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Catalyst-Controlled Regioselective Chlorination of Phenols and Anilines through a Lewis Basic Selenoether Catalyst

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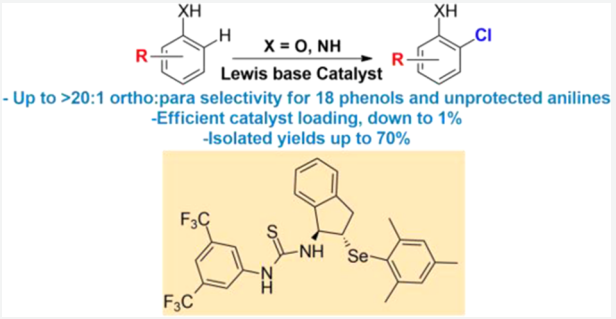
ABSTRACT: We report a highly efficient ortho-selective electrophilic chlorination of phenols utilizing a Lewis basic selenoether catalyst. The selenoether catalyst resulted in comparable selectivities to our previously reported bis-thiourea ortho-selective catalyst, with a catalyst loading as low as 1%. The new catalytic system also allowed us to extend this chemistry to obtain excellent ortho-selectivities for unprotected anilines. The selectivities of this reaction are up to >20:1 ortho/para, while the innate selectivities for phenols and anilines are approximately 1:4 ortho/para. A series of preliminary studies revealed that the substrates require a hydrogen-bonding moiety for selectivity.



INTRODUCTION

Halogenation of aromatics via aromatic electrophilic substitution (S_EAr) is one of the most ubiquitous reactions in modern synthesis, largely because halogenated aromatics are among the most utilized precursors in modern cross-coupling chemistry and other common reactions.[1−6] Furthermore, the incorporation of halogen atoms is commonly used to modulate the physicochemical properties of small-molecule drug leads.[7] While S_EAr has been extensively studied for over a century,[8−13] it often yields mixtures of constitutional isomers, representing a major synthetic challenge. For example, electron-rich aromatic scaffolds such as phenols and anilines yield a mixture of para- and ortho-functionalized products, with the para-constitutional isomer typically favored due to innate electronic properties.[12,14−17]

While there are synthetic strategies to access ortho-halogenated phenols and anilines, these strategies usually involve low regioselectivities, utilize multistep processes, or contain harsh conditions that restrict the chemistry to a narrow substrate scope.[18−25] Recently, we and others have demonstrated that catalysts can control the regiochemical outcome of S_EAr on both simple aromatics and complex natural products.[26] Gnaim and Snider have shown that secondary ammonium chlorides and SO_2Cl_2 provide chlorinated phenols in high ortho-selectivity.[27,28] We have reported a highly ortho-selective chlorination of phenols utilizing Nagasawa's bis-thiourea catalyst **1** and *N*-chlorosuccinimide (NCS). We hypothesize that one of the thiourea moieties activates NCS via a Lewis basic mechanism,[11,29−31] while the other thiourea interacts with the phenol via hydrogen bonding, leading to the ortho direction of chlorination (Scheme 1A).[32] Yeung and co-workers have also demonstrated that the catalytic quantities of secondary ammonium chlorides can affect the chlorination of protected anilines and phenols in excellent ortho-selectivity with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (Scheme 1A).[33,34] Additionally, Yeung has demonstrated that bifunctional urea catalysts are able to affect the regio- and enantioselective halogenation of bisphenol scaffolds.[35]

To better understand the mechanism of action for catalyst **1**, we synthesized isotopically labeled catalyst analogues and followed the reaction under optimal conditions via ^{15}N and ^{13}C NMR (see the Supporting Information). We were somewhat surprised to observe that **1** converted to a new species during the reaction. Isolation and analysis of the observed byproduct led us to identify it as a guanidinium salt **1a** (Scheme 1B),[36] which we found to be catalytically inactive. We hypothesized that this catalyst degradation attenuated the observed catalyst activities, perhaps limiting the scope of chemistry that could be affected. This led us to explore the development of a second-generation ortho-selective catalyst. We hypothesized that replacing one of the thioureas with another Lewis basic moiety such as a chalcogenide ether would lead to a longer-lived catalyst that would not undergo the intramolecular cyclization we observed with **1**.

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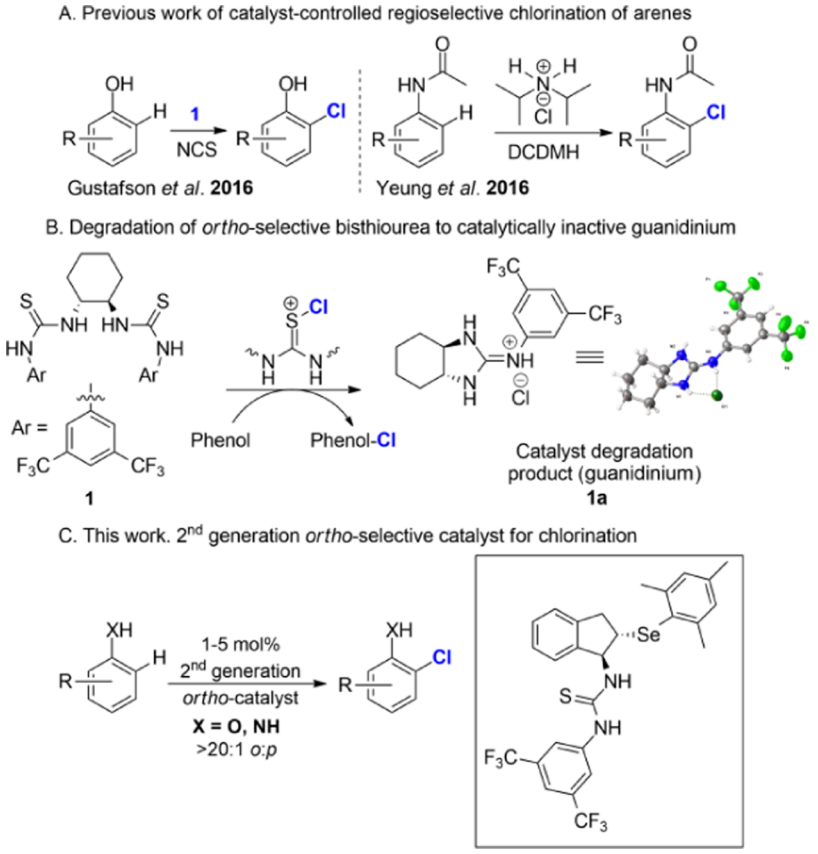
Scheme 1. Catalyst Controlled Regioselective Methodologies



RESULTS AND DISCUSSION

Zhao and co-workers have developed a series of chiral bifunctional Lewis base chalcogenides derived from the 1-amino indanol scaffold and have successfully implemented them in the context of diverse electrophilic olefin functionalizations.[37−43] Inspired by this work, we initially synthesized and evaluated a series of thioether catalysts based on Zhao's scaffold that possessed varying directing groups of the 1-amino group and evaluated their selectivity on phenol **2a**. However, these catalysts offered little perturbation from the "innate" regioselectivity observed with triphenylphosphine sulfide **3** (Table 1, entries 2−6). We chose catalyst **3** and NCS as a control for "innate" selectivity as our previous work has demonstrated that these catalyst conditions result in regioselectivities that match a noncatalyst system for phenols at an accelerated rate. Interestingly, 10 mol % of indanol catalyst **7**, which possesses an electron-poor thiourea and is perhaps a direct analogue of our original ortho-selective catalyst **1**, displayed preliminary levels of ortho-selectivity (1.5:1.0 of **2b**/**2c**), albeit with modest conversion. To increase conversion, we kept the thiourea functional group constant and began varying the Lewis base moiety. When the aryl substitution of the thioether was made more electron-rich as in catalyst **8**, we observed increased conversion, albeit with equal amounts of constitutional isomers (85% conversion, 1.0:1.0 of **2b**/**2c** (Table 1, entry 7)). Incorporating a sterically bulky 2,4,6-trimethyl substitution of the thioether aryl, as in catalyst **9**, increased the ortho-selectivity to 2.5:1.0 **2b**/**2c**, albeit with a decrease in conversion to 49% (Table 1, entry 8).

Guided by Zhao's recent work on the activation of a weakly electrophilic SCF_3 reagent with selenoethers,[38] we replaced the thioether with a selenoether in catalyst **10**, observing a notable increase in ortho-selectivity and conversion (Table 1, entry 9). Finally, lowering the catalyst loading of **10** from 10 to 1 mol % yielded significantly improved conversion and regioselectivity (70% conversion; **2b**/**2c** > 20:1; Table 1, entry 10). This result is in line with the observations from the Seidel group,[44] wherein they observed that at higher concentrations thioureas can aggregate, attenuating their catalytic efficiency. To put these selectivities in perspective, the difference in energy between a catalyst such as **3** that yields 1:4 ortho/para and a catalyst such as **10** that yields 20:1 ortho/para (defined as $\Delta\Delta G^{\ddagger}$; see Table 1, footnoted for definition) is 2.58 kcal/mol.

We next sought to define the substrate scope of this chemistry across simple phenols (Scheme 2). Each reaction was repeated two times on an NMR scale (0.03 mmol) in $CDCl_3$ to obtain conversions and regioselectivities and then repeated two more times on a preparative scale (1 mmol) in $CHCl_3$ to obtain the yield of the major constitutional isomer after purification. Spot checking of the crude NMRs revealed minimal variance in regioselectivity between the NMR scale and preparative scale reactions. To avoid the formation of dichlorinated products, which could lead to an overestimation of regioselectivity via a "secondary resolution", we ran each reaction with 1.2 equiv of NCS, resulting in conversions typically in the 50−70% range of the major constitutional isomer with minimal to no observation of dichlorination.

Electron-poor-substituted phenols yielded excellent ortho-selectivities in line with phenol. For example, **10** affected the chlorination of 2-phenyl- and 2-cyano-substituted phenols (**11a** and **12a**) exclusively at the ortho-position to provide **11b**

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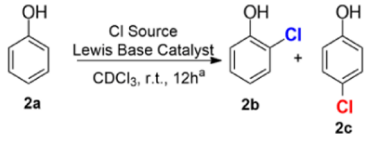
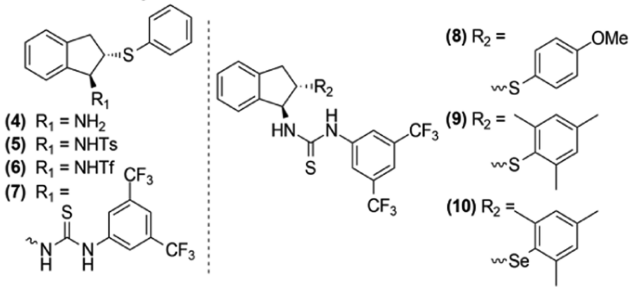
Table 1. Catalyst Evaluation for Ortho-Selective Chlorination of Phenol



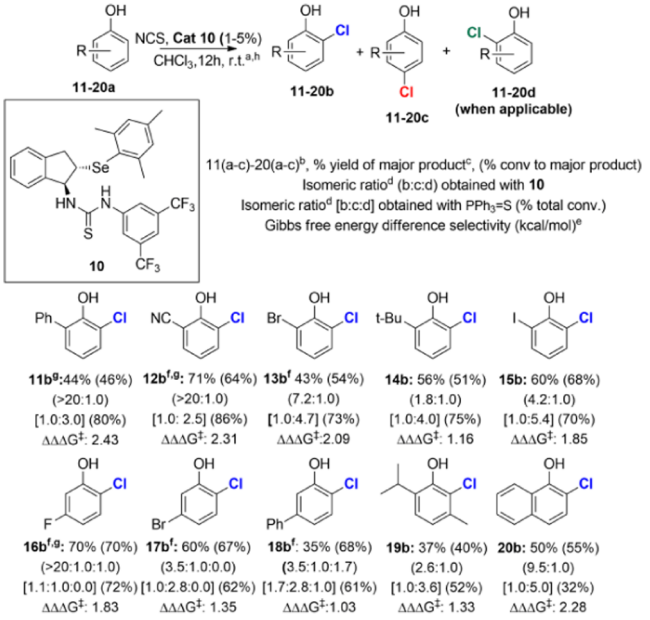
Entry	Cat (%)	Cl Source	Conv.(%)[b]	2b:2c[c]	ΔΔG‡(kcal/mol)[d]
1	None	NCS	0	N/A	N/A
2	PPh_3=S **3** (10%)	NCS	85	1.0:4.0	0.0
3	**4** (10%)	NCS	40	1.0:3.0	0.17
4	**5** (10%)	NCS	46	1.0:3.5	0.07
5	**6** (10%)	NCS	56	1.0:2.7	0.23
6	**7** (10%)	NCS	51	1.5:1.0	1.05
7	**8** (10%)	NCS	85	1.0:1.0	0.81
8	**9** (10%)	NCS	49	2.5:1.0	1.35
9	**10** (10%)	NCS	72	4.5:1.0	1.71
10	**10** (1%)	NCS	70	>20:1.0	2.59
11	**10** (1%)	DCDMH	90	2.0:1.0	1.22

Lewis Base Catalyst:



[a]All reactions were performed with 0.03 mmol of **2a**, stirred with $CDCl_3$ and catalyst, followed by addition of 0.036 mmol of NCS. [b]Conversion is the sum of both regioisomers **2b** and **2c** and represents an average of three trials using tetramethylsilane (TMS) as the internal standard. [c]Regioisomeric ratios were determined by ^{1}H NMR and represent an average of three trials. [d]$\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G_{entry\#}^{\ddagger} - \Delta\Delta G_{entry2}^{\ddagger}$, with ortho-selectivity defined as $\Delta\Delta G^{\ddagger}$ and para-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. $\Delta\Delta G^{\ddagger}$ is derived from the Eyring equation, where $\Delta\Delta G^{\ddagger} = -RT\ln[\text{para}]/[\text{ortho}]$ based on our previous definition.

Scheme 2. Expanded Scope for Ortho-Selective Chlorination of Substituted Phenols



[a]Optimized reaction conditions were used with respect to the catalyst. [b]Only the major product is shown. [c]Yields were determined on a 1 mmol scale, using $CHCl_3$ as the solvent, and represent an average of two trials. [d]Reactions were run on a 0.03 mmol scale in $CDCl_3$; conversions and isomeric ratios were determined by ^{1}H NMR with a TMS internal standard and represent an average of two trials. [e]$\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G_{entry\#}^{\ddagger} - \Delta\Delta G_{entry2}^{\ddagger}$, with ortho-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and para-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. $\Delta\Delta G^{\ddagger}$ is derived from the Eyring equation, where $\Delta\Delta G^{\ddagger} = -RT\ln[\text{para}]/[\text{ortho}]$ based on our previous definition. [f]The following substrates required a 5% catalyst loading. [g]Substrate provided exclusively the ortho regioisomer; 20:1.0 is the estimated ratio used to calculate the $\Delta\Delta\Delta G^{\ddagger}$ value. [h]Ratios hold for small and large scales.

and **12b** in yields of 44 and 71%, respectively, significantly overriding the para-selectivity observed with triphenylphosphine sulfide **3**. On the other hand, we observed a decrease in ortho-selectivities once we introduced bulkier substituents at the 2-position; nonetheless, there was still a significant overriding of the innate para-selectivity. For example, 2-bromophenol (**13a**), 2-*tert*-butylphenol (**14a**), and 2-iodophenol (**15a**) all provided the ortho-substituted regioisomers as the major product (**13b**, **14b**, **15b**), affording ortho/para ratios between 1.8:1.0 and 7.2:1.0. One possible explanation for this decrease may be due to steric hindrance of the bulky substituents, interfering with the hydroxy group forming hydrogen bonds with the thiourea moiety.

Catalyst **10** also directed chlorination to the least hindered ortho (6)-position of 3-substituted phenols. For example, the chlorination of 3-fluorophenol (**16a**) yielded exclusive ortho-selectivity at the 6-position to give **16b** in a 70% yield. 3-Bromophenol (**17a**) resulted in lower ortho-selectivities with 5 mol % **10** (3.5:1.0 **17b**/**17c**); nonetheless, **17b** was furnished as the major product in good yields. Phenyl-substituted **18a** was also predominantly chlorinated at the least hindered position (3.5:1.0:1.7 **18b**/**18c**/**18d**); however, in this case, some halogenation at the more hindered ortho-position was also observed. Despite a general decrease in ortho-selectivity for 3-substituted phenols compared to other substitution patterns, the ortho-preference of catalyst **10** over the "innate" furnished by triphenylphosphine sulfide **3** is still significant, with $\Delta\Delta\Delta G^{\ddagger}$ ranging from 1.03 to 1.83 kcal/mol. The terpenoid thymol (**19a**) also provided ortho-selectivity (2.6:1.0 **19b**/**19c**). Finally, α-naphthol (**20a**) afforded ortho-selectivity (9.5:1.0 **20b**/**20c**) to give (**20b**) with a moderate yield of 50%. Overall, we show that this chemistry can be applied for a diversity of substituted phenols. For the most part, 1 mol % catalyst **10** yielded results comparable to 10 mol % catalyst **1**; however, it should be noted in some examples that there was a notable loss in regioselectivity when compared to catalyst **1** (i.e., **14a** and **15a**). It should also be noted that Yeung's aforementioned work on phenols provides an efficient route toward ortho-chlorinated phenols and is likely the superior route from a cost perspective.

We next evaluated whether Lewis base catalysts could affect ortho-selective chlorination on anilines. Anilines are typically more reactive substrates for S_EAr than phenols; indeed, no catalyst is needed to affect the chlorination of anilines. Furthermore, anilines typically display innate para-selectivities on par with that of phenols. To overcome these issues, the Yeung group has studied ortho-selective halogenation on protected anilines;[34] however, unprotected anilines have

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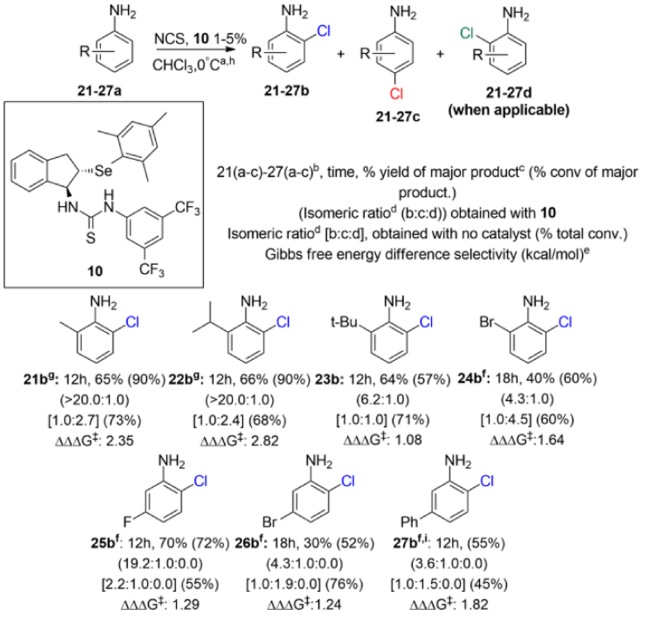
proven recalcitrant to catalyst-controlled regioselectivity. Initial attempts for chlorination of unprotected anilines with Nagasawa's catalyst **1** provided no discernible chlorinated products. On the other hand, chlorination of several simple anilines in the presence of 1 mol % of catalyst **10** resulted in nearly exclusive ortho chlorination (Scheme 3). For example,

Scheme 3. Expanded Scope of Ortho-Selective Chlorination of Substituted Unprotected Anilines

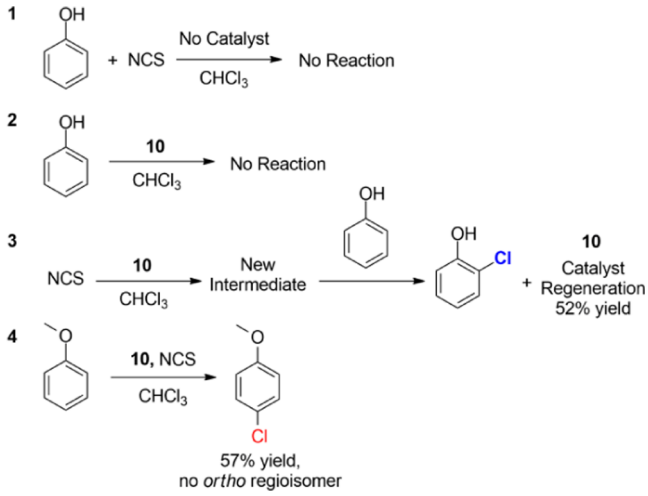


[a]Reactions were quenched with vinyl ether after completion. [b]Only the major product is shown. [c]Yields were determined on a 1 mmol scale, using $CHCl_3$ as the solvent, and represent an average of two trials. [d]Reactions were run on a 0.03 mmol scale in $CDCl_3$; conversions and isomeric ratios were determined by ^{1}H NMR with a TMS internal standard and represent an average of two trials. [e]$\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G_{entry\#}^{\ddagger} - \Delta\Delta G_{entry2}^{\ddagger}$, with ortho-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and para-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. $\Delta\Delta G^{\ddagger}$ is derived from the Eyring equation, where $\Delta\Delta G^{\ddagger} = -RT\ln[\text{para}]/[\text{ortho}]$ based on our previous definition. [f]The following substrates required a 5% catalyst loading. [g]Substrate provided exclusively the ortho regioisomer. 20:1.0 is the estimated ratio used to calculate the $\Delta\Delta\Delta G^{\ddagger}$ value. [h]Ratios hold for small and large scales. [i]Only conversion is reported due to impurity of the starting material in the scale-up.

alkyl-substituted anilines such as 2-methylaniline and 2-isopropylaniline (**21a** and **22a**) gave significant ortho-selectivities at greater than 20:1, allowing for isolation of the product in good yields. For comparison, each of these substrates yielded primarily para-chlorinated products in the absence of catalyst (1.0:2.7 and 1.0:2.4 o/p, respectively). As with phenols, ortho *tert*-butyl substitution (**23a**) is met by a decrease in the ortho-selectivity at 6.2:1.0 o/p (compared to 1.0:1.0 o/p in the absence of catalyst). 2-Bromoaniline (**24a**) also provided reduced ortho-selectivity, giving an o/p ratio of 4.3:1.0 at a moderate conversion of 60%. 3-Fluoroaniline (**25a**) provided excellent ortho-selectivities for **25b** with trace amounts of the other two regioisomers in a 70% yield. However, 3-bromoaniline and 3-phenylaniline (**26a** and **27a**) resulted in lower yields and selectivity for the less hindered ortho-substituted product (**26b** and **27b**). Overall, the ortho bias demonstrated by **10** for substituted anilines (compared to the para innate selectivity in the absence of catalyst) is similar to that observed for phenols, with $\Delta\Delta\Delta G^{\ddagger}$ ranging from 1.08 to 2.82 kcal/mol.

To gain insight into the catalytic mechanism, we first completed a series of control experiments utilizing **2a** under optimal conditions and followed conversion via ^{1}H NMR. Stirring 1 equiv of phenol and NCS in the absence of catalyst provided no reaction (Scheme 4, reaction 1). A mixture of

Scheme 4. Preliminary Mechanistic Studies



phenol with 1 equiv of **10** also showed no change in NMR spectrum (Scheme 4, reaction 2). On the other hand, subjecting **10** to 20 equiv of NCS under reaction conditions resulted in marked shifts of the resonances of several key catalyst hydrogens and the formation of a new intermediate; quenching with phenol after 30 min provides the observed ortho-selectivities of **2a**. This reaction was then repeated on a 1 g scale of phenol, wherein the ortho-chlorinated product was obtained in a 65% yield with regeneration of the catalyst in a 52% yield (Scheme 4, reaction 3). These results differ from what we observed with Nagasawa's bis-thiourea **1**, wherein prestirring with NCS resulted in the formation of the catalytically inactive guanidinium and thus no conversion after the addition of phenol. Finally, the chlorination of anisole with **10** provided exclusively the para-regioisomer in a 57% yield (Scheme 4, reaction 4), implying that there is a substrate−catalyst interaction via the hydrogen bond handle of the phenol.

Based on these preliminary experiments, a plausible catalytic mechanism for **10** is shown in Scheme 5. First, the Lewis basic selenium in **10** will nucleophilically attack NCS to form a selenium-bound halenium adduct **A**, perhaps aided by NCS activation via H-bonding with the thiourea. The formed succinimide anion will then coordinate with the urea N−H bonds to give B. It should be noted that control experiments with the addition of excess succinimide yielded no perturbations in conversion or selectivity of the reaction (see the Supporting Information). At this point, the succinimide can deprotonate the phenol or aniline, and the new anion will now hydrogen-bond to the thiourea to provide **C**. This interaction will position the Se−halenium adduct adjacent to the ortho-position of the substrate, explaining the observed selectivity. Canonical S_EAr completes the cycle and the regeneration of the selenoether catalyst **10**.

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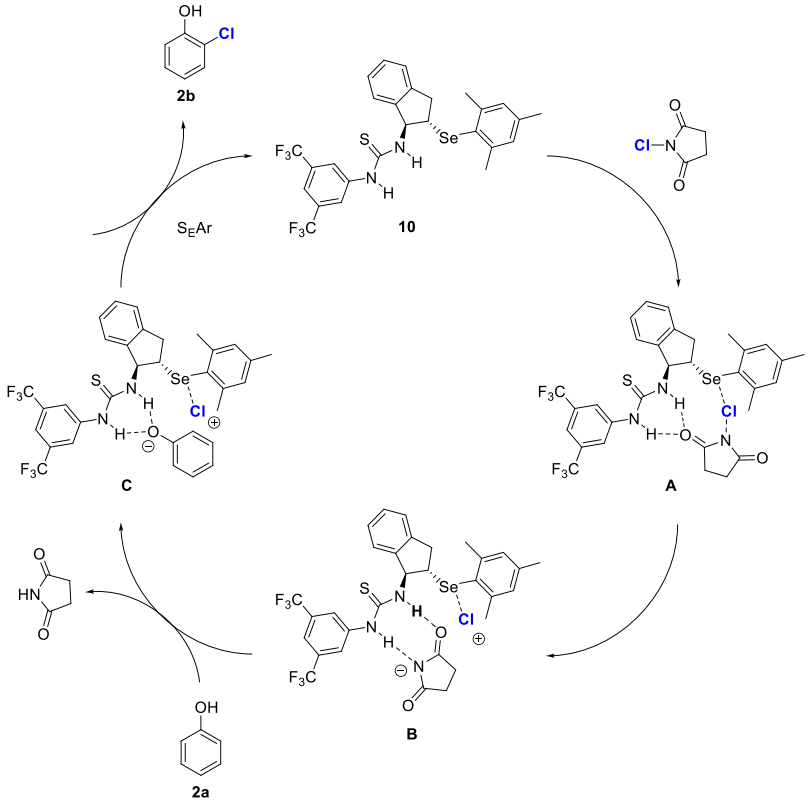
Scheme 5. Proposed Catalytic Cycle



In conclusion, we have developed a second-generation Lewis base selenoether catalyst, which can regioselectively chlorinate phenols in an ortho fashion. Our new catalyst **10** provides comparable selectivity relative to our previously reported catalyst **1** at significantly lower catalyst loading. Catalyst **10** also enabled us to achieve high ortho-selectivities to unprotected anilines, which possess a significant para-selective background reaction. We hope this strategy can be applied for other catalyst-controlled functionalizations, including the late-stage functionalization of complex pharmaceutical intermediates.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VNMRS 400 MHz, Bruker Avance III 400 MHz, and Varian Inova 500 MHz at room temperature (r.t.). High-resolution mass spectra of new compounds were recorded on an Agilent 6530 Accurate-Mass Q-TOF LC/MS. All chemical shifts were reported in parts per million (δ) and were internally referenced to residual protio solvents, unless otherwise noted. All spectral data were reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling. Fluorine spectra were recorded with internal fluorine standards (i.e., trifluoroacetic acid). Some proton NMR spectra were taken in an aprotic solvent (dimethyl sulfoxide (DMSO)-d_6) to prevent proton exchange and improve signal resolution. Conventional mass spectra were obtained using Advion expression^{s} CMS APCI/ASAP. For the chlorination of substrates, purchased (*N*)-chlorosuccinimide was recrystallized from water before use. $CDCl_3$ was run through basic alumina before use in NMR experiments. All other chemicals used were purchased from Sigma-Aldrich, TCI, Frontier Scientific, Acros Organics, Strem, Oakwood, Cambridge Isotope Laboratories, or Fisher and were used as received without further purification or recrystallization. All flash column chromatography (FCC) was performed using grade 60 silica gel (230−400 mesh) purchased from Fisher Scientific. All thin-layer chromatography (TLC) preparatory plates were performed using grade 60 silica gel with fluorescent indicator F_{254} and were purchased from Fisher Scientific. All reactions that required elevated temperatures were heated with an oil bath.

Syntheses of Guanidinium Intermediate and Verification. *N-(Hexahydro-1H-benzo[d]imidazol-2(3H)-ylidene)-3,5-bis-(trifluoromethyl)aniline (**1a**).* The guanidinium intermediate was first isolated in the chlorination of phenol following the optimized procedure from our previously reported manuscript.[32] The crystal structure was obtained from material from the chlorination. We then synthesized and isolated the intermediate on a preparatory scale using two different methodologies. The second synthesis was used to isolate ^{15}N labeled **1a**, which was used to confirm that the observed byproduct from regioselective chlorination was indeed the guanidinium salt.

Synthesis from Chlorination Conditions. Nagasawa's bis-thiourea (compound **1**, 100 mg, 0.15 mmol, 1 equiv) was dissolved in $CHCl_3$ (0.1 M). Then, *N*-chlorosuccinimide (20 mg, 0.15 mmol, 1 equiv) was added to the mixture and the reaction was stirred for 12 h. The reaction was concentrated down and purified by FCC (95:5::Hex/EtOAc) to give **1a**.

Synthesis from Diamine. This procedure is adapted from the following literature.[45] A solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (745 mg, 5 mmol) in 10 mL dichloromethane (DCM) was added dropwise to a solution of a (1*S*,2*S*)-cyclohexane-1,2-diamine (570 mg, 5 mmol). The reaction was stirred overnight for 12 h, concentrated, and purified by FCC (30:70::Hex/DCM) to give 1-[(1*S*,2*S*)-2-aminocyclohexyl]-3-[3,5-bis(trifluoromethyl)phenyl] thiourea.

Next, the following procedure is adapted from the following literature.[36] 420 mg of the thiourea (1.1 mmol, 1.0 equiv) was dissolved in toluene (0.1 M). 224 mg of DCC (1.1 mmol, 1.0 equiv) in 5 mL toluene was added to the solution, and the reaction was brought to reflux. The reaction was stirred for 24 h. The solid was

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filtered, and filtrate was collected, concentrated, and purified by FCC (50:50::Hex/EtOAc) to give **1a** in a 62% yield, 240 mg, as a white flaky solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.40 (s, 2H), 3.19-3.06 (m, 2H), 2.06−1.92 (m, 2H), 1.87−1.77 (m, 2H), 1.54−1.22 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.0, 150.9, 132.3 (q, J = 32.7 Hz), 125.6 (d, J = 272.7 Hz), 123.0 (d, J = 13.2 Hz), 121.2 (d, J = 272.7 Hz), 115.0, 61.7, 29.4, 23.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.72. High-resolution mass spectrometry (HRMS): calcd for $C_{15}H_{15}F_6N_3$ $[M + H]^+$ = 352.1248. Found 352.1254.

General Synthesis of Selenoether Catalyst Precursor. *(1S,2R)-1-((tert-Butoxycarbonyl)amino)-2,3-dihydro-1H-inden-2-yl methanesulfonate.* To a round-bottom flask and dry stir bar was added 5 g of (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (5 g, 33.5 mmol, 1.0 equiv) into a solution of tetrahydrofuran (THF)/H_2O (~70 mL of both, 0.5 M). $NaHCO_3$ (4.2 g, 50.3 mmol, 1.5 equiv) was added to the solution and stirred for 5 min. Boc_2O (8.0 g, 36.8 mmol, 1.1 equiv) was then added to the solution. The reaction was then stirred at r.t. for 24 h and then diluted with EtOAc (2 × 30 mL). The organic layer was separated, washed with brine, and dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl ((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)carbamate as a viscous brown oil. No further purification was needed. The NMR spectra match the literature precedence.[46]

The product was dissolved in anhydrous DCM (~50 mL, 0.5 M). Et_3N was syringed (4.8 mL, 34.5 mmol, 1.5 equiv) into the solution, and the reaction was cooled down to 0 °C. MsCl (1.96 mL, 25.3 mmol, 1.1 equiv) was syringed slowly into the reaction, warmed to r.t., and stirred for 12 h. The reaction was quenched with 1 M $NaHCO_3$ solution and then extracted with DCM (2 × 30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give (1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2,3-dihydro-1*H*-inden-2-yl methanesulfonate, as a brownish-white solid. No further purification was needed. The NMR spectra match the literature precedence.[47]

1,2-Dimesityldiselane. *N*-Bromosuccinimide (2.2 g, 1 equiv) and selenium metal powder (1.2 g 1.2 equiv) were added to a round-bottom flask, and then MeCN (~60 mL, 0.2 M) was added to the mixture and stirred at 60 °C for 10 min. Mesityl boronic acid (2.0 g, 1 equiv) was added followed by the addition of pyridine (2.5 mL, 22.5 equiv). The reaction turns an orange color immediately after addition. The reaction was left stirring in open air at 60 °C for 12 h. The reaction was concentrated under reduced pressure, dissolved in EtOAc, washed with 1 M HCl (30 mL × 3) and brine (30 mL × 3), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (hexanes/EtOAc = 100:0−99:1) afforded the desired product in a 55% yield, 1.3 g, as an orange crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 4H), 2.27 (s, 6H), 2.25 (s, 12H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 143.4, 138.8, 128.1, 128.0, 23.9, 20.8. HRMS: calcd for $C_{18}H_{22}Se_2$ $[M + H]^+$ = 399.0133. Found 399.0046 m/z plus multiplets from selenium isotopes.

General Synthesis of Lewis Base Substitution. *Substitution of Benzenethiols.* To an oven-dried round-bottom flask with a stir bar were added (1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (1 equiv) and K_2CO_3 (3 equiv). The flask was sealed with a rubber stopper, evacuated, and back-filled with inert nitrogen. Then anhydrous dimethylformamide (DMF) (0.2 M) was syringed into the flask and stirred for 10 min. Benzenethiol (1 equiv) was added to the flask, and the reaction was stirred at 100 °C for 12 h. The reaction was cooled to r.t., quenched with 1 M HCl, extracted with EtOAc (20 mL × 3), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (hexanes/EtOAc::100:0−85:15) afforded the desired product.

Substitution of Diselenides. The following synthesis is adapted from a general procedure from the published literature.[40] To an oven-dried round-bottom flask with a stir bar was added a solution of diselenide (0.5 equiv) in EtOH (0.15 M) under an inert atmosphere. $NaBH_4$ (2 equiv) was added, and the mixture was stirred at r.t. for 10 min. Then, a solution of (1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (1 equiv) in anhydrous THF (0.6 M) was slowly added. The resulting mixture was stirred at reflux for 12 h. The reaction was quenched with aqueous saturated NH_4Cl. The organic phase was extracted with DCM (20 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (hexanes/EtOAc::100:0−85:15) afforded the desired product.

tert-Butyl ((1S,2S)-2-(Mesitylthio)-2,3-dihydro-1H-inden-1-yl)-carbamate. Prepared and purified according to the general procedure A: To an oven-dried round-bottom flask with a stir bar were added 300 mg of (1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2,3-dihydro-1*H*-inden-2-yl methanesulfonate and 379 mg of K_2CO_3. The flask was sealed with a rubber stopper, evacuated, and back-filled with an inert nitrogen gas. Then, 4.5 mL of anhydrous DMF was syringed into the flask and stirred for 10 min. 112 mg of 2,4,6-trimethylthiophenol was added to the flask, and the reaction was stirred at 100 °C for 12 h. Purification through flash column chromatography (hexanes/EtOAc::100:0−85:15) afforded the desired product in a 75% yield, 264 mg, as a white flaky solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21−7.11 (m, 4H), 6.94 (s, 2H), 5.06 (t, J = 7.8 Hz, 1H), 4.60 (d, J = 7.8 Hz, 1H), 3.42 (q, J = 7.8 Hz, 1H), 3.15 (dd, J = 7.5 Hz, 7.8 Hz, 1H), 2.90−2.84 (m, 1H), 2.51 (s, 6H), 2.27 (s, 3H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.4, 143.2, 129.0, 128.0, 127.1, 124.4, 124.0, 61.9, 54.4, 37.9, 28.3, 22.1, 21.0. HRMS: calcd for $C_{23}H_{29}NO_2S$: $[M + H]^+$ = 384.1997. Found 422.1762 m/z, which is $[M + H + K]^+$.

tert-Butyl ((1S,2S)-2-(Mesitylselanyl)-2,3-dihydro-1H-inden-1-yl)-carbamate. Prepared and purified according to the general procedure B: To an oven-dried round-bottom flask with a stir bar was added 589 mg (1.37 mmol) of 1,2-dimesityldiselane in 9 mL (0.15 M) of EtOH under an inert atmosphere. 104 mg of $NaBH_4$ (2.74 mmol) was added, and the mixture was stirred at r.t. for 10 min. Then, a solution of 900 mg (2.74 mmol) of (1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2,3-dihydro-1*H*-inden-2-yl methanesulfonate in 6 mL anhydrous THF (0.6 M) was slowly added. Purification through flash column chromatography (hexanes/EtOAc::100:0−85:15) afforded the desired product in a 45% yield, 532 mg, as a flaky white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.12 (m, 4H), 6.94 (s, 2H), 5.11 (t, J = 7.8 Hz, 1H), 4.61 (d, J = 7.8 Hz, 1H), 3.48 (q, J = 7.8 Hz, 1H), 3.18 (dd, J = 7.5 Hz, 7.8 Hz, 1H), 2.89−2.84 (m, 1H), 2.54 (s, 6H), 2.27 (s, 3H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.4, 143.7, 141.3, 128.5, 128.0, 127.0, 124.3, 123.9, 47.3, 38.3, 28.3, 24.7, 20.9. HRMS: calcd for $C_{23}H_{29}NO_2Se$: $[M + H]^+$ = 431.1365. Found 452.1267 m/z plus multiplets from selenium isotopes, which is $[M + H + Na]^+$.

GENERAL SYNTHESIS OF BOC-DEPROTECTION

The following synthesis is adapted from a general procedure from the published literature.[40] A solution of 6 M HCl (10 equiv) was added to a solution of dioxane (0.1 M) and Boc-protected reagent. The mixture was stirred at 60 °C for 6 h and then quenched with 1 M NaOH solution until pH 14. Then, the solution was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (DCM/MeOH::100:0−80:20) afforded the desired product.

(1*S*,2*S*)-2-(Phenylthio)-2,3-dihydro-1*H*-inden-1-amine (4). A solution of 6 M HCl (480 μL) was added to a solution of 2.9 mL dioxane and 100 mg (0.29 mmol) of *tert*-butyl ((1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-yl) carbamate. The mixture was stirred at 60 °C for 6 h. The synthesis and spectral data are in agreement with the literature.[42]

(1*S*,2*S*)-2-(Mesitylthio)-2,3-dihydro-1*H*-inden-1-amine. A solution of 6 M HCl (650 μL) was added to a solution of 3.9 mL dioxane and 150 mg (0.39 mmol) of *tert*-

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butyl ((1*S*,2*S*)-2-(mesitylthio)-2,3-dihydro-1*H*-inden-1-yl)-carbamate. The mixture was stirred at 60 °C for 6 h. Purification through flash column chromatography (DCM/MeOH::100:0−80:20) afforded the desired product in an 81% yield, 89 mg, as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.0 Hz, 1H), 7.24−7.17 (m, 2H), 7.13 (d, J = 6.6 Hz, 1H), 6.96 (s, 2H), 4.24 (d, J = 7.8 Hz, 1H), 3.24 (dd, J = 16.7, 7.5 Hz, 1H), 3.15 (dd, J = 15.5, 7.5 Hz, 1H), 2.85 (dd, J = 15.5, 9.0 Hz, 1H), 2.56 (s, 6H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.2, 143.1, 140.6, 138.4, 129.1, 129.0, 127.6, 126.9, 124.2, 123.4, 63.6, 58.5, 38.0, 22.2, 21.0. HRMS: calcd for $C_{18}H_{21}NS$ $[M + H]^+$: 284.1473. Found 267.1205 m/z, which is $[M + H - NH_2]^+$.

(1*S*,2*S*)-2-(Mesitylselanyl)-2,3-dihydro-1*H*-inden-1-amine. A solution of 6 M HCl (940 μL) was added to a solution of 5.6 mL dioxane with 244 mg (0.56 mmol) of *tert*-butyl ((1*S*,2*S*)-2-(mesitylselanyl)-2,3-dihydro-1*H*-inden-1-yl)-carbamate. The mixture was stirred at 60 °C for 6 h. Purification through flash column chromatography (DCM/MeOH::100:0−80:20) afforded the desired product in a 78% yield, 144 mg, as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.1 Hz, 1H), 7.23−7.17 (m, 2H), 7.14 (d, J = 7.1 Hz, 1H), 6.96 (s, 2H), 4.26 (d, J = 7.8 Hz, 1H), 3.30 (dd, J = 16.8, 7.6 Hz, 1H), 3.21 (dd, J = 15.7, 7.6 Hz, 1H), 2.91−2.85 (m, 1H), 2.59 (s, 6H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.4, 143.5, 141.3, 138.5, 128.6, 127.5, 126.9, 126.7, 124.1, 123.4, 64.1, 52.2, 38.2, 24.9, 21.0. HRMS: calcd for $C_{18}H_{21}NSe$ $[M + H]^+$: 332.0918. Found 315.0635 m/z plus multiplets from selenium isotopes, which is $[M + H - NH_2]^+$.

4-Methyl-*N*-((1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-yl)benzenesulfonamide (5). To a solution of 250 mg (1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-amine (0.63 mmol, 1 equiv) in 3.1 mL DCM (0.2 M) were added 132 μL Et_3N (0.95 mmol, 1.5 equiv) and 136 μL TsCl (0.95 mmol, 1 equiv) at r.t. The solution was stirred for 12 h and then quenched with water and extracted with DCM (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−90:10) afforded the desired product. The spectral data are in agreement with the literature.[42]

1,1,1-Trifluoro-*N*-((1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide (6). *N*,*N*-Diisopropylethylamine (DIPEA) (250 μL, 1.5 mmol) was added to a solution of (1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-amine in 15 mL dry DCM (0.1 M) under an inert atmosphere. Then, triflic anhydride (185 μL, 1.1 mmol) was added slowly. The reaction was stirred at r.t. for 3 h. Then, a 1 M HCl solution was added and the solution was extracted with DCM (15 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−90:10) afforded the desired product. The spectral data are in agreement with the literature.[42]

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-yl)thiourea (7). One hundred and twenty milligrams (0.50 mmol, 1 equiv) of (1*S*,2*S*)-2-(phenylthio)-2,3-dihydro-1*H*-inden-1-amine was dissolved in 2.5 mL (0.2 M) of anhydrous THF under an inert atmosphere. Then, 136 mg (0.50 mmol, 1 equiv) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added to the reaction. The mixture was stirred at r.t. for 4 h and then immediately concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−85:15) afforded the desired product in a 67% yield, 171 mg, as a pale white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.79 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 1.6 Hz, 2H), 7.75 (s, 1H), 7.56−7.43 (m, 2H), 7.38−7.14 (m, 7H), 6.02 (s, 1H), 4.07 (q, J = 8.0 Hz, 1H), 3.43 (dd, J = 16.0, 7.6 Hz, 1H), 2.85 (dd, J =16.0, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 181.1, 161.6, 140.7, 133.1, 129.4, 128.2, 127.7, 124.9, 124.2, 124.1, 121.4, 119.5, 113.1, 65.8, 54.1, 38.0. HRMS: calcd for $C_{24}H_{18}F_6N_2S_2$ $[M + H]^+$: 513.0894. Found 513.0893 m/z.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-((4-methoxyphenyl)thio)-2,3-dihydro-1*H*-inden-1-yl)-thiourea (8). One hundred and fifty milligrams (0.28 mmol, 1 equiv) of (1*S*,2*S*)-2-((4-methoxyphenyl)thio)-2,3-dihydro-1*H*-inden-1-amine was dissolved in 1.4 mL (0.2 M) of anhydrous THF under an inert atmosphere. Then, 76 mg (0.28 mmol, 1 equiv) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added to the reaction. The mixture was stirred at r.t. for 4 h and then immediately concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−85:15) afforded the desired product in a 65% yield, 98 mg, as a pale white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.74 (d, J = 8.5 Hz, 1H), 8.20 (s, 2H), 7.7.6 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.33−7.11 (m, 4H), 6.91 (d, J = 8.4 Hz, 2H), 5.97 (t, J = 8.4 Hz, 1H), 3.85 (t, J = 8.4 Hz, 1H), 3.71 (s, 3H), 3.25 (dd, J = 16.1, 7.8 Hz, 1H), 2.79 (dd, J = 15.9, 8.8 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 181.1, 160.3, 140.7, 136.7, 132.5, 129.1, 127.6, 124.8, 124.3, 122.6, 121.4, 119.3, 114.9, 105.0, 65.3, 55.3, 55.0, 37.4. HRMS: calcd for $C_{25}H_{20}F_6N_2OS_2$ $[M + H]^+$: 543.0999. Found 543.1001 m/z.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(mesitylthio)-2,3-dihydro-1*H*-inden-1-yl)thiourea (9). One hundred and twenty milligrams (0.42 mmol, 1 equiv) of (1*S*,2*S*)-2-(mesitylthio)-2,3-dihydro-1*H*-inden-1-amine was dissolved in 2.1 mL (0.2 M) of anhydrous THF under an inert atmosphere. Then, 115 mg (0.42 mmol, 1 equiv) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added to the reaction. The mixture was stirred at r.t. for 4 h and then immediately concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−85:15) afforded the desired product in a 72% yield, 167 mg, as a dark yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.52 (s, 1H), 8.19 (s, 2H), 7.75 (s, 1H), 7.40−7.14 (m, 4H), 6.94 (s, 2H), 5.83 (s, 1H), 3.80 (q, J = 6.9 Hz, 1H), 3.18 (dd, J = 16.2, 7.3 Hz, 1H), 2.73 (dd, J = 16.1, 6.8 Hz, 1H), 2.44 (s, 6H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 180.9, 143.5, 139.6, 129.5, 128.0, 125.1, 123.8, 121.7, 119.8, 110.0, 52.1, 37.4, 22.1, 20.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.87 MS (atmospheric pressure chemical ionization (APCI)): calcd for $C_{27}H_{24}F_6N_2S_2$ $[M + H]^+$: 555.1363. Found 555.1363 m/z.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(mesitylselanyl)-2,3-dihydro-1*H*-inden-1-yl)thiourea (10). One hundred and thirty milligrams (0.33 mmol, 1 equiv) of (1*S*,2*S*)-2-(mesitylselanyl)-2,3-dihydro-1*H*-inden-1-amine was dissolved in 6.6 mL (0.2 M) of anhydrous THF under an inert atmosphere. Then, 100 mg (0.37 mmol, 1 equiv) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added to the reaction. The mixture was stirred at r.t. for 4 h and then immediately concentrated under reduced pressure. Purification through flash column chromatography (Hex/EtOAc::100:0−85:15) afforded the desired product in a 67% yield, 133 mg, as

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a pale white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.57 (s, 1H), 8.20 (s, 2H), 7.75 (s, 1H), 7.34 (s, 1H), 7.22 (bs, 3H), 6.94 (s, 2H), 5.89 (s, 1H), 3.87 (q J = 7.0 Hz, 1H), 3.20 (dd, J = 16.3, 7.4 Hz, 1H), 2.75 (dd, J = 15.8, 7.5 Hz, 1H), 2.46 (s, 6H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 180.8, 143.7, 142.1, 129.1, 129.0, 127.7, 125.2, 124.2, 121.5, 119.8, 45.0, 37.6, 24.6, 20.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.92 MS (APCI): calcd for $C_{27}H_{24}F_6N_2SSe$ [M + H]$^+$: 603.0809. Found 603.0603 m/z plus multiplets from selenium isotopes.

GENERAL ORTHO-CHLORINATION SYNTHESIS OF PHENOLS AND ANILINES

Substrate (0.030 mmol, 1 equiv), catalyst (0.00030 mmol, 0.01 equiv unless specifically mentioned otherwise), and $CDCl_3$ (0.05 M) were added to an NMR tube followed by the addition of tetramethylsilane (TMS) as an internal standard. *N*-Chlorosuccinimide (0.036 mmol, 1.2 equiv) was then added to the NMR tube, and the reaction was monitored by ^{1}H NMR. The reaction was considered complete once the substrate conversion had ceased. Isomeric ratios were determined via integration of the aromatic peaks of each product. Conversion to mono-Cl products represents the sum of the conversions of all identified mono-chlorinated products, and the value was determined via integration of mono-chlorinated products with respect to TMS. Isomeric ratios were determined by the analysis of nonobscure peaks. When necessary, clear coupling patterns were partially integrated, and full integration value was extrapolated from the partial integration. If multiple peaks were clear, the average of those peaks was used to determine the isomeric ratio. Each experiment in Table 1 was performed in triplicate, and the reported ratios are the average of the three trials.

Yields were determined on a 1 mmol scale using $CHCl_3$; all reagents and solvents were scaled equally, omitting TMS. Phenols were stirred at room temperature, while anilines were stirred at 0 °C. Upon reaction completion, as determined by thin-layer chromatography (TLC), the reaction was filtered through a short normal phase silica plug with DCM to remove succinimide. The solvent was then removed by rotovap, and, for almost all substrates, the resulting crude mixture was purified by flash column chromatography (FCC) on normal phase silica gel, eluting with hexanes and ethyl acetate (hexanes/ethyl acetate::100:0 → 99:1 → 98:2 → 97:3 → 95:5), unless otherwise noted. Each experiment in Schemes 2 and 3 was done in duplicate, and the reported ratios, conversions, and yields are the average of the two trials.

The relative energies are determined based on the experimental constitutional isomeric ratios, finding the difference in energy between a reaction that is catalyst-controlled versus one that possesses innate selectivity of the substrate. The equation for transition-state relative energy is derived from the Eyring equation. $\Delta\Delta\Delta G^{\ddagger} = \Delta\Delta G_{\text{catalyst1}}^{\ddagger} - \Delta\Delta G_{\text{innate}}^{\ddagger}$, with ortho-selectivity defined as positive $\Delta\Delta G^{\ddagger}$ and para-selectivity defined as negative $\Delta\Delta G^{\ddagger}$. $\Delta\Delta G^{\ddagger} = -RT \ln[\text{para}]/[\text{ortho}]$.

3-Chloro-[1,1′-biphenyl]-2-ol (11b). **11b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 44% yield, 90 mg, as a pale white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.52 (m, 2H), 7.47 (t, 7.5 Hz, 2H), 7.41−7.38 (m, 1H), 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.95 (td, 7.8, 2.3 Hz, 1H), 5.71 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.4, 137.1, 129.7, 129.4, 129.2, 128.5, 128.3, 127.8, MS (APCI): calcd for $C_{12}H_{10}ClO$ [M + H]$^+$: 205.0. Found 205.0 m/z. The data matches references found in the literature.[48]

3-Chloro-2-hydroxybenzonitrile (12b). **12b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 71% yield, 109 mg, as a white solid. A 5% catalyst loading was used. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dq, J = 8.0, 1.3 Hz, 1H), 7.48 (dq, J = 7.9, 1.4 Hz, 1H), 7.02−6.93 (m, 1H), 6.25 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.8, 133.7, 132.1, 121.5, 121.1, 115.0, 101.3. MS (APCI): calcd for C_7H_4ClNO [M + H]$^+$: 154.57. Found 154.57 m/z. The data matches references found in the literature.[32]

2-Bromo-6-chlorophenol (13b). **13b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 43% yield, 89 mg, as a clear oil. A 5% catalyst loading was used. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dq, J = 8.1, 1.6 Hz, 1H), 7.30 (dq, J = 8.1, 1.6 Hz, 1H), 6.76 (ddd, J = 8.0, 2.0 Hz, 1H), 5.88 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.7, 131.4, 129.0, 121.8, 120.8, 110.3. MS (APCI): calcd for C_6H_4BrClO [M + H]$^+$: 208.45. Found 208.45 m/z. The data matches references found in the literature.[33]

2-(*tert*-Butyl)-6-chlorophenol (14b). **14b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 56% yield, 103 mg, as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 7.3 Hz, 2H), 6.80 (td, J = 8.0, 2.2 Hz, 1H), 5.85 (s, 1H), 1.41 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.7, 137.6, 126.4, 125.7, 120.9, 120.3, 35.2, 29.3. MS (APCI): calcd for $C_{10}H_{13}ClO$ [M + H]$^+$: 185.66. Found 185.66 m/z. The data matches references found in the literature.[32]

2-Chloro-6-iodophenol (15b). **15b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 60% yield, 153 mg, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.0, 2.0 Hz, 1H), 7.31 (dd, J = 8.1, 1.8 Hz, 1H), 6.63 (td, J = 8.9, 8.5, 1.9 Hz, 1H), 5.94 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.9, 137.8, 129.6, 122.8, 119.2, 83.5. MS (APCI): calcd for C_6H_4ClIO [M + H]$^+$: 255.45. Found 255.45 m/z. The data matches references found in the literature.[32]

2-Chloro-5-fluorophenol (16b). **16b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 70% yield, 102 mg, as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.23 (m, 1H), 6.76 (dd, J = 9.6, 2.9 Hz, 1H), 6.61 (ddd, J = 8.9, 8.0, 2.9 Hz, 1H), 5.66 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 246 Hz), 152.3 (d, J = 12.7 Hz), 129.4 (d, J = 9.9 Hz), 115.0, 108.5 (d, J = 23.3 Hz), 104.0 (d, J = 26.6 Hz) ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.46 (m) MS (APCI): calcd for C_6H_4ClFO [M + H]$^+$: 147.55. Found 147.55 m/z. The data matches references found in the literature.[32]

5-Bromo-2-chlorophenol (17b). **17b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 60% yield, 124 mg, as a dark brown oil. A 5% catalyst loading was used. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.17 (m, 2H), 7.01 (dt, J = 8.6, 1.9 Hz, 1H), 5.58 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.0, 129.9, 124.5, 121.3, 119.6, 119.0. MS (APCI): calcd for C_6H_4BrClO [M + H]$^+$: 208.45. Found 208.45 m/z. The data matches references found in the literature.[32]

4-Chloro-[1,1′-biphenyl]-3-ol (18b). **18b** was prepared according to the general procedure on a 1 mmol scale and

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obtained in a 35% yield as a white solid. A 5% catalyst loading was used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.53 (m, 2H), 7.45−7.41 (m, 4H), 7.38−7.35 (m, 2H), 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 5.59 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.5, 141.9, 139.8, 129.2, 129.1, 128.8, 128.1, 127.7, 127.0, 123.0, 120.1, 114.8. MS (APCI): calcd for $C_{12}H_9ClO$ $[M + H]^+$: 205.65. Found 205.65 m/z. The data matches references found in the literature.[49]

2-Chloro-6-isopropyl-3-methylphenol (19b). **19b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 37% yield, 68 mg, as a brownish-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 5.69 (s, 1H), 3.28 (hept, J = 4.2 Hz, 1H), 2.34 (s, 3H), 1.24 (d, J = 9.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.5, 133.4, 133.2, 124.1, 121.9, 120.3, 27.6, 22.4, 19.9. MS (APCI): calcd for $C_{10}H_{13}ClO$ $[M + H]^+$: 185.66. Found 185.67 m/z. The data matches references found in the literature.[50]

2-Chloronaphthalen-1-ol (20b). **20b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 50% yield, 89 mg, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.55−7.47 (m, 2H), 7.37 (t, J = 1.3 Hz, 2H), 5.99 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.0, 133.2, 127.6, 126.6, 126.1, 125.9, 124.4, 122.1, 120.9, 113.5. MS (APCI): calcd for $C_{10}H_7ClO$ $[M + H]^+$: 179.61. Found 179.61 m/z. The data matches references found in the literature.[51]

2-Chloro-6-methylaniline (21b). **21b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 65% yield, 92 mg, as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.63 (dd, J = 7.9, 2.5 Hz, 1H), 4.01 (bs, 2H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.1, 128.7, 127.0, 123.5, 119.1, 118.3, 17.9. MS (APCI): calcd for C_7H_8ClN $[M + H]^+$: 142.60. Found 142.61 m/z. The data matches references found in the literature.[52]

2-Chloro-6-isopropylaniline (22b). **22b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 66% yield, as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 7.9, 1.5 Hz, 1H), 7.05 (dd, J = 7.9, 1.4 Hz, 1H), 6.70 (t, J = 7.8 Hz, 1H), 4.11 (s, 2H), 2.90 (hept, J = 7.0 Hz, 1H), 1.27 (d, J = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 139.9, 133.8, 126.7, 123.7, 119.8, 118.6, 28.4, 22.1. HRMS: calcd for $C_9H_{12}ClN$ $[M + H]^+$: 170.0737. Found 170.0747 m/z.

2-(*tert*-Butyl)-6-chloroaniline (23b). **23b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 64% yield, 117 mg, as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (ddd, J = 10.7, 7.9, 1.4 Hz, 2H), 6.65 (t, J = 7.9 Hz, 1H), 4.35 (s, 2H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.9, 134.9, 127.3, 125.0, 121.2, 118.0, 34.7, 29.5. MS (APCI): calcd for $C_{10}H_{14}ClN$ $[M + H]^+$: 184.0893. Found 184.0895 m/z.

2-Bromo-6-chloroaniline (24b). **24b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 40% yield, 82 mg, as a brownish-white solid. Five percent of catalyst was used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.0, 1.4 Hz, 1H), 7.21 (dd, J = 8.0, 1.4 Hz, 1H), 6.55 (t, J = 8.0 Hz, 1H), 4.50 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.1, 131.0, 128.5, 119.3, 118.7, 109.2. MS (APCI): calcd for C_6H_5BrClN $[M + H]^+$: 205.93. Found 205.93 m/z. The data matches references found in the literature.[53]

2-Chloro-5-fluoroaniline (25b). **25b** was prepared according to the general procedure on a 1 mmol scale, obtained in a 70% yield, 101 mg, as a brown-orange oil. Five percent of catalyst was used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.8, 5.7 Hz, 1H), 6.47 (dd, J = 10.1, 2.9 Hz, 1H), 6.40 (td, J = 8.4, 2.9 Hz, 1H), 4.14 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.2 (d, J = 244 Hz), 144.1 (d, J =11.3 Hz), 130.2 (d, J = 10.0 Hz), 114.1 (d, J = 2.9 Hz), 105.7 (d, J = 23.4 Hz), 102.5 (d, J = 26.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.84 (m) MS (APCI): calcd for C_6H_5ClFN $[M + H]^+$: 145.56. Found 145.56 m/z. The data matches references found in the literature.[54]

5-Bromo-2-chloroaniline (26b). **26b** was prepared according to the general procedure on a 1 mmol scale and obtained in a 30% yield, 62 mg, as a brown-orange oil. Five percent of catalyst was used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4, 1H), 6.90 (d, J = 2.3 Hz, 1H), 6.79 (dd, J = 8.5, 2.2, 1H). 4.09 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.1, 130.5, 121.7, 121.7, 118.3, 118.1. MS (APCI): calcd for C_6H_5BrClN $[M + H]^+$: 207.9350 Found 207.9352 m/z.

4-Chloro-[1,1′-biphenyl]-3-amine (27b). **27b** was prepared according to the general procedure on a 1 mmol scale, obtained as a brown-orange oil. Five percent of catalyst was used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.38 (m, 5H), 7.30 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.92 (dd, J = 8.2, 2.1 Hz, 1H), 4.12 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 143.0, 141.0, 140.4, 129.6, 129.3, 128.7, 127.9, 127.4, 127.0, 120.8, 118.0, 114.4. MS (APCI): calcd for $C_{12}H_{10}ClN$ $[M + H]^+$: 204.0580. Found 204.0581 m/z.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01917.

Crude NMR spectra for the determination of regioselectivity NMR spectra of purified products; crystal structure information; isotopically labeled experiments; and preliminary mechanistic experiments with catalyst **10** (PDF)

Crystallographic data file (CIF)

Guanidinium crystal structure (ZIP)

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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