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Chiral Anion Phase-Transfer Catalysis Applied to the Direct Enantioselective Fluorinative Dearomatization of Phenols

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Supporting Information

ABSTRACT: Chiral anion phase-transfer catalysis has enabled the direct and highly enantioselective fluorinative dearomatization of phenols catalyzed by a BINOL-derived phosphate. The process efficiently transforms simple, readily available phenols into fluorinated chiral small molecules bearing reactive functionality under ambient reaction conditions with high enantioselectivity. The close relationship of the products with well-studied *o*-quinols provides numerous avenues for synthetic elaboration and exciting opportunities for bioisosteric replacement of hydroxyl with fluorine in natural products.

The rapid and controlled generation of complex, readily functionalizable three-dimensional structures from simple planar starting materials is a highly attractive goal, as it allows fast access to diverse molecular architectures. Dearomatization of arenes is a powerful approach that has been proposed as a key component in putative biosynthetic pathways for a range of bioactive natural products, inspiring a range of elegant syntheses.[1] A highly desirable factor in such constructions is the induction of asymmetry into the product, which has generally been achieved by three distinct chemical approaches: diastereoselective dearomatization of a substrate bearing an existing stereocenter;[1b,2] dearomatization followed by enantioselective desymmetrization of the prochiral intermediate;[3] and finally, direct asymmetric dearomatization, which requires discrimination between the enantiotopic faces of the arene during the dearomatizing event. The last category represents a significant challenge, and to date, several elegant albeit noncatalytic metal-[4] and hypervalent iodine-mediated[5] approaches have been reported. To the best of our knowledge, only a handful of direct *catalytic* asymmetric arene dearomatization protocols exist (all but one[6] being intramolecular), although the benefits are evident.[7] Herein we report an *inter*molecular dearomatization that incorporates a quaternary fluorine stereocenter into the product, which is desirable because of the current interest in the effect of fluorine incorporation into pharmaceuticals but has been restricted by the limited number of general approaches to the asymmetric construction of such stereocenters.[8]

We recently reported a *chiral anion phase-transfer catalysis* (PTC) strategy[9] enabling the development of highly enantioselective halocyclization of alkenes[9b,10] and fluorination of enamides.[11] This strategy hinges upon the ability of a chiral BINOL-derived phosphate to undergo anion exchange with poorly soluble cationic halogenating reagents such as Selectfluor® reagent, permitting solubility only upon association with the lipophilic chiral anion and thus eliminating significant racemic background reaction. Compared with conventional phosphoric acid (PA) catalysis, the electrophile in chiral anion PTC is associated with the catalyst via ion-pairing rather than H-bonding interactions (Figure 1a).[12] This distinction is crucial in

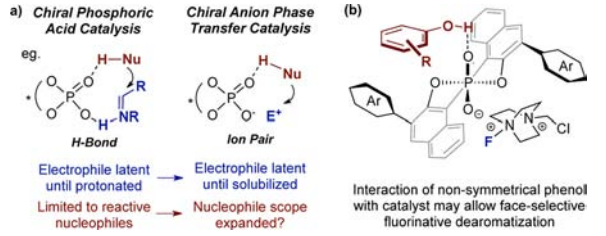

Figure 1. (a) Distinction of our approach from existing PA catalysis. (b) Initial hypothesis for fluorinative phenol dearomatization.

that the privileged BINOL-derived PA catalyst scaffold can potentially be combined with new classes of electrophiles for which ionic charge rather than Brønsted basicity is a prerequisite. Specifically, we anticipated that moving away from protonative activation to "phase-transfer" activation should enable the use of less reactive nucleophiles than are typically employed with chiral PA catalysts, since highly reactive cationic electrophilic reagents (such as Selectfluor) may be used without the excessive background reaction that may be anticipated in more conventional homogeneous variants. In particular, while there exist many reports on the use of more reactive heteroarene nucleophiles such as indoles, pyrroles, and furans in combination with chiral PA catalysts,[12b] there are few examples of the use of less activated, more ubiquitous arene nucleophiles such as phenols.[13] This limitation presumably arises due to insufficient reactivity of these aromatic nucleophiles with reagents that are activated by protonation alone.

We anticipated that our strategy might enable simple phenols to act as nucleophiles in an asymmetric dearomatizing fluorination process. On the basis of our previous observations in enamide fluorination,[11a] we hypothesized that H-bonding of the chiral phosphate−Selectfluor ion pair with a phenol −OH group by means of the remaining phosphoryl oxygen might enable discrimination between the enantiotopic faces of the phenol (Figure 1b). In our previous chiral anion-catalyzed fluorinations,[9b,10,11] the presence of an *N*-benzoyl group in the substrate, presumably acting as a H-bond donor, was crucial for

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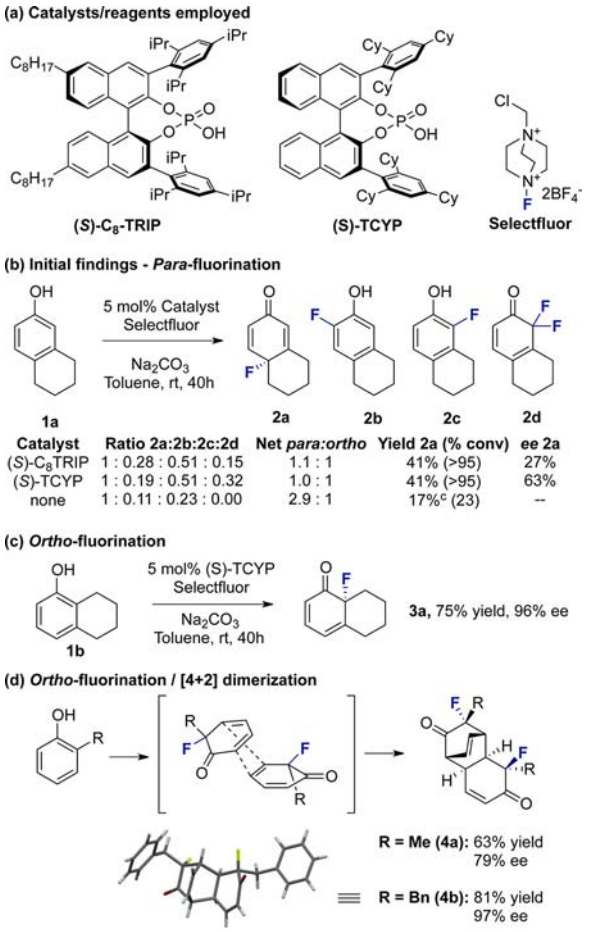
obtaining the highest levels of enantioselectivity. Thus, we were aware that progressing to a simple phenol could present a significant challenge, especially in light of the dearth of examples in which phenols have successfully been employed with PA catalysts. Furthermore, the reaction of Selectfluor with phenols under homogeneous conditions was previously shown to give multiple products, including those of dearomatizing addition, electrophilic aromatic substitution, ipso substitution, and oxidation, depending on substrate and conditions.[14]

We began by using 5,6,7,8-tetrahydro-2-naphthol (**1a**), as this had previously been shown to selectively deliver **2a** under racemic conditions (Scheme 1b).[14a] Using **C_8-TRIP** (Scheme 1a) as the catalyst and toluene as the solvent gave **2a** in low yield but with an encouraging 27% ee. The balance of the material consisted of a regioisomeric mixture of ortho-fluorinated phenols **2b** and **2c** and geminally difluorinated **2d**. A solvent screen revealed that toluene gave an optimal balance of yield and enantioselectivity and a survey of catalysts showed that among a range of chiral PAs, our previously reported catalyst **TCYP**[15] gave the highest enantioselectivity [63% ee; see the Supporting Information for details]. Under our PTC conditions, the evident inclination of **1a** toward ortho fluorination, while frustrating our efforts to achieve high yields of dearomatized product, nevertheless suggested that the intended catalyst-directed fluorination (via binding to the phenol oxygen; Figure 1b) likely occurred. Indeed, with **TCYP** (produced from the parent PA in situ using Na_2CO_3) as the catalyst, we observed para and ortho fluorination in a net ratio of ~1:1. In contrast, in the absence of catalyst, para fluorination was favored by a factor of 3, albeit with low conversion (Scheme 1b). Hence, we next examined isomeric 5,6,7,8-tetrahydro-1-naphthol (**1b**) with the intent not only that ortho-selective fluorinative dearomatization would constitute the major product but also that the greater steric differentiation between the two sides of the substrate close to the putative point of binding to the catalyst would increase the enantioselectivity (Figure 1b). Gratifyingly, under our thus-far optimal conditions, **1b** exclusively formed ortho-fluorinated product **3a** in 75% yield with 96% ee (Scheme 1c). When a more elementary substrate, *o*-cresol, was tested, the isolated product was found to be dimer **4a** resulting from [4 + 2] cycloaddition of the chiral 2,4-cyclohexadienone intermediate (Scheme 1d). While the enantioselectivity was still short of excellent (79% ee), we regard this as remarkable given the simplicity of the substrate. In accordance with our earlier hypothesis, increasing the steric demand of the ortho substituent by using *o*-benzylphenol gave **4b** with excellent enantioselectivity (97% ee), and the relative and absolute stereochemistries were confirmed by X-ray crystallography. The observed product dimerization in the absence of substitution at the 3-position is in agreement with precedent from studies on *o*-quinols and is completely regio- and diastereoselective.[2]

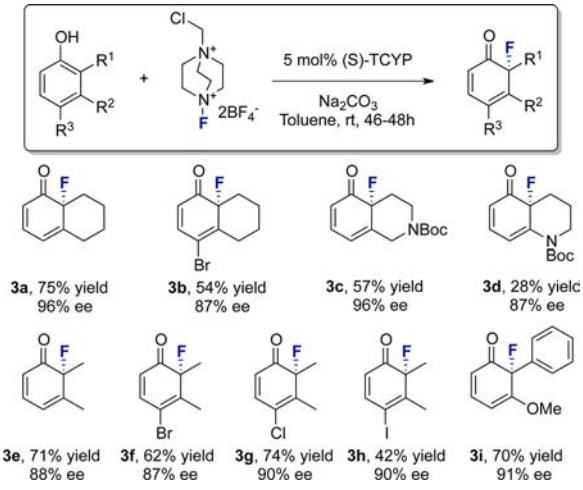
We first focused on 2,3-di- and 2,3,4-trisubstituted phenols (Table 1). A 4-bromo analogue of our initial substrate delivered a versatile vinyl bromide-containing product (**3b**). Two isomeric N-heterocyclic versions of this scaffold having potential utility in medicinal chemistry also gave high selectivity (**3c** and **3d**); however, in the case where the N was directly substituted on the phenol ring, the yield of the doubly vinylogous amide product **3d** was reduced due to formation of ring fluorination byproducts. Simple 2,3-dimethylphenol was an effective substrate (**3e**), as were its 4-bromo (**3f**), 4-chloro (**3g**), and even 4-iodo (**3h**) analogues.[16] Despite the reduced yield, the last case highlights the relatively benign and functional-group-tolerant nature of our solid–liquid PTC conditions. Specifically, aryl iodides are readily oxidized to I(III) by Selectfluor; attempts at homogeneous

Scheme 1. Preliminary Investigation and Selected Optimization of the Effect of Phenol Substitution[a,b]



[a]Isolated yields after chromatography on silica gel are shown. [b]The ee values were determined by HPLC. [c]Yield determined by ^{1}H NMR analysis using an internal standard.

Table 1. Scope of Fluorinative Phenol Dearomatization[a]



[a]Absolute stereochemistries were assigned by analogy with **4b**.

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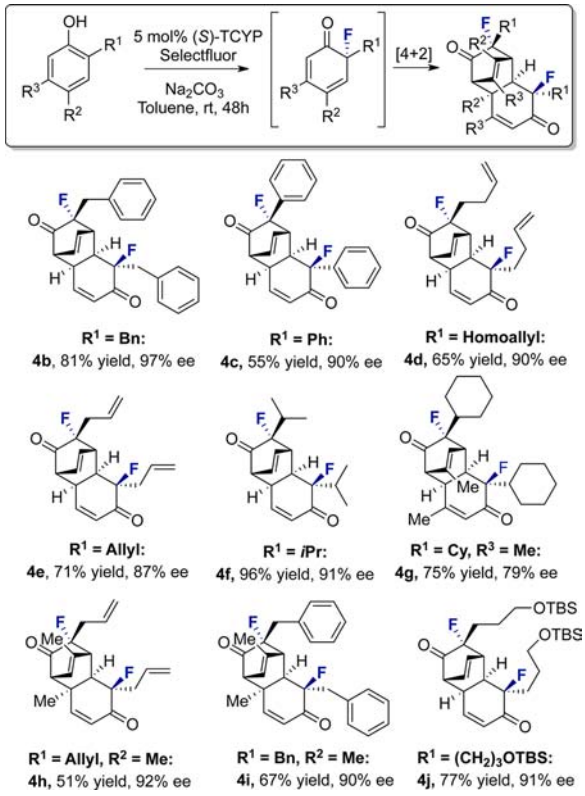
fluorination of this substrate in MeCN led to an intractable mixture.[17] Other moderate yields were largely due to incomplete conversion rather than byproduct formation. Finally, a methoxy-substituted phenol delivered doubly vinylogous ester **3i**.

Substrates with various substituents at the 2-, 2,4-, and 2,5-positions (Table 2), including benzyl (**4b**), phenyl (**4c**),

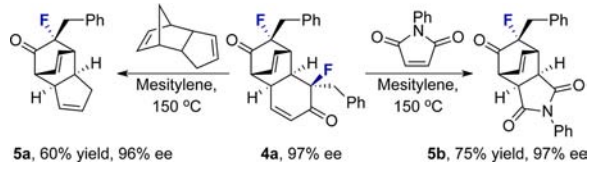
Table 2. Fluorination/[4 + 2] Dimerization of Phenols Lacking 3-Substitution



isopropyl (**4f**), and cyclohexyl (**4g**), delivered the [4 + 2] dimer products with high enantioselectivities. The participation of phenols bearing allyl (**4e**, **4h**) and homoallyl (**4d**) groups shows the highly chemoselective nature of our transformation. Under these mild conditions, the alkene functionality remained untouched by Selectfluor, as did a silyl-protected primary alcohol (**4j**). Furthermore, substitution at the phenol 4-position (**4h**, **4i**) was well-tolerated without affecting the selectivity. Interestingly 5-substitution (**4g**) decreased the enantioselectivity somewhat, suggesting that steric differentiation of the two sides of the phenol is important. Elegant prior work has shown that closely related *o*-quinol dimers are effectively masked dienes and can be readily made to undergo retro-[4 + 2] reactions in the presence of a broad range of dienophiles.[2,18] We demonstrated the compatibility of our fluorinated products in the form of retro-[4 + 2]/[4 + 2] reactions with *N*-phenylmaleimide and cyclopentadiene dimer (Scheme 2).[18c] These reactions gave single diastereoeomers with no loss of enantioenrichment, and the similar sequences could potentially provide rapid access to a diverse range of complex fluorinated scaffolds.[19]

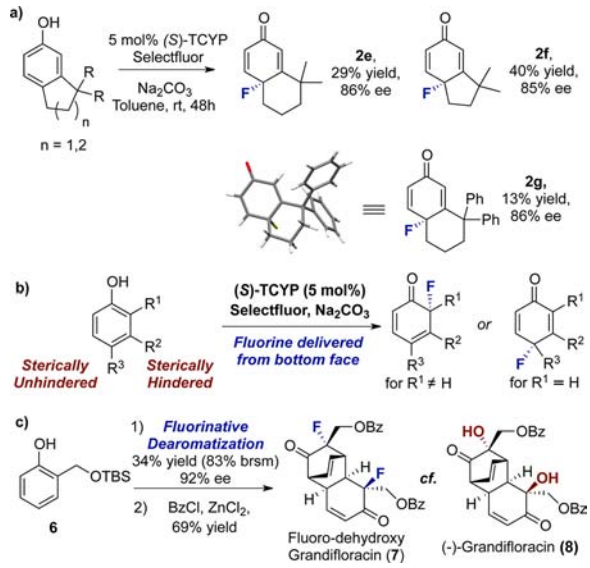
Having shown that our catalytic system delivers fluorine to the ortho position of a range of substituted phenols with high enantioselectivity, we returned to our initial challenge of dearomatizing para fluorination to test whether the fluorine may still be delivered with high selectively to a position a further

Scheme 2. Retro-[4 + 2]/[4 + 2] Derivatization of Products



two carbons away. Our earlier observation that a clear steric distinction between the two sides of the phenol was required to achieve the highest enantioselectivities for ortho fluorination (e.g., Scheme 1d, **4a** vs **4b**; Table 2, **4f** vs **4g**) led us to hypothesize that our original peak selectivity of 63% ee for para fluorination of **1a** (Scheme 1b) might be improved by incorporating geminal 8,8′ disubstitution to better sterically distinguish the enantiotopic faces of the phenol without the possibility of ortho dearomatization. As previously, competitive S_EAr arene fluorination at the ortho position led to impaired yields, but the para-fluorinated products **2e** and **2g** were formed with much-improved 86% ee and indanol-derived **2f** with 85% ee (Scheme 3a). Although its practicality is at present limited by the

Scheme 3. (a) Para-Selective Fluorinative Dearomatization; (b) Predictable Selectivity Based on Phenol Sterics; (c) Asymmetric Synthesis of Grandifloracin Analogue 7



low yields, we believe that this method for rapid access to enantioenriched, fluorinated 2,5-cyclohexadienones, in addition to the 2,4-cyclohexadienones above, represents a powerful new strategy for the synthesis of versatile small molecules of potential pharmaceutical relevance. The absolute stereochemistry of **2g** was determined by X-ray crystallography, which suggested that for both ortho and para fluorination, the facial selectivity of fluorination may be reliably predicted by a mnemonic that takes into account both the phenol structure and the catalyst enantiomer employed (Scheme 3b). This outcome is also consistent with the tentative stereochemical model depicted in Figure 1b, in which the substrate is bound with the aromatic ring of the phenol residing in an "open" quadrant of the catalyst and the sterically demanding substituents being projected away from the catalyst.

To underline the general utility and expediency of our approach, we demonstrate the asymmetric synthesis of **7**, a fluoro

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analogue of the natural product (−)-grandifloracin (**8**)[20] in which the −OH groups of the natural product are substituted with −F, an established bioisostere for −OH (Scheme 3c).[8a,21] Fluorination of readily prepared silyloxymethylphenol **6** proceeded with moderate conversion (the corresponding benzoyloxymethylphenol gave only trace conversion) but excellent enantioselectivity to give a dimer in which the TBS groups could be readily exchanged to benzoyl, delivering **7** in three steps. In contrast, while racemic **8** has been accessed in two steps,[22a] the only asymmetric synthesis of **8** to date employs seven steps to access the unnatural isomer using enzymatic methods.[22b]

In summary, we have demonstrated the broad generality of our *chiral anion phase-transfer catalysis* strategy by applying it to the asymmetric fluorinative dearomatization of phenols. Notably, it represents a rare application of chiral phosphoric acid catalysts to simple phenol nucleophiles by virtue of our chiral-anion PTC approach to activation of Selectfluor. The small but densely functionalized products incorporating an enantioenriched quaternary F-containing stereocenter represent valuable building blocks of potential interest in synthetic and medicinal chemistry. Their close relationship to well-studied *o*-quinols provides numerous avenues for elaboration as well as exciting opportunities for bioisosteric replacement of −OH with −F in the numerous natural products thought to be derived from *o*-quinols.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. 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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