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Synthesis of Chiral Fluorides by Sequential Organocatalyzed Desymmetrization of Glutaric Anhydrides and Photoredox-Catalyzed Decarboxylic Fluorination

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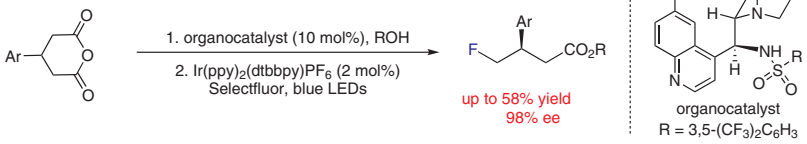

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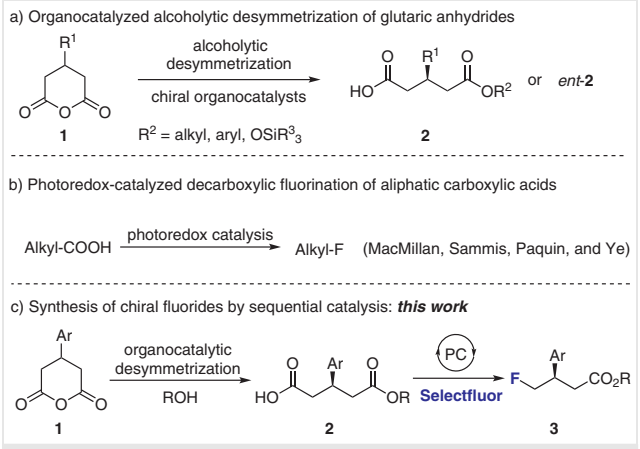
Abstract We have developed an efficient method for the preparation of chiral fluorinated compounds by sequential organocatalyzed desymmetrization of 3-substituted glutaric anhydrides and photoredox-catalyzed decarboxylic fluorination. Chiral fluorides can be prepared in yields of up to 58% and with excellent enantioselectivities of up to 98% ee.

Key words sequential catalysis, organocatalysis, photoredox catalysis, fluoro compounds, asymmetric catalysis, desymmetrization

The pharmaceutical industry has seen a steady increase in the number of drug candidates containing one or more fluorine atoms.[1] Many fluorinated analogues of natural products have been synthesized because of the special properties of the fluorine atom, such as its strong electronegativity, its capacity to enhance metabolic stability, its small size, and the low polarizability of the C–F bond.[2] Chiral fluorides have a remarkable record in medicinal chemistry, and will play a continuing role in providing lead compounds for therapeutic applications.[3] Due to the prevalence of fluorinated pharmaceuticals and pesticides, asymmetric incorporation of fluorine into organic molecules has attracted considerable attention from chemists.

Enantioselective desymmetrization is a powerful method for generating complex chiral compounds from relatively simple achiral or *meso* starting materials.[4] Cyclic *meso*-anhydrides are frequently used as substrates for enantioselective desymmetrization by nucleophilic ring-opening reactions. A variety of nucleophiles, including alcohols and amines, have been widely used in this reaction. The resultant chiral carboxylic acids can undergo a variety of transformations. Over the past two decades, various organocatalytic systems have been employed for the alcoholytic desymmetrization of *meso*-glutaric anhydrides **1** to produce chiral 3-substituted glutaric acid monoesters **2** (Scheme 1a).[5] On the other hand, because of their stability, operability, ready availability, and low cost, carboxylic acids are regularly used as raw materials in organic synthesis.[6] Because of its excellent site selectivity, decarboxylative functionalization has become an important strategy for constructing new C–C or C–X bonds. The groups of MacMillan[7], Sammis[8], Paquin[9], and Ye[10] have recently developed decarboxylative fluorinations of alkanoic acids by photoredox catalysis, providing effective methods for constructing C–F bonds (Scheme 1b).



Scheme 1 Synthesis of chiral fluorides by sequential catalysis

Inspired by organocatalyzed desymmetrization and photoredox-catalyzed decarboxylic fluorination, we attempted to synthesize chiral fluorides by sequential organocatalyzed desymmetrization of 3-substituted glutaric anhydrides and photoredox-catalyzed decarboxylic fluorination of the resultant chiral carboxylic acids (Scheme 1c).[11]

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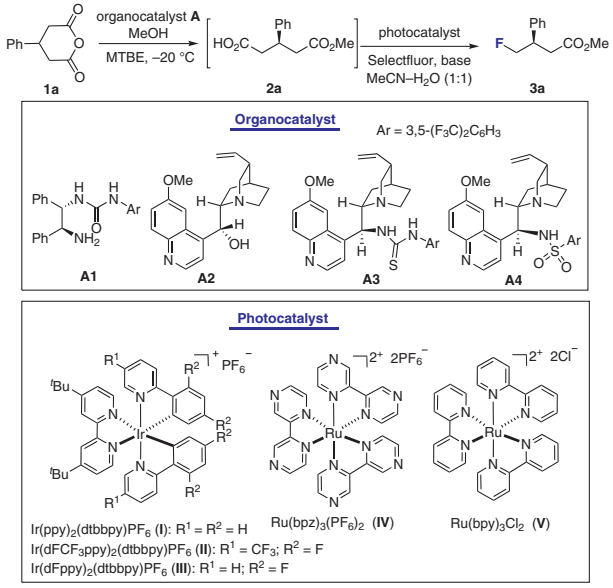
This project started with the conversion of 3-phenylglutaric anhydride (**1a**) into the chiral fluoride **3a** in a two-step one-pot manner. Enantioselective methanolysis of anhydride **1a** with MeOH (10 equiv) in MTBE at –20 °C for 24 hours was catalyzed by organocatalyst **A** (10 mol%). When the first step of the reaction was complete, the solvent was evaporated and the resultant chiral acid **2a** was redissolved in a 1:1 mixture of acetonitrile and water. The mixture was irradiated by 45 W blue LEDs in the presence of an Ir or Ru photocatalyst (2 mol%), Selectfluor (3 equiv), and a base (2 equiv) for 12 hours at ambient temperature under N_2. The final chiral fluoride **3a** was isolated upon purification. In attempts to improve this result, organocatalysts **A1**–**4** (Table 1, entries 1–4), photocatalysts **I**–**V** (entries 4–8), and several bases (entries 8–10) were tested [for the comprehensive optimization of the conditions, see the Supporting Information (SI)]. We found that a combination of sulfonamide **A4**[5c] as the organocatalyst, iridium complex **I**[7] as the photocatalyst, and Na_2HPO_4 as the base gave the optimal results in terms of yield and enantioselectivity (36% yield, 92% ee; entry 4). The yield was further improved to 58% without affecting the enantioselectivity when the reaction was irradiated by 40 W blue LEDs at the precise wavelength of 456 nm for 12 hours at 25 °C (entry 11).[12,13] No reaction was observed without visible-light irradiation (entry 12), and both the bifunctional organocatalyst **A4** and the Ir-based photocatalyst **I** were necessary to this transformation (entries 13 and 14).

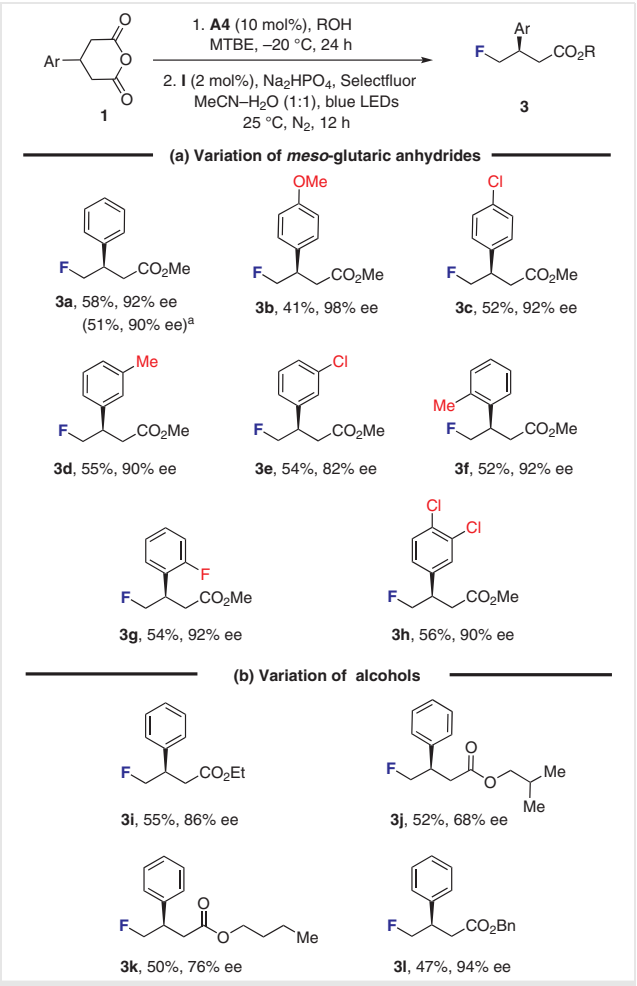
We next investigated the generality and limitations of this reaction under the optimized reaction conditions. A variety of 3-substituted glutaric anhydrides **1** were converted into the corresponding chiral fluorinated compounds **3a**–**h** in good yields (41–58%) and excellent enantioselectivities (82–98% ee) (Scheme 2a). Substituted 3-phenylglutaric anhydrides with an electron-donating group (MeO) or an electron-withdrawing group (Cl) in the *para*-position of the phenyl ring gave products **3b** and **3c**, respectively, with excellent enantioselectivities. 3-Phenylglutaric anhydrides with substituents in the *meta* (**3d** and **3e**) or *ortho* (**3f** and **3g**) positions of the phenyl ring were also amenable to this transformation, affording the corresponding products in satisfactory yields (52–55%) and good enantioselectivities (82–92% ee). 3-(3,4-Dichlorophenyl)glutaric anhydride was also compatible with this reaction, and provided the product **3h** in good yield (56%) and high enantioselectivity (90% ee). We then examined desymmetrization of 3-phenylglutaric anhydride (**1a**) with various alcohols (Scheme 2b). EtOH, BuOH, and BnOH gave the desired products **3i**, **3k**, and **3l** in good yields of 55, 50, and 47%, respectively, and with high enantioselectivities (86, 76, and 94% ee, respectively). Bulky isobutanol also gave a good yield of the corresponding product **3j** (52%), but with a lower enantioselectivity (68% ee). Substrates with electron-deficient aromatic, furyl, or alkyl substituents were not successful (For the details, see the SI). This reaction of **3a** was scaled up to 5 mmol scale with only slight decrease in yield (51%) and enantioselectivity (90% ee).

Table 1 Optimization of the Reaction Conditions[a]



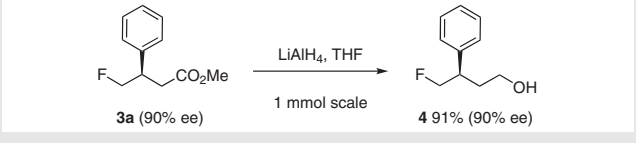
Entry	Catalyst	Photocatalyst	Base	Yield[b] (%)	ee[c] (%)
1	**A1**	**I**	Na_2HPO_4	12	–14
2	**A2**	**I**	Na_2HPO_4	11	26
3	**A3**	**I**	Na_2HPO_4	17	82
4	**A4**	**I**	Na_2HPO_4	36	92
5	**A4**	**II**	Na_2HPO_4	35	90
6	**A4**	**III**	Na_2HPO_4	35	90
7	**A4**	**IV**	Na_2HPO_4	25	90
8	**A4**	**V**	Na_2HPO_4	13	90
9	**A4**	**I**	K_2HPO_4	17	92
10	**A4**	**I**	Na_2CO_3	9	90
11[d]	**A4**	**I**	**Na_2HPO_4**	**58**	**92**
12[e]	**A4**	**I**	Na_2HPO_4	NR[f]	–
13	**–**	**I**	Na_2HPO_4	NR	–
14	**A4**	**–**	Na_2HPO_4	NR	–

[a] Reaction conditions: **1a** (0.10 mmol), MeOH (1 mmol), organocatalyst **A** (0.01 mmol, 10 mol%), MTBE (3.0 mL), –20 °C, 24 h. After solvent removal, **2a**, photocatalyst (0.002 mmol, 2 mol%), Selectfluor (0.3 mmol), base (0.2 mmol), 1:1 MeCN–H_2O (1.0 mL), 45 W blue LEDs, r.t., 12 h.
[b] Isolated yield.
[c] Determined by HPLC on a chiral stationary phase.
[d] 40 W blue LEDs (456 nm) at 25 °C.
[e] In darkness.
[f] NR = no reaction.



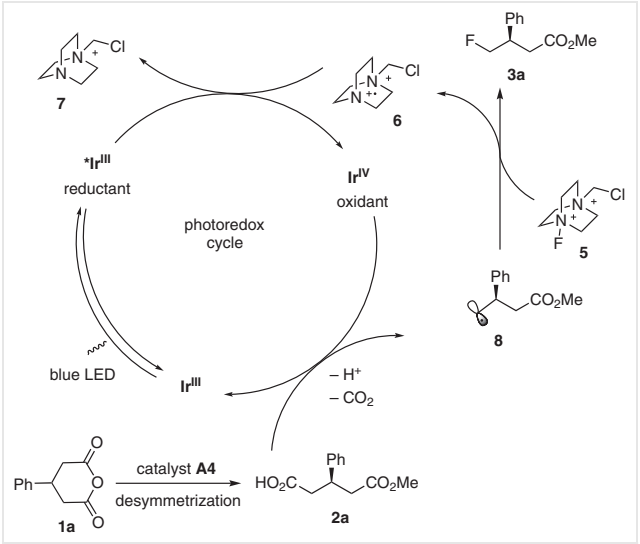
Scheme 2 Scope of the 3-arylglutaric anhydride. *Reagents and conditions*: **1** (0.50 mmol), MeOH (5 mmol), **A4** (0.05 mmol, 10 mol %), MTBE (15.0 mL), –20 °C, 24 h; then (after solvent removal), **2**, photocatalyst **I** (0.010 mmol, 2 mol %), Selectfluor (1.5 mmol), Na_2HPO_4 (1 mmol), 1:1 MeCN–H_2O (5.0 mL), 40 W blue LEDs (456 nm), 25 °C, 12 h. [a] 5 mmol scale.

The synthetic utility of the present procedure was further demonstrated by the reduction of the chiral fluorinated ester **3a** to the fluorinated alcohol **4** without loss of enantiopurity (Scheme 3).



Scheme 3 Transformation of enantioenriched **3a**

Based on reported precedents,[5c,7] a plausible reaction pathway is outlined in Scheme 4. Initially, glutaric anhydride **1a**, upon alcoholytic desymmetrization by bifunctional organocatalyst **A4**, gives the chiral glutaric acid monoester **2a**. Concurrently, photoexcitation of the ground-state photocatalyst Ir(III) by visible light leads to excited *Ir(III). Excited *Ir(III) undergoes oxidative quenching in the presence of a sacrificial quantity of Selectfluor reagent, affording the Ir(IV). The chiral glutaric acid monoester **2a** undergoes deprotonation, oxidation, and sequential elimination of CO_2 with the assistance of the Na_2HPO_4 and oxidized photocatalyst Ir(IV), delivering the alkyl radical intermediate **8** and regenerating the photocatalyst. After fluorine transfer from Selectfluor to the alkyl radical species **8**, the chiral fluorinated product **3a** is ultimately produced, together with radical cation **6**.



Scheme 4 Proposed mechanism

In conclusion, we have developed a method for the synthesis of chiral fluorides. This method involves sequential organocatalyzed desymmetrization of 3-substituted glutaric anhydrides and photoredox-catalyzed decarboxylic fluorination of the resultant chiral carboxylic acids. This strategy provides an efficient way to access chiral fluorinated compounds in a highly enantioselective manner.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707295.

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(12) **Alkyl 3-Aryl-4-fluorobutanoates 3; General Procedure**
MTBE (15 mL) was added to a mixture of the appropriate 3-arylglutaric anhydride **1** (0.5 mmol) and catalyst **A4** (0.05 mmol), and the mixture was stirred at –20 °C for 30 min. MeOH (5 mmol) was added, and stirring was continued at –20 °C for 24 h. When the reaction was complete, the solvent was evaporated under reduced pressure without further purification. The residue was dissolved in 1:1 MeCN–H_2O (5.0 mL) and $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) (0.010 mmol, 2 mol%), Selectfluor (1.5 mmol), and Na_2HPO_4 (1 mmol) were added. The mixture was irradiated by 40 W (456 nm) blue LEDs for 12 h at 25 °C under N_2 until the reaction was complete. The reaction was then quenched with aq NaCl, the mixture was extracted with Et_2O, and the extracts were purified by preparative TLC.

(13) **Methyl (*R*)-4-Fluoro-3-phenylbutanoate (3a)**
Purified by preparative TLC (PE–EtOAc, 10:1) to give a white oil; yield: 56.8 mg (58%, ee 92%); $[\alpha]_D^{20}$ = –37.9 (*c* 2.15, $CHCl_3$). HPLC [Daicel Chiralpak OD-H, hexane–*i*-PrOH (98:2), flow rate: 1.0 mL/min, T = 25 °C, λ = 220 nm]: t_R = 8.292 min (major), t_R = 14.765 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 2 H), 7.28–7.22 (m, 3 H), 4.68–4.41 (m, 2 H), 3.62 (s, 3 H), 3.59–3.46 (m, 1 H), 2.89 (dd, *J* = 16.0, 6.9 Hz, 1 H), 2.70 (dd, *J* = 16.0, 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 139.5, 128.7, 127.8, 127.4, 86.1 (*J* = 173.0 Hz), 51.7, 42.6, 36.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –219.8. ESI (FTMS): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{13}FNaO_2$: 219.0798; found: 219.0801.

