Asymmetric Synthesis

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Rhodium-Catalyzed Enantioselective Nucleophilic Fluorination: Ring Opening of Oxabicyclic Alkenes**

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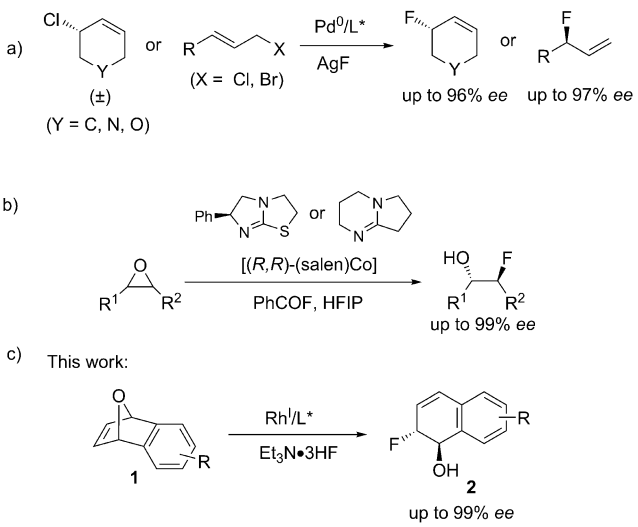
The application of organofluorine compounds in pharmaceuticals, agrochemicals, high performance materials, and medical imaging [e.g., positron emission tomography (PET)] agents has seen an explosive increase in the past decade.[1] Great strides have been made for developing new methods to introduce fluorine into organic molecules, particularly in the emerging area of transition-metal-catalyzed C–F bond formation.[2] While aryl fluoride bond formation has been extensively studied,[3] asymmetric aliphatic C–F bond formation remains challenging and less developed.[4] In this regard, the majority of the reported methods relied on using electrophilic "F^+" equivalents to achieve highly enantioselective α fluorination of carbonyl-containing compounds by employing elegantly designed chiral metal complexes, Lewis acids, and organocatalysts.[5] However, the disadvantages of using electrophilic fluorine sources are their high costs, limited reactivity choices, and lower specific activity in PET applications. In contrast, the use of more abundant and inexpensive nucleophilic "F^-" equivalents such as metal fluorides or HF-containing reagents becomes highly desirable and provides complementary reactivity which can lead to useful fluorinated scaffolds which are more amenable to ^{18}F radiolabeling.[2a] While racemic palladium- and iridium-catalyzed nucleophilic allylic fluorinations have been successfully developed,[6] to the best of our knowledge, only a few examples of transition-metal-catalyzed enantioselective nucleophilic fluorination methods exist. Doyle and co-workers have recently developed powerful protocols of this type of fluorination.[7] For example, asymmetric palladium-catalyzed fluorination of cyclic and acyclic allylic halides using AgF gave chiral allylic fluorides (Scheme 1a). A salen/cobalt catalyst with an amine cocatalyst led to enantioselective ring opening of epoxides using benzoyl fluoride as a latent source of fluoride and provided chiral fluorohydrins (Scheme 1b).[8] We herein report the first rhodium-catalyzed asymmetric ring opening (ARO) of oxabicyclic alkenes (**1**) using triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) as the source of nucleophilic fluorine (Scheme 1c). The chiral ring-opened products **2** contain both allylic fluoride and fluorohydrin moieties.[9,4d]



Scheme 1. Transition-metal-catalyzed enantioselective nucleophilic fluorinations. HFIP = 1,1,1,3,3,3-hexafluoroisopropyl alcohol.

Our group has demonstrated that rhodium-catalyzed ARO of strained bicyclic alkenes is a highly efficient and enantioselective process for generating a functionalized dihydronaphthalene core.[10] Chiral rhodium(I) complexes catalyze the ring-opening reaction of oxa- and azabicyclic alkenes with a variety of nucleophiles such as amines and alcohols in high yield and enantioselectivity.[11] The products are generated by an S_N2' nucleophilic displacement of the bridgehead leaving group with inversion to give the 1,2-*trans* product as a single regio- and diastereomer.[10a]

The use of a halide as the nucleophile in ARO has not been demonstrated, and the stereochemical outcome (*trans*/*cis*) of the halogenated ring-opened product is unknown. We envisioned that by employing a suitable fluoride nucleophile and a chiral rhodium(I) catalyst, the ARO of **1** could lead to the direct construction of an aliphatic C–F bond for the rapid synthesis of the chiral fluorinated scaffolds **2**.

One major challenge lies in identifying the best fluoride source because of the dual reactivity profile of fluoride (nucleophile versus base). It is known that the nucleophilicity of fluoride is significantly reduced in its solvated form, whereas desolvated fluoride can act as a strong base which causes a competitive elimination pathway.[2a,9a] To this end, we began by reacting oxabenzonorbornadiene (**1a**) with a variety

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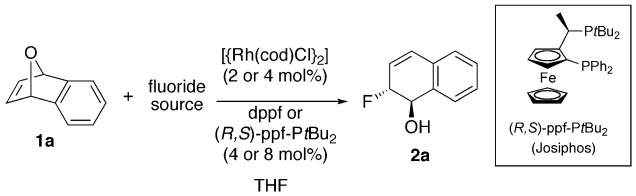
of fluoride sources under rhodium(I) catalysis conditions (Table 1). A large excess of KHF_2, HF-pyridine (Olah's reagent), KF, or TBAF showed no reactivity (entries 1–4). The conditions use by Kalow and Doyle failed to give any

Table 1: Optimization of rhodium(I)-catalyzed ARO of the oxabicyclic alkene **1a** with fluoride sources.

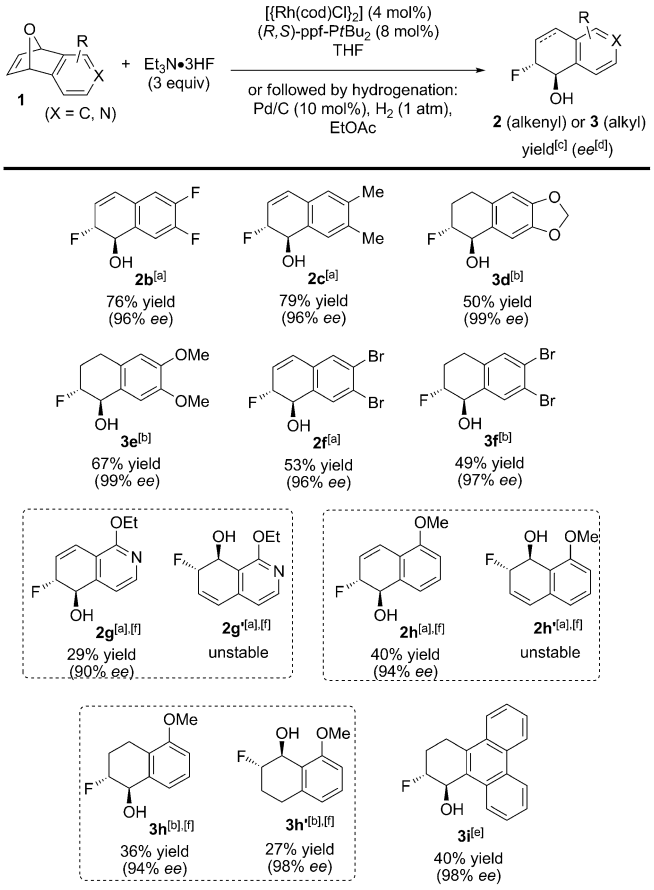


Entry	Fluoride source (equiv)	Ligand	T [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	KHF_2 (5.0)	dppf	80	17	< 5	–
2[c]	HF-pyridine (5.0)	dppf	80	17	< 5	–
3[c,e]	KF (5.0)	dppf	80	17	< 5	–
4[c,e]	TBAF[g] (5.0)	dppf	80	17	< 5	–
5[c]	benzoylfluoride/ HFIP/Et_3N (5.0)	dppf	80	17	< 5	–
6[c]	$Et_3N{\cdot}3HF$ (3.0)	dppf	80	17	48	–
7[d]	$Et_3N{\cdot}3HF$ (3.0)	(*R*,*S*)-ppf-P*t*Bu_2	50	0.5	88	98
8[d]	$Et_3N{\cdot}3HF$ (2.0)	(*R*,*S*)-ppf-P*t*Bu_2	50	0.5	79	98
9[d]	$Et_3N{\cdot}3HF$ (1.0)	(*R*,*S*)-ppf-P*t*Bu_2	50	17	57	98
10[c]	$Et_3N{\cdot}3HF$ (3.0)	(*R*,*S*)-ppf-P*t*Bu_2	RT	17	61	98
11	$Et_3N{\cdot}3HF$ (3.0)	none[f]	80	17	< 5	–

[a] Yield of isolated product. [b] Enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral stationary phase. [c] 4 mol% [{Rh(cod)Cl}$_2$]/8 mol% ligand. [d] 2 mol% [{Rh(cod)Cl}$_2$]/4 mol% ligand. [e] Reaction was run in THF/H_2O (20:1 v/v) to increase solubility. [f] Reaction was run without rhodium catalyst and ligand. [g] Tetra-*n*-butylammonium fluoride (TBAF) hydrate was used. dppf = 1,1′-bis(diphenylphosphino)ferrocene, THF = tetrahydrofuran.

product (entry 5).[8a] Commercially available $Et_3N{\cdot}3HF$ proved to be an effective fluorinating reagent and afforded **2a** in 48% yield (entry 6).[12] With the use of the chiral Josiphos ligand (*R*,*S*)-ppf-P*t*Bu_2 at a lower catalyst loading, we were able to isolate **2a** in good yield (88%) and excellent enantioselectivity (98% *ee*; entry 7). The reaction was complete at 50°C after only 30 minutes. Lower conversions were observed when the number of equivalents of $Et_3N{\cdot}3HF$ was decreased even after a prolonged reaction time (entries 8 and 9), but the *ee* values remained high. The reaction was more sluggish at room temperature and the enantioselectivity remained the same (entry 10), and a control experiment showed no background ring-opening reaction in the absence of the catalyst and ligand (entry 11). We also screened other solvents, ligands, and catalysts. Cationic [Rh(cod)$_2$OTf] (cod = cycloocta-1,5-diene, Tf = trifluoromethanesulfonyl) was shown to be equally effective (76% yield, 98% *ee*).[13] All reactions were run in standard glass vessels because of the unique properties of $Et_3N{\cdot}3HF$ compared to other harsh fluorinating reagents.[12a]

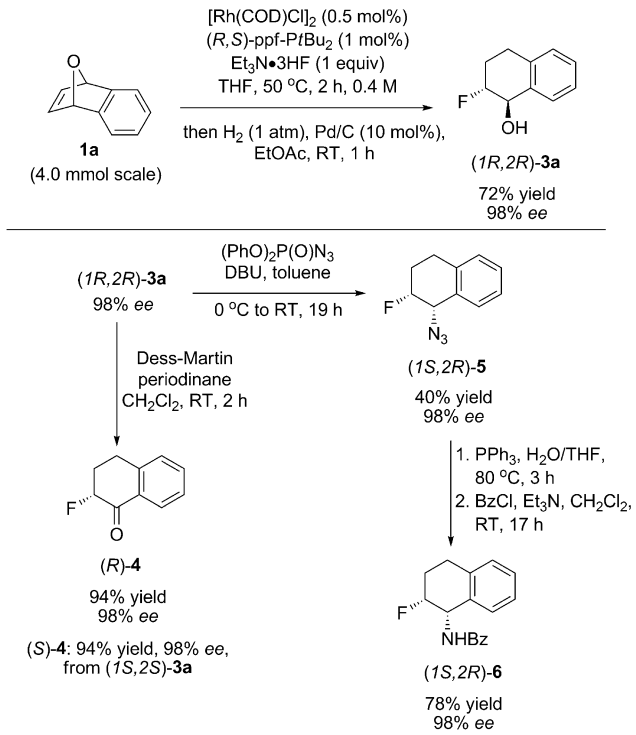
We next examined a range of oxabicyclic alkenes (**1**) under the optimized reaction conditions (Scheme 2). Reactions of difluoro-, dimethyl-, and dibromo-substituted oxabicyclic alkenes afforded the corresponding alkenyl fluorohydrin products **2b**, **2c**, and **2f** in good yields and excellent enantioselectivities at 50°C within 1 hour. The oxabicyclic alkenes bearing electron-donating groups such as methylenedioxy and dimethoxy groups were much more reactive and the conversion was complete at room temperature after only 15 minutes.[14] However, the ring-opened products decomposed to 1-naphthol by elimination on silica gel during column chromatography or after prolonged reaction time. To circumvent this problem, we opted to reduce the double bond produced after ring opening by using mild hydrogenation conditions (10 mol% Pd/C, 1 atm H_2, RT, 1 h) after a rapid aqueous work-up, thus affording the stable alkyl fluorohydrin products **3d** and **3e**, which were isolable by column chromatography and had excellent enantioselectivities. A similar protocol was also applied to obtain the dibromo-substituted **3f**. By using our previously reported regiodivergent resolution of unsymmetrical oxabicyclic alkenes,[15] the pyridine-



Scheme 2. Scope of oxabicyclic alkenes **1** in rhodium(I)-catalyzed ARO with $Et_3N{\cdot}3HF$. [a] Rhodium-catalyzed ARO reaction conditions: substrate **1** (0.2 mmol), $Et_3N{\cdot}3HF$ (3.0 equiv), [{Rh(cod)Cl}$_2$] (4 mol%), (*R*,*S*)-ppf-P*t*Bu_2 (8 mol%), THF (0.1 M), RT or 50°C, 15 min to 2 h. [b] Two-step sequence: ARO and subsequent hydrogenation: Pd/C (10 mol%), H_2 (1 atm), EtOAc (0.1 M), RT, 1 h. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Two-step sequence: ARO and subsequent hydrogenation: tosylhydrazine (5.0 equiv), sodium acetate (10.0 equiv), THF/H_2O (1:1), reflux, 17 h. [f] The maximum yield of this product from the ARO reaction was 50%.

containing fluorohydrin product **2g** was obtained in 90% *ee* as one of the two possible regioisomers from a racemic unsymmetrical substrate.[16] In contrast, both regioisomers **3h** and **3h′** can be obtained in good enantioselectivities from the racemic unsymmetrical oxabicyclic alkene.[17] The structurally interesting triaryl fluorohydrin product **3i** was isolated with an excellent *ee* value after diimide reduction. The absolute configuration of the ring-opened product and relative *trans* stereochemistry of the F and OH groups was unambiguously established by single-crystal X-ray analysis of compound **3d** (see the Supporting Information).[18]

To demonstrate the utility of the ring-opened product, the saturated fluorohydrin (1*R*,2*R*)-**3a** was prepared in an ARO/hydrogenation sequence and subjected to further transformations (Scheme 3). The ARO reaction of **1a** was run on a larger scale (4.0 mmol) at a higher concentration (0.4 M), the catalyst loading was decreased to 0.5 mol%, and only 1.0 equivalent



Scheme 3. Scale-up synthesis and elaboration of the fluorohydrin (1*R*,2*R*)-**3a**.

of $Et_3N{\cdot}3HF$ was used. The product (1*R*,2*R*)-**3a** was obtained cleanly in 72% yield and 98% *ee* after two steps. Oxidation using the Dess–Martin reagent afforded the α-fluorotetralone product (*R*)-**4** smoothly in high yield without erosion of the *ee* value. The enantiomer (*S*)-**4** can be obtained in equally high enantioselectivity by using (1*S*,2*S*)-**3a**. Most strategies for preparing α fluorotetralones involve the use of enolate and enamine chemistry, but few have achieved high enantioselectivities.[19] Our method offered an alternative approach to access these useful enantioenriched compounds. By employing modified Mitsunobu conditions using diphenyl phosphoryl azide,[20] the enantioenriched β-fluoroazide (1*S*,2*R*)-**5** was synthesized with complete inversion of stereochemistry at the benzylic position. Subsequent reduction (Staüdinger reaction) and protection yielded chiral *cis*-β-fluorobenzamide (1*S*,2*R*)-**6**, which complements the literature report on *trans*-β-fluorobenzamide.[21]

In conclusion, we have successfully developed a rhodium(I)-catalyzed enantioselective nucleophilic fluorination protocol by utilizing the asymmetric ring-opening (ARO) reaction of oxabicyclic alkenes with triethylamine trihydrofluoride as the nucleophile. The method is mild, safe, efficient, and highly enantioselective. Current limitations lie in the substrate scope as nonbenzofused substrates, bridgehead-substituted substrates, and azabicyclic alkenes were unreactive under the reaction conditions. Certain substrates gave reduced yields because of competitive elimination which led to 1-naphthol formation. The exact nature of the fluoride species in the reaction mechanism is still unclear and the formation of *trans* products was not intuitive. Both *cis*- and *trans*-ring-opened products are known and harder nucleophiles usually lead to *cis* products (fluorides are classically considered as hard nucleophiles).[22] However, the observation of *trans* stereochemistry of the ring-opened products suggested that the reaction followed a similar pathway to that of soft nucleophiles (S_N2' nucleophilic displacement)[10a] and ruled out the likelihood of fluorometallation as a mechanistic pathway.

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