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Enantioselective Ring Opening of Epoxides by Fluoride Anion Promoted by a Cooperative Dual-Catalyst System

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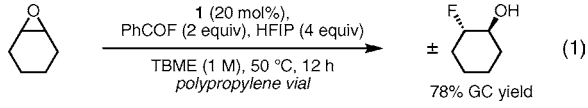
Methods for the catalytic incorporation of fluorine into organic molecules are sought because of the unique properties of organofluorine derivatives as pharmaceuticals, agrochemicals, and materials.[1] Previous reports have described asymmetric methods for catalytic C−F bond formation with electrophilic "F^+" equivalents to access highly enantioenriched α-fluorocarbonyl compounds and allylic fluorides.[2] The development of complementary methods for nucleophilic fluorination would be of significant value, providing access to distinct chiral building blocks using relatively abundant and inexpensive fluoride sources. Progress toward this goal has been made using stoichiometric chiral reagents,[3] but successful catalytic asymmetric variants are not known. We describe herein a dual-catalyst system that promotes the highly enantioselective fluoride ring opening of meso and terminal epoxides. These reactions proceed efficiently at room temperature using commercial benzoyl fluoride as a latent source of fluoride.

Methods for C−F bond formation using readily available fluoride sources typically require forcing reaction conditions.[4] In protic media, fluoride is rendered unreactive by solvation, while the "naked" anion usually reacts as a Brønsted base. Thus, the chief obstacle to the development of asymmetric methods is the identification of a fluoride source that permits mild conditions and efficient catalysis. HF-containing reagents such as Olah's reagent (pyridine·9HF) are known to exhibit unsurpassed reactivity in racemic epoxide ring-opening reactions.[5] These reactions conducted in combination with a chiral Lewis acid, however, suffer from competitive background pathways and catalyst inhibition.[3c] To overcome these problems, we pursued a strategy for the amine-catalyzed generation of HF from benzoyl fluoride and an alcohol. We anticipated that this protocol would not only provide a convenient fluoride source for catalytic C−F bond-forming reactions[6] but also yield an enantioselective process through the intermediacy of a chiral amine−HF salt or by chiral Lewis acid/amine cocatalysis.

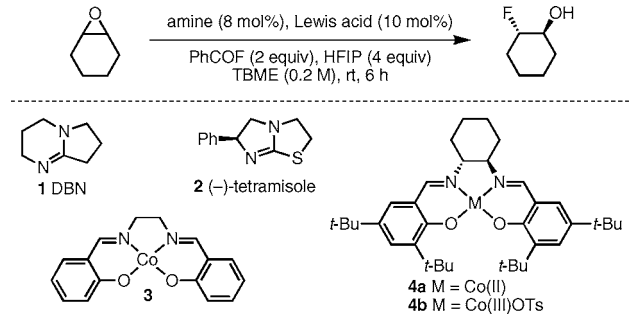


(1)

Initial experiments established the feasibility of a catalytic approach: cyclohexene oxide was found to undergo efficient hydrofluorination at 50 °C in the presence of benzoyl fluoride, 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP), and catalytic 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **1**) (eq 1). Spectroscopic and kinetic studies revealed that a **1**·$(HF)_4$ adduct likely mediates hydrofluorination under these conditions.[7] Accordingly, the reactions were less efficient when conducted in glass vessels.

Neither **1** nor chiral analogues [e.g., commercial (−)-tetramisole (**2**)[8]] induced measurable reactivity or enantioselectivity in reactions carried out at room temperature (Table 1, entries 1 and 2). However, when **2** and achiral Lewis acid **3** were used as cocatalysts,

Table 1. Enantioselective Fluorohydrin Synthesis: Catalyst Optimization



entry	amine	Lewis acid	conv. (%)[a]	yield (%)[a]	ee (%)[b]
1	**1**	none	39	2	NA
2	**2**	none	31	2	<5
3	**2**	**3**	41	10	54
4	**2**	(*R*,*R*)-**4a**	95	64	77
5	**2**	(*S*,*S*)-**4a**	42	7	−23
6	**1**	(*R*,*R*)-**4a**	80	50	62
7	none	(*R*,*R*)-**4a**	46	16	52
8[c]	**2**	(*R*,*R*)-**4b**	83	68	92

[a] Determined by GC using 1-decene as an internal quantitative standard. [b] Determined by chiral GC analysis using commercial chiral columns. [c] Reaction conducted in *t*-AmOH for 12 h.

fluorination proceeded in 54% ee (entry 3). Notably, the combination of **2** and chiral (salen)Co complex **4a** led to a pronounced matched/mismatched effect; in the matched case, product was obtained in 64% yield and 77% ee, while the use of *ent*-**4a** provided fluorohydrin in 7% yield and −23% ee (entries 4 and 5). Although chiral Lewis acid/amine cocatalysis has been described in the literature,[9] a cooperative effect *on enantioselectivity* has minimal precedent.[10] As a further demonstration of the relative role of the two chiral catalyst environments, replacing **2** with **1** resulted in depressed yield and ee values (entry 6). Whereas **4a** is a highly effective catalyst for enantioselective epoxide ring-opening reactions with a variety of nucleophiles, control experiments revealed that it alone is only marginally effective for fluoride addition (entry 7).[11] Additional studies indicated that improved enantiocontrol (92% ee) could be achieved using (salen)Co(III)OTs (**4b**) and **2** in *tert*-amyl alcohol (*t*-AmOH) (entry 8);[12] however, **4a** proved optimal for all other substrates examined.

Application of this cocatalytic method to the ring opening of various meso epoxides illustrates its synthetic scope (Table 2). Five-, six-, seven-, and eight-membered cyclic epoxides afford fluorohydrins in 85−95% ee. Alkene, ester, and protected amine functionalities are all well-tolerated. However, acyclic substrates and those containing more Lewis basic groups undergo reaction with lower selectivity (e.g., entry 8).[7] Conveniently, the nucleophilic fluorinations do not require exclusion of oxygen or moisture.[13] Moreover, fluorinations with the two-catalyst system can be conducted in

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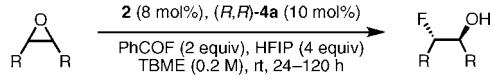
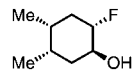
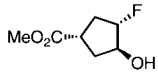
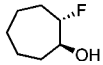
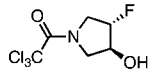
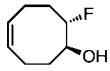
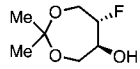
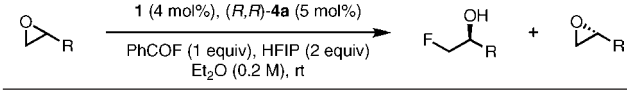
Table 2. Enantioselective Fluoride Ring Opening of Meso Epoxides



entry	product	yield[a], ee[b]	entry	product	yield[a], ee[b]
1[c]		77% yield (93) **85% ee**	5[e,f]		75% yield **90% ee**
2[d,e]		65% yield (87) **93% ee**	6		88% yield **86% ee**
3		82% yield **90% ee**	7[e]		84% yield **80% ee**
4		87% yield **95% ee**	8		55% yield **58% ee**

[a] Isolated yield for reactions carried out on a 1 mmol scale for 24 h (entry 2), 72 h (entries 1, 3, and 4), or 120 h (entries 5−8). Yields in parentheses are GC yields. [b] Determined using chiral GC or HPLC analysis on commercial columns. [c] Reaction conducted in Et_2O on a 2 mmol scale. [d] Reaction conducted with (*R*,*R*)-**4b** on a 5 mmol scale. [e] Reaction conducted in *t*-AmOH. [f] Epoxide is a 10:1 mixture of diastereomers.

Table 3. Enantioselective Fluoride Ring Opening of Terminal Epoxides



entry	R	time (h)	yield (%)[a]	ee (%)[b]	k_{rel}
1[c]	*n*-Bu	30	36 (47)	99	>300
2	Ph	10	44	99	>300
3	$TBSOCH_2$	24	44	88	32

[a] Isolated yield of fluorohydrin for reactions carried out on a 5 mmol scale. The yield in parentheses is a GC yield. [b] Determined using chiral GC analysis on commercial columns. [c] Reaction conducted with 1.6 mol % **1** and 2 mol % **4a**, with the product isolated as the TBDPS ether.

standard glassware. While further effort is necessary to improve the rate of these reactions, complementary access to this class of products by electrophilic fluorination of cycloalkanones generally suffers from low enantioselectivity during C−F bond formation and low diastereoselectivity during ketone reduction.[14]

On the basis of the ability of **4a** to catalyze highly selective hydrolytic kinetic resolutions of terminal epoxides,[13] we also investigated this substrate class for fluoride ring opening (Table 3). Treatment of hexene oxide with 1.6 mol % **1** and 2 mol % **4a** provided enantioenriched fluorohydrin in 36% yield with a selectivity factor of >300.[15] Regioselective opening at the terminal position was observed for all epoxides examined, including traditionally challenging substrates such as styrene oxide (entry 2).[16] In comparison with existing methods for fluoride ring opening of enantioenriched terminal epoxides, this cocatalytic reaction offers a remarkably mild and operationally simple approach to nucleophilic fluorination.[17] Although silyl protecting groups are generally incompatible with fluoride reagents, including **1**·$(HF)_4$, we found that a glycidyl epoxide containing a silyl ether was tolerated, demonstrating the unique reactivity of the fluoride species generated under the cocatalytic conditions (entry 3).

Reactions with the dual-catalyst system display marked differences in chemo- and regioselectivity relative to the racemic reaction catalyzed by **1**. These differences are best explained by the generation of a (salen)Co(III) fluoride under the cocatalytic conditions. However, the origin of a cooperative effect with the amine remains unclear. Possibilities include its serving as an axial ligand for cobalt, participating in either epoxide activation or fluoride delivery, or partitioning (salen)Co species toward a selective bimetallic process.[18] The scope and mechanism of this dual-catalyst system will be the subject of future investigations.

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Supporting Information Available: Experimental procedures, optimization studies, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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