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Regiodivergent Halogenation of Vinylogous Esters: One-Pot, Transition-Metal-Free Access to Differentiated Haloresorcinols

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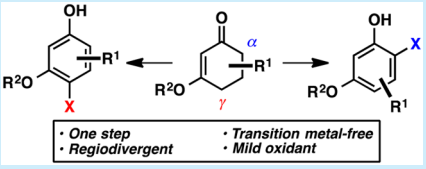
Supporting Information

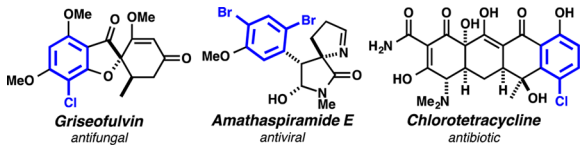
ABSTRACT: We report an efficient method for the regiodivergent synthesis of halogenated resorcinol derivatives using readily available vinylogous esters and sulfonyl halide halogen donors. Either the 4- or 6-haloresorcinol isomer is accessible from a common precursor. In contrast to conventional oxidants for arene halogenation, mild sulfonyl halides allow broad functional group compatibility. The strategy inherently differentiates the two resorcinol oxygen atoms and enhances the potential for complex molecule synthesis.



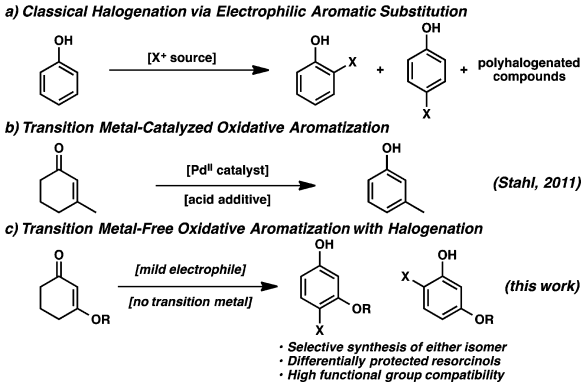
Substituted aromatic systems are principal substructures in a wide variety of important organic molecules including bioactive natural products (Scheme 1), pharmaceuticals, agrochemicals, and polymers.[1] The advent of efficient cross-coupling protocols predicated on the availability of aryl halide feedstocks has enhanced arene synthesis significantly.[2] However, the preparation of substituted haloarenes is not always straightforward. Classical electrophilic aromatic substitution reactions between arenes and strong electrophiles such as elemental halogens (Scheme 2a)[3] are complicated by issues of regioselectivity and overhalogenation, particularly with electron-rich aromatics,[4] and much effort has been exerted to overcome these limitations with transition-metal-catalyzed substitutions.[5] Recently, alternative strategies have accessed arenes via oxidation of cyclohexenone derivatives.[6] For instance, Stahl and co-workers described Pd-catalyzed oxidation methods that transfer existing substitution patterns from the nonaromatic compound to the arene (Scheme 2b).[6a] Herein we report a novel strategy that requires no harsh oxidants or transition metals and enables not only regiochemical transfer but also concomitant regioselective introduction of a halogen into the resulting arene (Scheme 2c).

We hypothesized that regioselective synthesis of monohalogenated, electron-rich arenes could be achieved by a halogenation/aromatization cascade from unsaturated cyclic ketone substrates (Scheme 3). Enones are poised for regiodivergent functionalization through the corresponding dienolates that possess multiple nucleophilic sites, and our strategy thus relies on engaging these ambident nucleophiles in a regioselective halogenation event. To address this regiocontrol issue, we chose to incorporate an alkoxy group on the enone to enhance electron density at the γ-carbon of the derived dienolate. There have been only sparse reports of γ-selective transformations in these systems,[7−9] with the predominant literature describing α-selective functionalization.[10] Koreeda[8] and Smith[9] have explored similar transformations but found an overall limited scope and poor results for oxidation reactions. Our design also benefits from the inherent differentiation of the two similarly reactive resorcinol oxygen atoms, obviating a later synthetic challenge.[11] Moreover, when coupled with Stork−Danheiser transformations,[10] the overall strategy could potentially functionalize all six positions about the arene ring.

Scheme 1. Naturally Occurring Bioactive Aryl Halides



Scheme 2. Strategies for Synthesis of Substituted Phenols and Resorcinols



To test our hypothesis, we surveyed various base/halogen donor combinations with readily available vinylogous ester **1a** (Table 1).[9,10,12] Utilizing the conditions of Koreeda[8] or Smith[9] predominantly led to α-functionalized products in moderate yield in the systems we examined. Although the majority of amide bases led to nonhalogenated phenol products, we observed that for compound **1a** the use of lithium hexamethyldisilazide (LiHMDS) as base in the presence of polar additives gave predominantly the haloarene **2**, presumably

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Scheme 3. Strategy for Regioselective Halogenation/ Aromatization Cascades

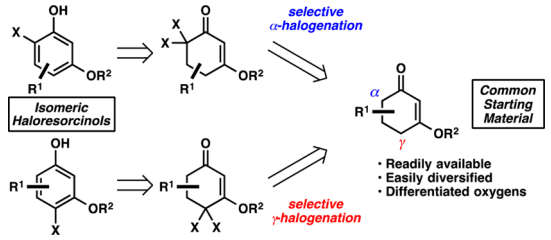
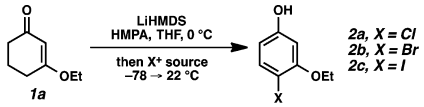


Table 1. Optimization of Halogen Donors[a]



entry	Cl+ source (X = Cl)	% yield
1	*N*-Chlorosuccinimide	82
2	1,3-Dichloro-5,5-dimethylhydantoin	92
3	SO_2Cl_2	10
4	$MeSO_2Cl$	0
5	$4\text{-}NO_2C_6H_4SO_2Cl$	90
6	$C_6H_5SO_2Cl$	93
7	$4\text{-}MeC_6H_4SO_2Cl$ (Ts–Cl)	93
8	$2,4,6\text{-}(i\text{-}Pr)_3C_6H_2SO_2Cl$	97
9	Me_2NSO_2Cl	90

entry	Br+ source (X = Br)	% yield
10	*N*-Bromosuccinimide	87
11	1,3-Dibromo-5,5-dimethylhydantoin	89
12	$BnEt_3NBr_3$	84
13	$4\text{-}MeC_6H_4SO_2Br$ (Ts–Br)	86

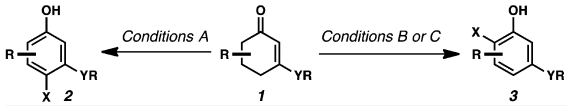
entry	I+ source (X = I)	% yield
14	*N*-Iodosuccinimide	0[b]
15	I_2	50
16	$4\text{-}MeC_6H_4SO_2I$ (Ts–I)	72

[a]Isolated yield of **2** from reactions with 1.0 mmol of substrate, 4.0 mmol of LiHMDS (1 M in THF), 2.1 mmol of X^+ source, and 2.5 mmol of HMPA, in 10 mL of THF. [b]3-Ethoxyphenol is the major product.

derived from the corresponding γ-dienolate, with hexamethylphosphoramide (HMPA) providing the best results.[13] The ratio of α- to γ-functionalization was dependent on a number of factors including concentration, temperature, and halogen donor.[13,14] Using *N*-chlorosuccinimide or a *N*,*N*′-dichlorohydantoin, the chlororesorcinol product predominated, but a significant amount of nonhalogenated resorcinol formed as a side product (entries 1 and 2). Among the halogen donors surveyed, sulfonyl halides emerged as especially effective, with the formation of only traces of the nonhalogenated arenes.[15] Aromatic sulfonyl chlorides provided good results, with trisyl chloride performing the best (entries 5−8).[16] Alkyl sulfonyl chlorides provided only traces of products (entry 4), but a sulfamoyl chloride performed well in the reaction (entry 9). Bromo- and iodoresorcinols could be accessed similarly by employing the corresponding tosyl halides[17] (entries 13 and 16), whereas the succinimide-based halogen donors did not provide the same consistency over the range of halides (entries 1, 10, and 14).[18] We ultimately settled upon a simple, one-pot procedure (conditions A, Table 2) that transforms enone **1** into the chlorinated resorcinol **2a** in 98% yield with commercial TsCl as the halogen donor.[13]

We were pleased to find that many 4-haloresorcinol derivatives could be formed following our protocol (Table 2). A reaction on 10 mmol scale occurs with no decrease in efficiency (**2a**). Bromination and iodination reactions proceed in good yield as well (**2b**, **2c**, **2l**, and **2m**). A number of carbon-based substituents are tolerated, including allyl and benzyl groups (**2d** and **2e**) that may not be compatible with conventional direct arene halogenation protocols. We successfully synthesized differentially functionalized diaryl ether **2f** by employing a phenyl ester substrate.[19] Despite the basic reaction conditions, the Boc group survives the transformation in fair yield (**2g**). Carbon substituents about the ring cause no complications leading to highly substituted arenes (**2h**−**k**). The mild sulfonyl halide electrophile is compatible with oxidizable heteroatom-containing

Table 2. Synthesis of 4- and 6-Haloresorcinols[a]



Conditions A: 3 equiv LiHMDS, HMPA, THF, 0 °C, 1 h, then 2.1 equiv Ts–X, –78 °C, 0.5 h, then 1 equiv LiHMDS, –78 → 22 °C, 0.5 h

Conditions B: 3 equiv LiHMDS, 2:1 pentane/THF, –78 °C, 0.5 h, then 2.1 equiv Ts–Cl, –78 °C, 0.5 h, then 1 equiv LiHMDS, –78 → 22 °C, 1 h

Conditions C: 3 equiv LiHMDS, PhMe, –78 °C, 0.5 h, then 2.1 equiv Ts–X, –78 °C, 0.5 h, then 1 equiv LiHMDS, –78 → 22 °C, 1 h

entry	substrate	Ts–X	conditions	product	% yield
1[b]	R = Et	Ts–Cl	A	**2a**	98
2	R = Et	Ts–Br	A	**2b**	87
3	R = Et	Ts–I	A	**2c**	72
4	R = allyl	Ts–Cl	A	**2d**	92
5	R = Bn	Ts–Cl	A	**2e**	94
6	R = Ph	Ts–Cl	A	**2f**	92
7	R = Boc	Ts–Cl	A	**2g**	67
8		Ts–Cl	A	**2h**	77
9		Ts–Cl	A	**2i**	96
10		Ts–Cl	A	**2j**	94
11		Ts–Cl	A	**2k**	75
12	R = SPh	Ts–Br	A	**2l**	57
13	R = NMe_2	Ts–Br	A	**2m**	92
14	R = 	Ts–Cl	A	**2n**	95
15	R = Me	Ts–Cl	B	**3a**	97
16	R = *t*-Bu	Ts–Cl	B	**3b**	93
17	R = allyl	Ts–Cl	B	**3c**	98
18	R = Piv	Ts–Cl	B	**3d**	86
19	R = Boc	Ts–Cl	B	**3e**	99
20		Ts–Cl	B	**3f**	90
21		Ts–Cl	B	**3g**	91
22	R = SPh	Ts–Cl	B	**3h**	90
23	R = OEt	Ts–Br	C	**3i**	94
24	R = O*i*-Pr	Ts–I	C	**3j**	87
24	R = OBoc	Ts–Br	C	**3k**	92
26[c]	R = SO_2Ph	Ts–Br	C	**3l**	89
27		Ts–Br	C	**3m**	92

[a]Reactions performed with 1.0 mmol of substrate, 4.0 mmol of LiHMDS (1 M in THF) total, and 2.1 mmol of Ts-X. For conditions A, 2.5 mmol of HMPA and 10 mL of THF are used as solvent and isolated yields are the average of three runs. For conditions B and C, 10 mL of solvent is used and isolated yields are the average of two runs. [b]Reaction on 10 mmol scale. [c]Reaction on 5 mmol scale.

functional groups including thioethers and tertiary amines with no evidence of oxidative decomposition (**2l**−**n**).

We next examined accessing 6-haloresorcinol derivatives by modifying the reaction conditions. In the absence of HMPA the 6-haloresorcinol predominated, presumably via α-enolization/ halogenation similar to that described by Brummond.[15e] The selectivity for the 6-halo isomer improved with nonpolar cosolvents, with pentane performing the best in the chlorination reaction (conditions B, Table 2). A variety of oxygen substituents may be incorporated into the substrate, highlighted by acid-labile

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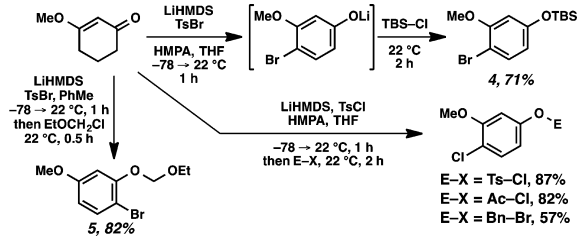
t-Bu ether, oxidizable allyl ether, and carbonyl-containing substrates (**3b**−**e**). Toluene proved to be the preferred solvent to access bromo- and iodoarenes **3i**−**m** (conditions C). Notably, a β-sulfonyl enone[20] proceeded to diaryl sulfone **3l** with no decrease in efficiency or change in regioselectivity.

Since a phenoxide is a likely intermediate, we pursued trapping of this nucleophile to access differentially protected resorcinol derivatives (Scheme 4). We added electrophiles directly to the

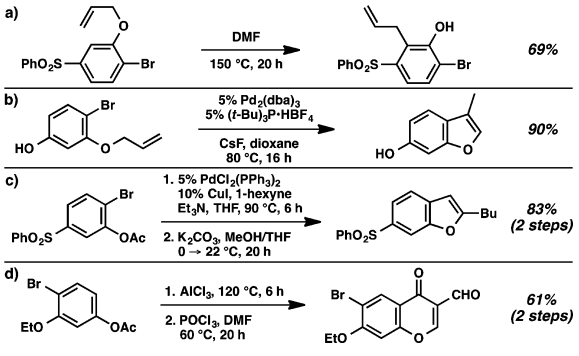
Scheme 4. One-Pot Aromatization/Phenoxide Trapping



reaction mixture after complete aromatization had occurred and found that *tert*-butyldimethylsilyl chloride (TBSCl) or chloromethyl ethyl ether could be employed to prepare arenes **4** or **5**, respectively. These functionalized intermediates were each previously synthesized from costly 4-bromoresorcinol in multiple steps.[21] We found that TsCl, AcCl, and BnBr are also suitable trapping agents, providing a diversified platform for further synthetic applications.

Haloarenes themselves are prevalent moieties in bioactive natural products (see Scheme 1).[1] However, we were also eager to engage our haloaromatics in other synthetic transformations. Claisen rearrangement[22] of an allyl aryl ether leads to a 1,2,3,4-substituted benzene with the halogen serving effectively as a directing group (Scheme 5a). Transition-metal-catalyzed trans-

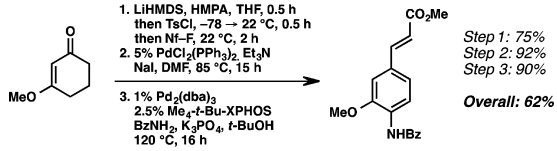
Scheme 5. Synthetic Transformations of Haloresorcinols



formations including Mizoroki−Heck cyclization (Scheme 5b)[23] and Sonogashira coupling (Scheme 5c)[24] demonstrate the potential to access functionalized heterocycles.[25] Toward other heterocyclic cores, regioselective Fries rearrangement of an acylated resorcinol occurs upon exposure to Lewis acid and in one further step a 4-chromone is formed (Scheme 5d).[26]

Given the recent advances in aryl chloride cross-coupling,[2b] we explored chemoselective cross-couplings of our resorcinol derivatives. To demonstrate this concept, we utilized our one-pot aromatization/phenoxide trapping protocol with nonafluorobutanesulfonyl fluoride (NfF) as an electrophile to access a resorcinol derivative containing both a reactive aryl nonaflate and a robust aryl chloride moiety (Scheme 6). Standard Mizoroki−Heck reaction conditions[23] led to reaction of the

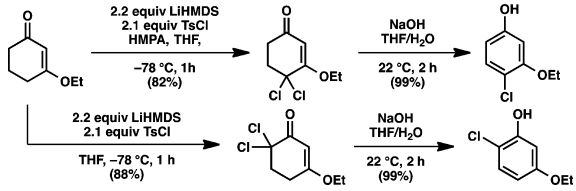
Scheme 6. Aromatization/Mizoroki−Heck/Buchwald−Hartwig Sequence



nonaflate moiety. Subsequently, Pd-catalyzed Buchwald−Hartwig amidation of the remaining aryl chloride was achieved with a Buchwald-type biaryl phosphine ligand.[27] Taken together, this three-step sequence is a powerful, efficient means for regiocontrolled formation of polysubstituted aromatics.

Since the reaction involves two oxidation events, we sought to establish the course of the halogenation reaction. Limiting the amount of base led to isolation of a γ,γ-dichlorinated vinylogous ester which aromatized upon exposure to hydroxide (Scheme 7).

Scheme 7. Isolation of Dichlorinated Intermediates



In the absence of HMPA, a similar sequence is observed via the α,α-dichlorinated intermediate. Although the intermediacy of α,γ-dichlorinated vinylogous esters cannot be rigorously excluded, the likelihood of high regioselectivity in a putative E2-type elimination step is small. Exposure of 3-methoxyphenol to our reaction conditions did not lead to any haloarene products, suggesting that halogenation precedes aromatization. These results additionally indicate a delicate balance of the rates of enolization/halogenation and the subsequent elimination step that is essential for high yield of the haloresorcinol. Stronger bases such as LDA are ineffective due to a combination of slow introduction of the second halogen atom and poor performance in elimination to form the arene. Similarly, succinimide-based halogen donors appear to transfer a second halogen atom slowly, allowing competitive elimination that leads to nonhalogenated arene side products.

In conclusion, we have developed two regiodivergent protocols that access specific halogenated resorcinol isomers in a single operation from one readily available precursor without transition metals or strong oxidants. These high-yielding transformations provide ready access to halogenated aromatics that are poised for further diversification. We anticipate that this chemistry will find use in natural product synthesis, medicinal chemistry, and materials synthesis, and we are currently pursuing these applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for details.

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(15) Few examples of sulfonyl chlorides as chlorenium donors appear in the literature. For selected examples with enolates, see: (a) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, *20*, 3643−3644. (b) Hirsch, E.; Hünig, S.; Reißig, H.-U. *Chem. Ber.* **1982**, *115*, 399−401. (c) Hirsch, E.; Hünig, S.; Reißig, H.-U. *Chem. Ber.* **1982**, *115*, 3687−3696. (d) Lee, K.; Shin, W. S.; Oh, D. Y. *Synth. Commun.* **1991**, *21*, 1657−1661. (e) Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231−2234.

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