# Enantioselective Nucleophile-Catalyzed Synthesis of Tertiary Alkyl Fluorides via the α-Fluorination of Ketenes: Synthetic and Mechanistic Studies

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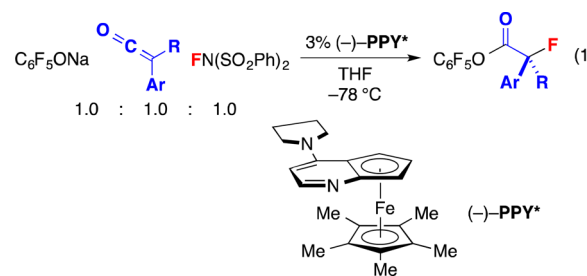[†]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

 Supporting Information

**ABSTRACT:** The catalytic asymmetric synthesis of alkyl fluorides, particularly α-fluorocarbonyl compounds, has been the focus of substantial effort in recent years. While significant progress has been described in the formation of enantioenriched secondary alkyl fluorides, advances in the generation of tertiary alkyl fluorides have been more limited. Here, we describe a method for the catalytic asymmetric coupling of aryl alkyl ketenes with commercially available N-fluorodibenzenesulfonimide (NFSI) and $C_6F_5ONa$ to furnish tertiary α-fluoroesters. Mechanistic studies are consistent with the hypothesis that the addition of an external nucleophile ($C_6F_5ONa$) is critical for turnover, releasing the catalyst (**PPY***) from an N-acylated intermediate. The available data can be explained by a reaction pathway wherein the enantioselectivity is determined in the turnover-limiting transfer of fluorine from NFSI to a chiral enolate derived from the addition of **PPY*** to the ketene. The structure and the reactivity of the product of this proposed elementary step, an α-fluoro-N-acylpyridinium salt, have been examined.

attempted to extend this halogenation strategy to an analogous enantioselective fluorination of ketenes, building in part on the pioneering work of Lectka on the cinchona alkaloid/palladium/$LiClO_4$-catalyzed synthesis of secondary alkyl fluorides from acid chlorides and N-fluorodibenzenesulfonimide (NFSI; commercially available),[4] we obtained discouraging results (eq 2).
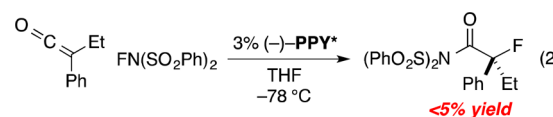


We postulated that our failure to achieve the desired catalytic asymmetric fluorination might be due to the stability of a potential N-acylpyridinium intermediate (e.g., **1**) toward $(SO_2Ph)_2N^-$. Consequently, we decided to determine if the
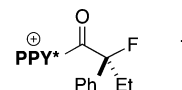


addition to the reaction mixture of a stoichiometric quantity of a more reactive nucleophile might be beneficial. We were, of course, cognizant of the possibility that the nucleophilic additive might react directly with the ketene to generate an achiral enolate and racemic product; fortunately, however, we were able to identify a nucleophile that allowed us to achieve our objective (Table 1).

Whereas the addition of MeOH or $PhNH_2$ did not result in a significant amount of the desired tertiary alkyl fluoride (Table 1, entries 1 and 2), the use of alkoxides led to a substantial quantity (entries 3–5). In the case of sodium *tert*-butoxide, the product

**B**ecause of properties such as the high electronegativity and the small size of fluorine, as well as the relative stability of the C–F bond, the incorporation of fluorine into organic molecules, including stereoselective processes, has become a widely used method in medicinal chemistry for altering the bioactivity of drug candidates.[1] The catalytic enantioselective α-fluorination of carbonyl compounds has been a subject of particular interest,[2] and an array of versatile methods have been described for the generation of such secondary alkyl fluorides.[3,4] In contrast, except in the case of doubly activated molecules,[2,5] there has been limited progress in the development of effective processes that furnish tertiary α-fluorocarbonyl compounds,[6−8] and we are not aware of any methods that directly afford esters,[9] with the exception of kinetic resolutions.[10] Here, we establish that a planar-chiral nucleophilic catalyst (**PPY***) can achieve the coupling of a ketene,[11] an electrophilic fluorine source,[12] and an alkoxide, thereby providing such tertiary alkyl fluorides with high enantioselectivity (eq 1). We also present mechanistic studies that help to illuminate the reaction pathway.

In an earlier study, we reported that **PPY*** can catalyze the asymmetric chlorination of ketenes by 2,2,6,6-tetrachlorocyclohexanone to produce tertiary α-chloroesters.[13] When we

**Table 1. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Effect of Added Nucleophile**[a]



| entry | Nu–M | yield (%)[b] | ee (%) |
|-------|------|--------------|--------|
| 1 | MeO–H | <5 | – |
| 2 | PhNH–H | <5 | – |
| 3 | t-BuO–Na | 54 | <2 |
| 4 | PhO–Na | 79 | 88 |
| 5 | C$_6$F$_5$O–Na | 98[c] | 99 |
| 6 | C$_6$F$_5$O–K | 98 | 99 |

[a]All data are the averages of two experiments. [b]Determined through GC analysis with the aid of an internal standard. [c]Yield of purified product.

was racemic (entry 3); on the other hand, sodium phenoxide furnished good enantioselectivity (entry 4), and a less nucleophilic phenoxide, sodium pentafluorophenoxide, provided excellent yield and ee (entry 5).[14]
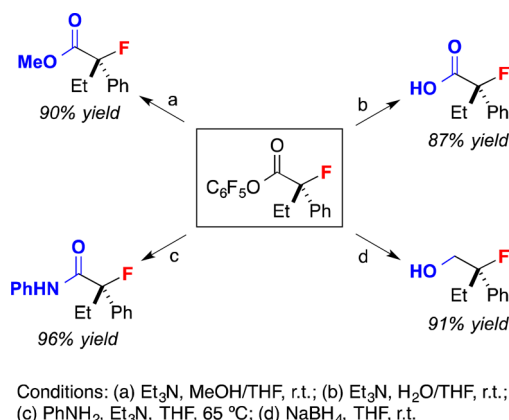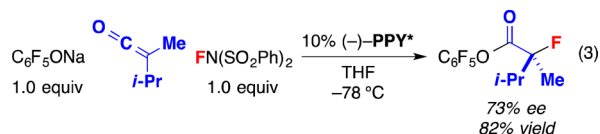
Our optimized method is effective for the catalytic enantioselective synthesis of tertiary $\alpha$-fluoroesters from an array of aryl alkyl ketenes (Table 2).[15] The alkyl group of the ketene can vary in size from Me to cyclopentyl (entries 1−5; lower ee is observed with larger alkyl groups), and the aromatic substituent can be electron-poor, electron-rich, para-substituted, or meta-substituted (entries 6−9), as well as naphthyl or heteroaryl (entries 10 and 11). On a gram scale, the fluorination illustrated in entry 2 of Table 2 proceeded in 99% ee and 90% yield.

**Table 2. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides**[a]

| entry | Ar | R | ee (%) | yield (%)[b] |
|-------|----|----|--------|--------------|
| 1 | Ph | Et | 99 | 98 |
| 2 | Ph | Me | 98 | 92 |
| 3 | Ph | i-Bu | 95 | 95 |
| 4 | Ph | Bn | 78 | 96 |
| 5[c] | Ph | cyclopentyl | 80 | 84 |
| 6 | 4-ClC$_6$H$_4$ | Et | 97 | 86 |
| 7 | 4-MeC$_6$H$_4$ | Et | 97 | 92 |
| 8 | 4-(OMe)C$_6$H$_4$ | Et | 97 | 91 |
| 9 | 3-MeC$_6$H$_4$ | Et | 97 | 97 |
| 10 | 2-naphthyl | Et | 94 | 89 |
| 11 | 3-thiophenyl | i-Bu | 98 | 94 |

[a]For the reaction conditions, see eq 1. All data are the averages of two experiments. [b]Yield of purified product (contains ≤5% of the non-fluorinated ester). [c]Catalyst loading: 10%.

Although our other chiral 4-(dimethylamino)pyridine (DMAP)-catalyzed reactions of ketenes have generally not been effective for dialkyl ketenes,[16] in the case of this asymmetric fluorination process, we have observed a promising level of enantioselectivity (eq 3).





Conditions: (a) Et$_3$N, MeOH/THF, r.t.; (b) Et$_3$N, H$_2$O/THF, r.t.; (c) PhNH$_2$, Et$_3$N, THF, 65 °C; (d) NaBH$_4$, THF, r.t.

**Figure 1.** Transformations of an enantioenriched tertiary $\alpha$-fluoroester.
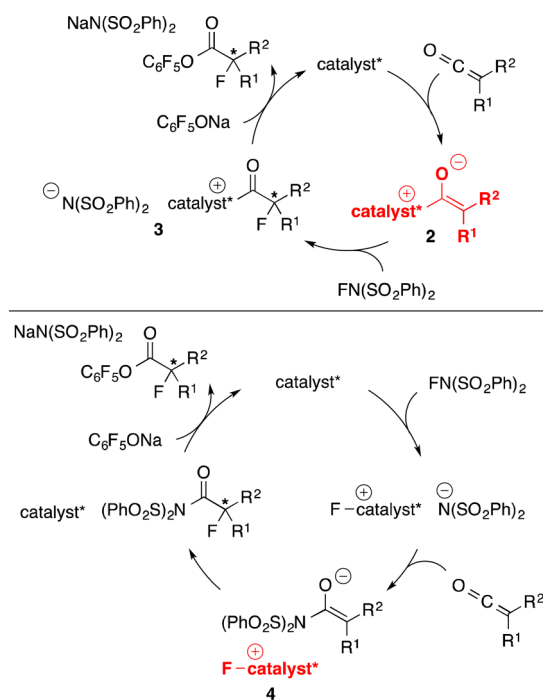


**Figure 2.** An outline of two of the possible mechanisms for the **PPY\***-catalyzed enantioselective $\alpha$-fluorination of ketenes: a "chiral enolate" pathway (top) and a "chiral fluorinating agent" pathway (bottom).

The enantioenriched $\alpha$-fluoroesters that are generated in this catalytic asymmetric C−F bond-forming process can be transformed in good yield into a variety of other tertiary alkyl fluorides (Figure 1).

Two of the possible pathways for the **PPY\***-catalyzed enantioselective fluorination of ketenes to generate enantioenriched tertiary $\alpha$-fluoroesters are illustrated in Figure 2. In one mechanism, a **PPY\***-derived chiral enolate (**2**) is a key intermediate (top), and in the other a **PPY\***-derived chiral fluorinating agent (**4**) is critical (bottom).[17] To gain insight into the operative pathway, we determined the rate law for the reaction of phenyl ethyl ketene, which is first order in **PPY\*** and in NFSI, and zeroth order in the ketene and in C$_6$F$_5$ONa.[18] The rate of product formation does vary with the identity of the ketene, suggesting that the ketene is involved in the rate-determining step.

These observations are consistent with a "chiral enolate" pathway (top of Figure 2; but not with a "chiral fluorinating

agent" pathway (bottom of Figure 2)[19]) wherein nucleophilic addition of **PPY\*** to the ketene affords enolate **2**, this enolate is the resting state of the catalytic cycle,[20] and, in the turnover-limiting step, enolate **2** is fluorinated by NFSI to provide enantioenriched N-acylpyridinium salt **3**. Reaction with the phenoxide then furnishes the tertiary α-fluoroester and regenerates the catalyst, **PPY\***.

In view of our earlier inability to achieve **PPY\***-catalyzed asymmetric fluorination of ketenes with NFSI in the absence of an added nucleophile (eq 2), we hypothesized that N-acylpyridinium salt **3** (Figure 2) might be isolable. Indeed, reaction of **PPY\***, phenyl benzyl ketene, and NFSI (1:1:1) provided α-fluorinated acylpyridinium salt **5** (eq 4).[21,22] This ion pair is stable at room temperature under nitrogen for at least 6 months.

(4)

(+)-**5**
*95% yield*
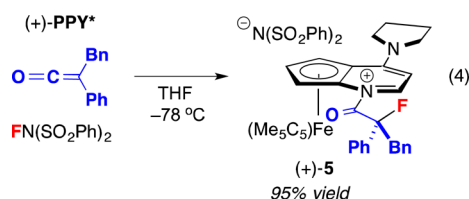
Although we were not able to obtain X-ray-quality crystals of the sulfonimide salt of the N-acylpyridinium ion, anion exchange of $N(SO_2Ph)_2$ for a carborane through treatment with $CsCB_{11}H_{12}$ furnished a suitable crystal (Figure 3).[23] The
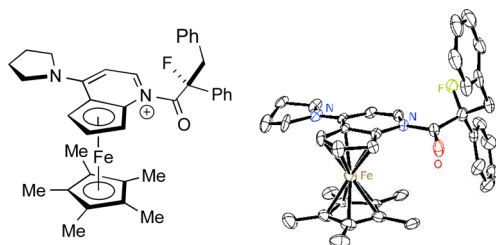
**Figure 3.** ORTEP diagram of N-acylated (+)-**PPY\***. Thermal ellipsoids are illustrated at the 35% probability level. For clarity, the carborane counteranion, the hydrogen atoms, the solvent, and the second molecule in the asymmetric unit are omitted, and only the major component of the disorder in the Cp\* group is shown.

pyrrolidino group, the pyridine ring, and the carbonyl group are approximately coplanar, consistent with extended conjugation of the π system, which decreases the electrophilicity of the carbonyl group. With regard to the orientation around the $N-C_{carbonyl}$ bond, the smaller group (carbonyl oxygen) is positioned on the side of the fused cyclopentadienyl ring, presumably to minimize unfavorable steric interactions. The stereochemistry of the fluorine-bearing carbon of the N-acylpyridinium ion is the same as for the major enantiomer of the α-fluoroester that is generated by (+)-**PPY\*** under our standard fluorination conditions.

We have confirmed that N-acylpyridinium salt **5** is a chemically and kinetically competent potential intermediate in the proposed catalytic cycle that leads to the enantioenriched tertiary α-fluoroester (top of Figure 2). Thus, upon treatment of this salt with $C_6F_5ONa$ in THF at −78 °C, the enantioenriched ester is formed with retention of stereochemistry (eq 5). It is interesting to note that this catalyst-regeneration issue from an N-acylated catalyst intermediate is not encountered in "related" processes such as the **PPY\***-catalyzed α-chlorination of ketenes[13] or the

(5)

*99% ee*
*>98% yield*
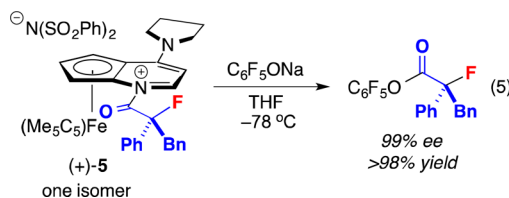
cinchona alkaloid-catalyzed α-fluorination of acid chlorides (via monosubstituted ketenes) to afford secondary α-fluoroesters.[4]

In conclusion, we have described a method for the catalytic enantioselective coupling of aryl alkyl ketenes (and a dialkyl ketene) with NFSI and $C_6F_5ONa$ to produce tertiary α-fluoroesters, a family of target molecules that have rarely been directly accessed via asymmetric catalysis. The addition of $C_6F_5ONa$ was critical to the success of this effort, as it enables regeneration of the catalyst (**PPY\***) from a relatively stable N-acylated intermediate, which we have synthesized and investigated independently. Our mechanistic studies are consistent with a catalytic cycle wherein **PPY\*** adds to the ketene and generates a chiral enolate which, in the stereochemistry- and rate-determining step, reacts with NFSI to furnish the enantioenriched N-acylpyridinium salt.

## ■ ASSOCIATED CONTENT

**Ⓢ Supporting Information**

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

## ■ AUTHOR INFORMATION

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**Notes**

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(14) When $C_6F_5OH$ was employed in place of $C_6F_5ONa$, essentially none of the desired product was observed.

(15) Notes: (a) Under our optimized condition, solutions of the ketene and the nucleophile are added dropwise via a syringe pump to a solution of the catalyst and NFSI; Selectfluor reagent is not a suitable substitute for NFSI; the ee of the product is constant during the course of the reaction; an *o*-tolyl-substituted and a *tert*-butyl-substituted ketene were not effective reaction partners. (b) Both enantiomers of **PPY*** are available from Strem Chemicals.

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(18) **PPY*** and *t*-BuONa react with phenyl ethyl ketene in THF-$d_8$ at −78 °C, whereas $C_6F_5ONa$ does not.

(19) In THF-$d_8$ at −78 °C, no reaction is observed when **PPY*** is mixed with NFSI.

(20) We have not yet been able to identify the resting state of the catalyst under our standard fluorination conditions.

(21) The yield was determined by $^1$H NMR spectroscopy with the aid of an internal standard.

(22) We were also able to prepare the corresponding *N*-acylpyridinium salt derived from phenyl ethyl ketene, but it was more difficult to purify than salt **4**.

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