium salt **1a** and tertiary amine-derived ammonium salt **1c** could catalyze the chlorination of phenols with certain level of *ortho*-selectivity (Table 1, entries 4 and 5). However, quaternary ammonium salt **1f** was found to be ineffective in the promotion of *ortho*-chlorination of phenol (**2a**) (Table 1, entry 8). We then attempted to probe the active species in order to get a better understanding on the catalytic cycle. Upon mixing **1a** and DCDMH in $CDCl_3$, new proton signals that correspond to species **A** were observed (Scheme 8, eq 1). However, the same species could not be obtained when mixing **1a** with *N*-chlorosuccinimide (NCS), attributable to the relatively weaker electrophilicity of the Cl in NCS (See SI). Indeed, replacing DCDMH with NCS in the *ortho*-chlorination of **2a** returned sluggish transformation (Scheme 8, eq 2). Thus, we believe that effective formation of the active species **A** might be the key of high *ortho*-selectivity.




**Scheme 8.** Experiments on probing the active species

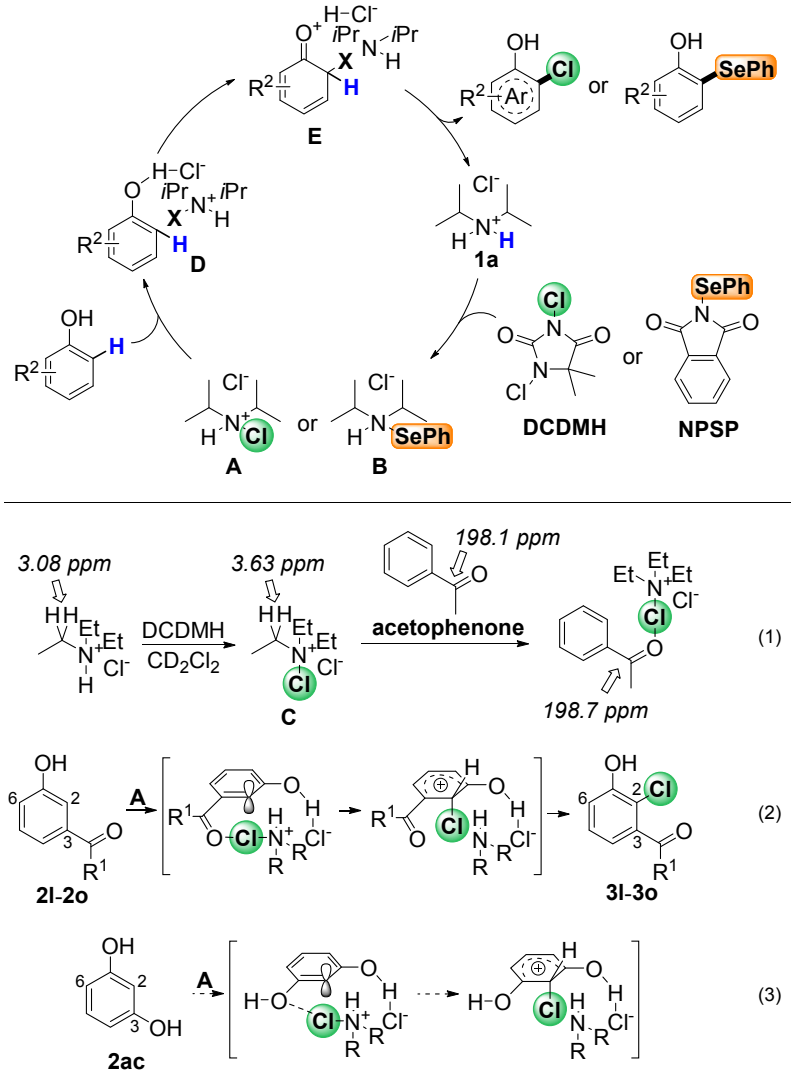
Species **A** might degrade to give *i*Pr$_2$NCl (through the elimination of HCl) or chlorine, and either of them might act as the chlorinating agent in the reaction. However, chlorination of phenol (**2a**) using *i*Pr$_2$NCl as the stoichiometric reagent gave poor *ortho*-selectivity. Using Et$_4$NCl$_3$ as the chlorinating agent also returned sluggish reaction. These results suggest that *i*Pr$_2$NCl or chlorine is not responsible for the observed *ortho*-selectivity, which is different from the mechanistic proposal in the literature method.[34-35] For the selenylation, species **B** was also identified upon mixing **1a** and NPSP (Scheme 8, eq 1) (See SI). Again, phenylselenium chloride might be formed through the degradation of species **B**. However, selenylation of phenol using PhSeCl gave only trace amount of **26a**, which indicates that PhSeCl might not be the active selenylation species in the *ortho*-selenylation reaction (Scheme 8, eq 2).

### 2.8 Plausible Catalytic Cycle

Based on the abovementioned studies, it appears that species **A** and **B** are the active intermediates in the *ortho*-selective halogenation and selenylation of phenols, respectively. A plausible catalytic cycle is constructed as illustrated in Scheme 9. We believe that species **A** or **B** could be formed in the reaction between **1a** and DCDMH or NPSP, respectively (Scheme 9). We suspect that the counter ion of the ammonium salts might play an important role in controlling the selectivity since ammonium salts **1d** and **1e** gave poorer selectivity (Table 1, entries 6 and 7).[68] A possible explanation is that the chloride anion in **1a** might be a better hydrogen-bond acceptor to interact with the phenolic proton, which could enhance the electron density of the phenol system (i.e. intermediate **D**). The hydrogen bond interaction might then bring the electrophilic halogen or selenium close proximity to the *ortho*-position of phenols and allow an effective atom transfer (intermediate **E**) to yield the desired *ortho*-functionalized products.

In terms of the site-selectivity with 3-carbonyl substituted substrates **2l**–**2o** that gave rise to the products **3l**–**3o** with the Cl at the sterically more congested C(2), we suspect that the carbonyl unit might provide a directing effect through a weak interaction with species **A**. This speculation is supported by the fact that in the $^{13}C$ NMR study (See SI), an appreciable downfield-shift of the carbonyl carbon signal of acetophenone was observed when mixing species **C** with acetophenone (Scheme 9, eq 1). The weak interaction could be attributed to the halogen-bond interaction[69-70] between the electrophilic Cl in species **C** and the carbonyl oxygen. Thus, we suspect that the synergistic effect of the OH group and the carbonyl group in **2l**–**2o** might promote the halogen transfer at C(2) to yield the desired products **3l**–**3o** (Scheme 9, eq 2). For the case of resorcinol (**2ac**) (Table 2), it appears that the synergistic effect of the two hydroxyl groups in bringing the

Cl atom to the C(2) position might be disfavored, potentially due to the rigid pseudo four-membered ring transition state (Scheme 9, eq 3).




**Scheme 9.** Plausible catalytic cycle

## 3. CONCLUSIONS

In summary, we have demonstrated that the ammonium chloride salts are powerful organocatalysts for highly *ortho*-selective halogenation and selenylation of phenols and BINOLs. The substrate scope is very board and the catalytic protocol provides an expeditious avenue

towards the preparation of highly functionalized biphenols and unsymmetrical BINOL ligands. Further investigation on the application of this catalytic protocol to other reactions is underway.

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### Notes

The authors declare no competing financial interest.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge.

Experimental details, CIF files, spectroscopic and analytical data for new compounds. (PDF)

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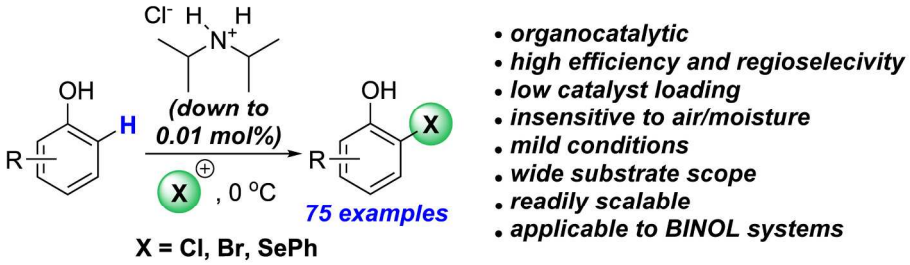


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