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The Catalyst-Controlled Regiodivergent Chlorination of Phenols

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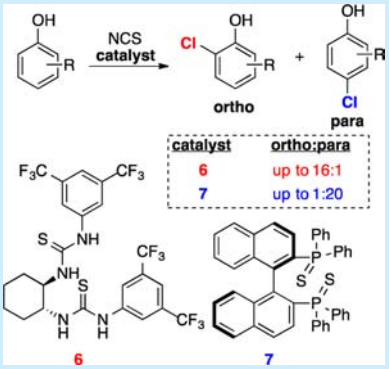
Supporting Information

ABSTRACT: Different catalysts are demonstrated to overcome or augment a substrate's innate regioselectivity. Nagasawa's bis-thiourea catalyst was found to overcome the innate *para*-selectivity of electrophilic phenol chlorination, yielding *ortho*-chlorinated phenols that are not readily obtainable via canonical electrophilic chlorinations. Conversely, a phosphine sulfide derived from 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) was found to enhance the innate *para*-preference of phenol chlorination.



Aryl chlorides are both versatile synthetic handles and common functionalities in drug discovery. As such, there are numerous methodologies to access them, with electrophilic aromatic substitution (EAS) representing a broadly utilized route. Traditional electrophilic halogenations[1−3] suffer from several drawbacks such as a reliance on harsh reaction conditions, reduced reactivity toward electron-poor arenes, and a lack of regioselectivity across many substrate classes. While recent advances[4−12] have largely addressed the first two issues, regioselectivity is still an unsolved problem as current electrophilic halogenations rely on substrate-controlled regioselectivity (Figure 1A) often resulting in a mixture of constitutional isomers. On the other hand, it becomes a synthetic challenge to obtain a nonfavored isomer when the substrate possess a strong innate preference.

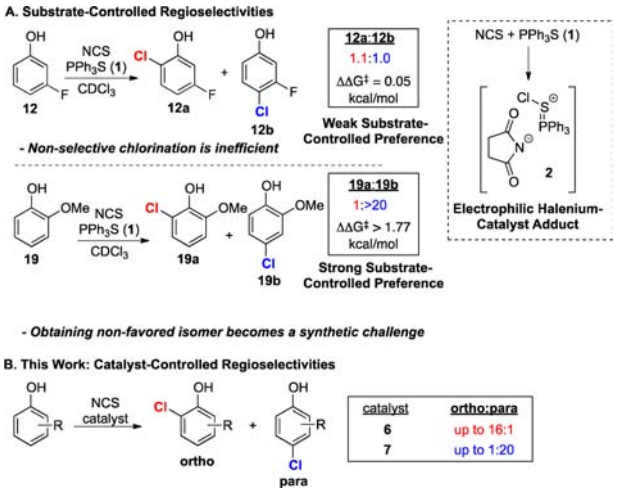


Figure 1. Regioselectivities in the chlorination of phenols.

There are relatively few examples of catalyst-controlled regioselectivities in the arena of EAS, with seminal work by Miller[13,14] on complex natural products exemplifying the small molecule approaches. Alternatively, Lewis[15,16] has engineered mutants of the enzyme RebH that can overcome the innate regioselectivity of heterocycle chlorination. Herein we disclose a novel approach to address these issues, in which we demonstrate the ability of different catalysts to control the regioselectivity of phenol halogenation in a divergent fashion.

We have recently[9] disclosed a mild catalytic electrophilic halogenation of arenes and heterocycles using catalytic Lewis bases[17−23] (i.e., phosphine sulfide **1**) to activate *N*-halosuccinimides (NXSs). These catalysts were able to effect the chlorination of diverse arenes according to the innate preference of a substrate with regioselectivities closely following those reported in literature.[8,10,12] Monitoring the course of the reaction by ^{31}P NMR (Figure S1) suggested the formation of an intermediate with a large degree of phosphonium character,[24] which would be expected if the chemistry proceeds through a catalyst−halenium[25,26] adduct such as **2** (Figure 1). This is corroborated by DFT (Scheme S1) studies that predict halogenation to proceed through such an intermediate.

As these data suggest the activated halenium is associated with the catalyst, we hypothesized that the Lewis base catalyst structure can alter the reaction outcome of electrophilic aromatic halogenation. As a proof of concept, we chose to test this in the context of the *ortho*-chlorination of phenols. Phenols are an

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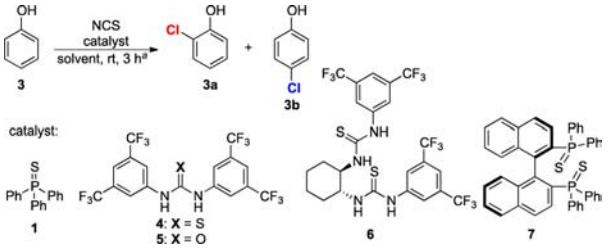
important class of arenes that typically display a moderate to high *para*-preference (see Figure 1; Table 1, entry 1). While bulky amines are known to effect the *ortho*-chlorination of phenols[3,27] these reactions operate under fairly harsh conditions (sulfuryl chloride at 70 °C) and have been shown to have limited substrate scope.[28] Other commonly employed routes to *ortho*-chlorinated phenols involve multistep processes that include arene oxidation,[29,30] dehalogenation,[31,32] or *O*-Methoxymethyl (MOM) directed lithiation.[33,34] A catalytic room temperature *ortho*-selective electrophilic chlorination would represent a more desirable approach that could be performed in one step with few precautions, lending it several practical advantages over current routes.

We began these studies by evaluating several privileged[35] catalyst structures that also possessed Lewis basic functional groups that are known to activate NXS.[18] Schreiner's thiourea[36,37] (**4**) efficiently catalyzed this reaction and yielded a 1.0:2.0 **3a**:**3b** ratio (Table 1, entry 2). While **4** still favored **3b**, we were intrigued by the moderate increase (compared to **1**) in *ortho*- isomer **3a** formed and decided to evaluate other thioureas. A slight increase in the selectivity for **3a** was observed with urea **5**, albeit at the expense of significantly reduced reactivity. We found that Nagasawa's bis-thiourea[38] (**6**) overcame the substrate's innate preference, yielding a 5.4:1.0 mixture of isomers favoring **3a** (Table 1, entry 4). This ratio could be improved to 27:1.0 by diluting the reaction concentration (Table 1, entry 8). This noticeable effect on the regioselectivity is likely due to a decrease in catalyst aggregation at lower concentration and is consistent with recent work by Seidel.[39] To put the efficiency of catalyst **6** in perspective, the $\Delta\Delta\Delta G^{\ddagger}$ between catalyst **6** and catalyst **1** toward *ortho*-chlorination is 2.77 kcal/mol, which would correspond to approximately 98% ee in the realm of enantioselective catalysis.

To define the generality of this catalyst-controlled *ortho*-chlorination, we applied catalyst **6** across a series of differentially substituted phenols, observing predominantly *ortho*-chlorination across the substrate set (Scheme 1). This was in contrast to catalyst **1**, which predominantly yielded *para*-chlorination. For example, **6** effected the chlorination of phenol **8** to give an *ortho*/*para* ratio (**8a**:**8b**) of 10:1.0, with **8a** being isolated in 75% yield. We observed a decrease in *ortho*-selectivity for 2-*tert*-butyl

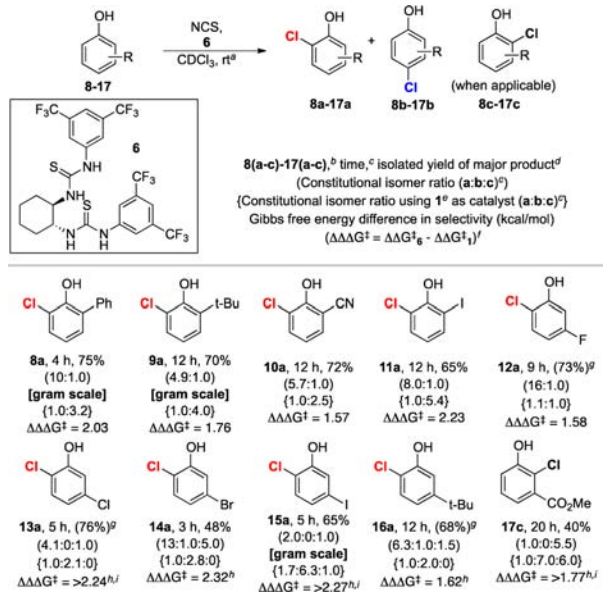
Table 1. Catalyst Exploration towards the *ortho*-Chlorination of Phenol



entry	catalyst (%)	solvent (molarity)[b]	conversion to **3a** (%)[c]	**3a**:**3b**[d]	$\Delta\Delta\Delta G^{\ddagger}$ (kcal/mol)[f]
1	**1** (10)	$CDCl_3$ (0.05)	23	1.0:4.0	0
2	**4** (10)	$CDCl_3$ (0.025)	33	1.0:2.0	0.41
3	**5** (10)	$CDCl_3$ (0.025)	14	1.0:1.1	0.76
4	**6** (10)	$CDCl_3$ (0.05)	67	5.4:1.0	1.82
5	**6** (10)	$CDCl_3$ (0.05)	48	3.2:1.0	1.49
6	**6** (10)	C_6D_6 (0.05)	55	6.4:1.0	1.92
7	**6** (5)	C_6D_6 (0.025	75	6.9:1.0	1.96
8	**6** (10)	$CDCl_3$ (0.025)	83	27:1.0	2.77
9	**6** (5)	$CDCl_3$ (0.025)	82	12:1.0	2.29
10	**1** (10)	$CDCl_3$ (0.025)	20	1.0:3.0	0.17
11	**7** (10)	$CDCl_3$ (0.05)	13	1.0:7.1	−0.33
12	**6** (10)	CD_2Cl_2 (0.025)	64	4.7:1.0	1.73
13	**7** (10)	CD_2Cl_2 (0.05)	16	1.0:5.0	−0.13

[a]All reactions were performed by addition of a catalyst, solvent, and 0.03 mmol of **3** at rt, followed by the addition of 0.036 mmol of NCS. [b]Molarity of the reaction is in reference to **3**. [c]Percent conversion to **3a** was determined by ^{1}H NMR and represents an average of three trials using tetramethylsilane or tetrakis(trimethylsilyl)methane as an internal standard. [d]Isomeric ratios were determined by ^{1}H NMR and represent an average of three trials. [e]We observed only minor decreases in selectivities with CD_2Cl_2 as the solvent, allowing us to reliably use DCM as our solvent upon scale-up to mitigate loss of volatile products. [f]$\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G^{\ddagger}_{\text{entry\#}} - \Delta\Delta G^{\ddagger}_{\text{entry 1}}$, with *ortho*-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and *para*-selectivity defined as negative $\Delta\Delta G^{\ddagger}$.

Scheme 1. *ortho*-Selective Chlorination of Substituted Phenols



[a]Optimized reaction conditions were used with respect to the catalyst (see Table 1). [b]Only the major product is shown. [c]Reaction times and constitutional isomer ratios were determined by ^{1}H NMR and represent an average of two trials using tetramethylsilane or tetakis(trimethylsilyl)methane (TTMSM) as an internal standard. [d]Isolated yields were determined on the 50−1000 mg scale, using DCM as the solvent (due to volatility), and represent an average of two trials (see Supporting Information). [e]The selectivities observed with catalyst **1** are included for comparison. [f]With *ortho*-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and *para*-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. [g]Due to product volatility, an isolated yield could not be reported; therefore, % conversion was reported as determined by ^{1}H NMR using TTMSM as an internal standard. [h]Both *ortho* products (**a** and **c**) combined to simplify calculation. [i]Assuming >20:1 *ortho*/*para* with **6**.

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substituted **9** (*ortho*/*para* ratio of 3:1), perhaps due to the bulky substituent interfering with a catalyst−substrate interaction. Nonetheless, we were able to isolate **9a** with a 70% yield. Nitrile-containing **10** and 2-iodophenol (**11**) also proved to be good substrates, affording *ortho*/*para* ratios of 5.7:1 and 8:1, respectively.

The chlorination of *meta*-substituted phenols also proceeded with *ortho*-selectivity in the presence of **6**. For example, the chlorination of 3-fluorophenol (**12**) yielded an excellent 16.0:1.0 **12a**:**12b** ratio. Substrates with less electronically withdrawing *meta*-substituents were also chlorinated *ortho*- to the phenol by **6**; however, now varying degrees of chlorination at the more hindered *ortho*-position were observed inline with expected electronic trends (see substrates **13**−**16** in Scheme 1). **17** possessed particularly interesting selectivity as **6** primarily effected halogenation at the more hindered *ortho*-position to give predominantly **17c** (1.0:0:5.5 ratio of **17a**:**17b**:**17c**). From an energetic perspective, catalyst **6** was less effective on these substrates than phenol; however, the $\Delta\Delta\Delta G^{\ddagger}$ between catalyst **6** and catalyst **1** were still quite good, corresponding to a range of 85% to 96% ee when an analogy to enantioselective catalysis is made.

With an *ortho*-selective catalyst in hand we then turned our attention to catalysts that augment the innate *para*-selectivity of phenols, finding that Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-derived phosphine sulfide **7** was able to improve upon the innate *para*-selectivity of phenol, yielding a **3a**:**3b** ratio of 1.0:7.1 (Table 1, entry 11).

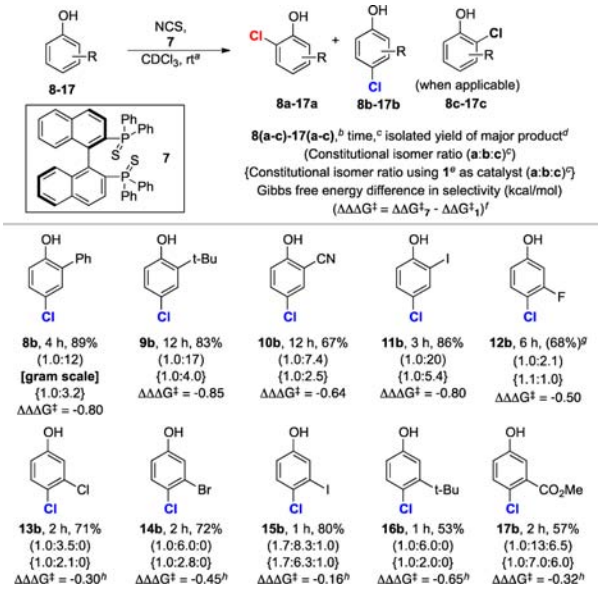
We then evaluated catalyst **7** across a set of substrates (Scheme 2). In general, **7** was found to yield markedly improved *para*-selectivities compared to those of **1**. For example, **7** effected the chlorination of phenols **8** and **9** with *ortho*/*para* ratios of 1.0:12 (compared to 1.0:3.2 and 1.0:4.0 respectively by **1**). We also observed a similar degree of *para* augmentation with **7** for nitrile containing **10** (**10a**:**10b** of 1.0:7.4 vs 1.0:2.5 for **1**) and 2-iodophenol (**11**) (*ortho*/*para* ratio of 1.0:20 vs 1:5.4). Catalyst **7** also augmented the *para*-selectivity of *meta*-substituted phenols when compared to catalyst **1**. For example, while fluorophenol **12** gave a ratio of **12a**:**12b** as 1.1:1.0 with catalyst **1**, chlorination of **12** with catalytic **7** altered the reaction outcome to give *para*-halogenated **12b** as the major product (ratio of **12a**:**12b** as 1.0:2.1). **7** also resulted in increases in *para* selectivity of 2−3-fold for phenols **14**, **16**, and **17**. It should be noted that, for some phenols, such as **13** and **15**, catalyst **7** increased selectivity minimally. Finally, the chlorination of ester-containing **17** was seemingly unselective with catalyst **1**, resulting in a mixture of **17a**:**17b**:**17c** as 1.0:7.0:6.0, yet in the presence of **7**, the chlorination proceeded to yield a *para*-favoring mixture of **17a**:**17b**:**17c** as 1.0:13:6.5. While the increases in *para* selectivity are moderate, the ability to augment *para*-selectivities when using catalyst **7** over catalyst **1** complements the catalyst-directed *ortho*-chlorinations in Scheme 1 and serves as another proof of concept that catalyst structure can both augment (as with **7**) or override (as with **6**) innate regioselectivities.

We next probed whether these catalysts could also effect regioselective brominations. While there are robust conditions for *ortho*-bromination,[40] catalyst controlled bromination might find utility in late stage functionalization. In these studies we found little difference between catalysts **1** and **7**, with both yielding predominantly *para*-brominated products; however, as with chlorination, **6** overcame this innate *para*-preference to give mostly *ortho*-brominated products. For example, phenol **3** yielded excellent regioselectivities (**3c**:**3d** ratio of 1.0:11, Figure 2A), albeit with a significant amount of polybromination, while **6** gave an observed **3c**:**3d** ratio of 3.3:1.0. *Ortho*-substituted phenols **8** and **18** proceeded more smoothly, with **1** yielding predominantly *para*-brominated **8d** and **18b**, and catalyst **6** favoring bromination *ortho*- to the hydroxy group each time (**8c**:**8d** ratio of 5:1; **18a**:**18b** ratio of 4:1). It should be noted that when using 1.2 equiv of NBS we observed some dibromination which complicated purification and resulted in isolated yields that were lower than observed NMR conversions.

We also evaluated the chlorination of substrates that possessed multiple directing groups such as guaiacol (**19**), finding catalyst **1** to effect chlorination exclusively *para*- to the phenol giving **19b** in high yields. Interestingly, catalyst **6** was able to overcome this large substrate preference to yield *ortho*-chlorinated **19a** as the major product, however, with a more modest ratio than other substrates in Scheme 1. It is worth mentioning that this modest selectivity is due to the large innate *para*- preference of **19**, as from an energy perspective catalyst **6** overcomes roughly 2.1 kcal/mol, comparable, if not better, than many of the substrates in Scheme 1.

In conclusion, we have demonstrated that the catalyst structure of Lewis bases can influence the regioselectivity of the electrophilic halogenation of phenols. A particularly exciting aspect of this work is the observed reversal of regioselectivity by Nagasawa's bis-thiourea **6**, presumably through a mechanism in which one thiourea interacts with the phenol hydroxy group, and the other activates NCS through a Lewis basic (analogous to that depicted in Figure 1) or a Brönsted acidic manifold (H-bonding

Scheme 2. Augmenting the Innate Chlorination of Phenol



[a]Optimized reaction conditions were used with respect to the catalyst (see Table 1). [b]Only the major product is shown. [c]Reaction times and constitutional isomer ratios were determined by ^{1}H NMR and represent an average of two trials using tetramethylsilane or tetakis(trimethylsilyl)methane as an internal standard. [d]Isolated yields were determined on the 50−1000 mg scale, using DCM as the solvent (due to volatility), and represent an average of two trials (See SI). [e]The selectivities observed with catalyst **1** are included for comparison. [f]With *ortho*-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and *para*-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. [g]Due to product volatility, an isolated yield could not be reported; therefore, % conversion was reported as determined by ^{1}H NMR using TTMSM as in internal standard. [h]Both *ortho* products (**a** and **c**) combined to simplify calculation.

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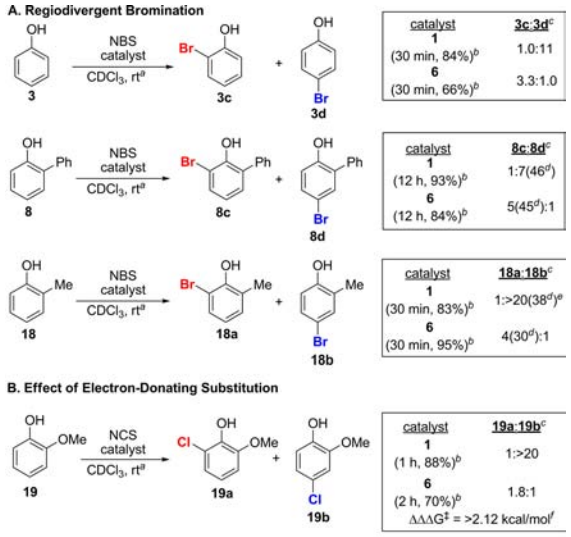

[a]Optimized reaction conditions were used with respect to the catalyst (See Table 1). [b]Reaction times and conversions to mono-brominated products were determined by ^{1}H NMR and represent an average of two trials using tetramethylsilane or tetrakis(trimethylsilyl)methane as an internal standard. [c]Ratios were determined by ^{1}H NMR and represent an average of three trials. [d]Isolated yields in parentheses were determined on the 50-100 mg scale, using DCM as the solvent (due to volatility), and represent an average of two trials (See SI). [e]Ratio could not be determined by ^{1}H NMR, however **18b** was the predominant isomer (See SI). [f] $\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G^{\ddagger}_6 - \Delta\Delta G^{\ddagger}_1$. *ortho*-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and *para*-selectivity defined as negative $\Delta\Delta G^{\ddagger}$.

Figure 2. Regiodivergent bromination and the *ortho*-chlorination of guaiacol.

with NCS carbonyl). Mechanistic studies to understand how this chemistry works are ongoing. These results represent a novel and facile route to access arene substitution patterns that are not currently readily available. More broadly, these results represent a key proof of concept that a catalyst can indeed alter the reaction outcome of electrophilic halogenation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02650.

Experimental procedures and analytical data for regioselective analyses and all new compounds, including ^{1}H and ^{13}C spectra are included in the Supporting Information (PDF)

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Notes

The authors declare no competing financial interest.

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