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应用苄位 C—H 氟化形式合成 α,β-二氟代-γ-氨基酸

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摘要 苄位 C—H 氟化已经成为一种向分子内引入氟原子的重要手段, 然而, 苄位 C—H 氟化反应还没有被应用到任何多步合成中. 由于氟的构象效应, α,β-二氟代-γ-氨基酸在生物化学中有着重要的应用, 但是其合成却具有一定的挑战性. 在本文中, 苄基 C—H 氟化作为关键步骤被成功用于 *syn*-α,β-二氟代-γ-氨基酸 **1** 的形式合成. 基于以下原因, 本工作的合成路线比文献中的路线更为实用: (1)没有使用具有腐蚀性和毒性的亲核氟代试剂; (2)总收率为 18% (以前的方法约为 5%); (3)关键苄位 C—H 反应被放大到了克量级. 在对反应进行优化的过程中, 观察到明显的氟效应, 即对于苄位 C—H 氟化反应, 邻位含有氟原子的碳比普通碳反应活性低很多.

关键词 C—H 氟化; 有机氟; 氨基酸

Application of Benzylic C—H Fluorination for the Formal Synthesis of *syn*-α,β-Difluoro-γ-amino Acid

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Abstract Benzylic C—H fluorination has emerged as a valuable tool for the introduction of fluorine. However, the powerfulness of benzylic C—H fluorination has not been tested in any multi-step synthesis. α,β-Difluoro-γ-amino acids are useful entities for biological application owing to the so-called fluorine conformational effect. In this work, benzylic C—H fluorination has been successfully utilized as the key step for the formal synthesis of *syn*-α,β-difluoro-γ-amino acid **1**, a very challenging but useful target. The approach developed in this work could be viewed as more practical compared to the previous one, because: (1) no corrosive and toxic nucleophilic fluorinating reagents are used, (2) the overall yield is 18% (the previous approach is about 5%), and (3) the key benzylic C—H reaction developed by Chen and co-workers was scaled up to one gram without decreasing its original efficiency. A striking fluorine effect was observed: a carbon with one fluorine atom on the adjacent carbon is much less reactive than an ordinary carbon for the benzylic C—H fluorination.

Keywords C—H fluorination; organofluorine; amino acid

1 Introduction

The introduction of fluorine often imparts organic molecules with desired properties owing to its unique properties. The formation of C—F bond has thus been an intensive research subject and gained impressive development in the past ten years.[1] Benzylic C—H fluorination has emerged as a valuable tool for the introduction of fluorine.[2] In this context, the research groups of Lectka,[3~6] Groves,[7] Inoue,[8] Tang[9] and Britton[10] have realized benzylic C—H bond fluorination with transition-metal catalysts, including copper, manganese, iron, silver and decatungstate catalysts. In a parallel, the research groups of Chen,[11] Inoue[8] Lectka,[12,13] Kappe[14] group achieved benzylic C—H bonds fluorination with the aid of visible light in the presence of an organocatalyst such as diarylketones, *N,N*-dihydroxypyromellitimide and 1,2,4,5-tetracyanobenzene. Method without using transition-metal catalysts and organocatalysts has also been developed.[15] In addition, the research groups of Groves[16] and Carrol[17] have developed successful protocols for benzylic fluorination with ^{18}F fluoride for positron emission tomography (PET). However, the powerfulness of benzylic C—H fluorination has not been tested in any multi-step synthesis. We report herein the successful application of benzylic C—H fluorination as a key step for the

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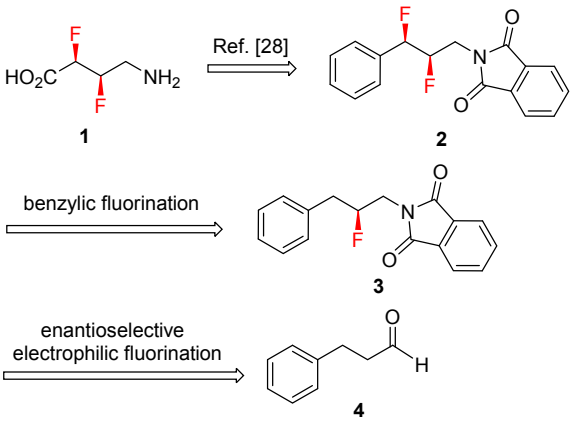
formal synthesis of *syn*-*α*,*β*-difluoro-*γ*-amino acid **1**, a very challenging target.

α,*β*-Difluoro-*γ*-amino acids are useful entities for biological application owing to the so-called fluorine conformational effect.[18~20] These molecules have found applications as subtype-selective *γ*-aminobutyric acid (GABA) receptor ligands and as components of shape-controlled peptides.[21~23] In order to meet the demand for application of *α*,*β*-difluoro-*γ*-amino acids, we and others[21,24] have devoted to develop scalable synthetic routes. However, all of the previous methods need to use nucleophilic fluorinating reagents such as triethylamine trifluoride and Deoxo-Fluor, which are both corrosive and toxic, thus potentially dangerous for handling. This has contributed largely to the difficulty for the synthesis of *syn*-*α*,*β*-difluoro-*γ*-amino acid **1** (the *syn*-isomer is much more difficult to synthesize than the *anti*-isomer), which could only be obtained in tens of milligram previously.[24]

2 Results and discussion

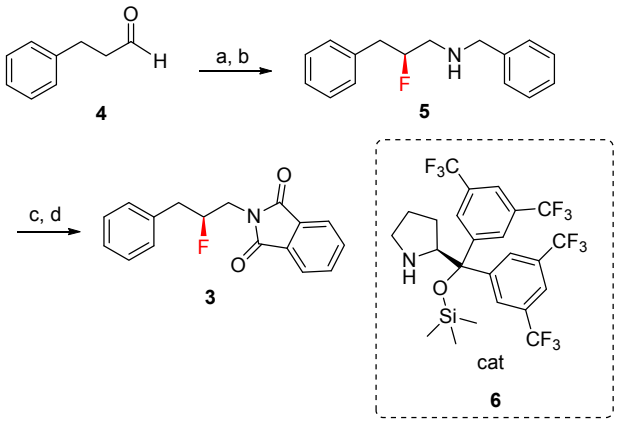
We envisioned that a more practical route for **1** was possible if benzylic C—H fluorination could be utilized for the introduction of fluorine atom to **3**, which could be readily prepared by an enantioselective electrophilic fluorination and reductive amination of **4** (Scheme 1).[25~28] This route could avoid nucleophilic fluorinating reagents by using safe and easy-to-handle electrophilic reagents, such as Selectfluor and NFSI.



Scheme 1 Retrosynthesis of *syn*-difluorianted amino acid **1** based on benzylic fluorination

As outlined in Scheme 1, the synthesis of **3** commenced with *α*-fluorination and *in-situ* reductive amination of phenylpropyl aldehyde **4**. This reaction could be conducted on a multi-gram scale, with no decrease of enantiomeric excess. Removal of the benzyl group of **5** and protection of the resulting amine with phthalic anhydride afforded the desired product **3** in an overall yield of 60% from **4**.

Initially, we carried out a model benzylic C—H fluorination using **7**, the non-fluorinated analogue of **3**. To have a good understanding of different methods (*e.g.*, ease of setting up, workup, efficiency *etc*.), we evaluated the reported standard conditions of representative methods. As shown in



Conditions: (a) NFSI, cat. **6** (5 mol%), then benzylamine; (b) KBH_3CN, pH<3, MeOH, 93%, 99% *ee*; (c) Pd/C, H_2, AcOH, r.t.; 24 h; (d) phthalic anhydride, toluene, reflux, 64%.

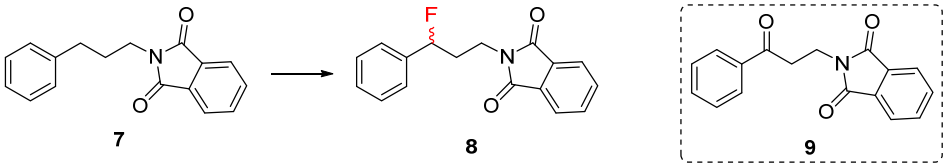
Scheme 2 Synthesis of mono-fluorinated substrate **3**

Table 1, the desired fluorination underwent smoothly under most conditions to afford the desired **8**. Even without optimization, the yields under conditions in Entries 1～5 are synthetically useful (given the difficulties encountered in the introduction of the second fluorine in the previous approachs.[21,24] It is important to point out that the solvent needed to be strictly degassed before use, otherwise significant amount of ketone **9** was obtained as the side product, which would decrease the yield and complicate the isolation of desired product **8**.

Encouraged by the positive results obtained with **7**, we next proceeded to conduct the benzylic fluorination of **3**. To our surprise, we found that the mono-fluorinated **3** was actually quite difficult for fluorination. As shown in Table 2, the previously established viable methods for **7**, such as conditions in Entries 1～4, gave either trace of no desired product. Optimization of the reaction conditions in Entries 1～3 proved to be fruitless. For example, increasing the reaction temperature had only marginal effect on the reaction efficiency (Entries 5～6, Table 2). These reactions along with the results obtained Entries 1～4 in Table 1 indicate that a vicinal fluorine atom may have a detrimental effect for the benzylic C—H fluorination.[29] To probe this fluorine effect further, we have synthesized compounds **10a**～**10c** and **11a**～**11c** and attempted the benzylic C—H fluorination under Chen's conditions.[11] As shown in Eq. 1, the non-fluorinated compounds **10a**～**10c** underwent the desired reaction successfully to furnish **12a**～**12b** in 55%～63% yields. In sharp contrast, no trace products could be observed for the fluorinated compounds **11a**～**11c**.

This "negative fluorine effect" thus posed significant challenge for the introduction of the second fluorine atom into compound **3**.[30] To our delight, however, the modified conditions of Chen's method[11,14] (Entry 4, Table 2) showed a promise for overcoming this fluorine effect, as the yield of the reaction was increased to 38% when the reaction temperature was increased (Entry **7**, Table 2). After extensive investigation (not shown), the products were obtained in

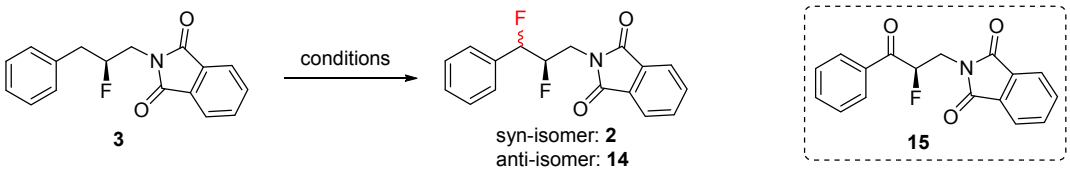
Table 1 Model fluorination of non-fluorinated substrate **7**



Entry	Conditions[a]	Yield[b]/%
1	9-Fluorenone (5 mol%)[11] Selectfluor (2 equiv), CFL, 25 ℃, 48 h	77
2	$Fe(acac)_2$ (10 mol%),[5] Selectfluor (2.2 equiv.), 50 ℃, 24 h	51
3	NDHPI (2.5 mol%),[8] Selectfluor (1.2 equiv.), 50 ℃ 24 h	33
4	Xanthone (5 mol%) Selectfluor (1.2 equiv.), Black-light lamp, 25 ℃, 24 h[14]	75
5	Xanthone (5 mol%) Selectfluor (1.2 equiv.), Black-light lamp, 40 ℃, 24 h[14]	43
6	$K_2S_2O_8$ (1.5 equiv.), Selectfluor (1.5 equiv.), 24 h[15]	18
7	Copper (I) bisimine complex (10 mol%), $KB(C_6F_5)_4$ (10 mol%), NHPI (10 mol%), Selectfluor (2.2 equiv.), 24 h[3]	0
8	Manganese-salen complext, PhIO, TREAT•HF (0.5 equiv.), AgF (3.0 equiv.), 24 h[7]	0

[a] Reactions were conducted on 0.07 mmol scale; [b] yields and ratio were calculated based on the integration of ^{19}F NMR.

Table 2 Optimization of the fluorination with mono-fluorinated **7**

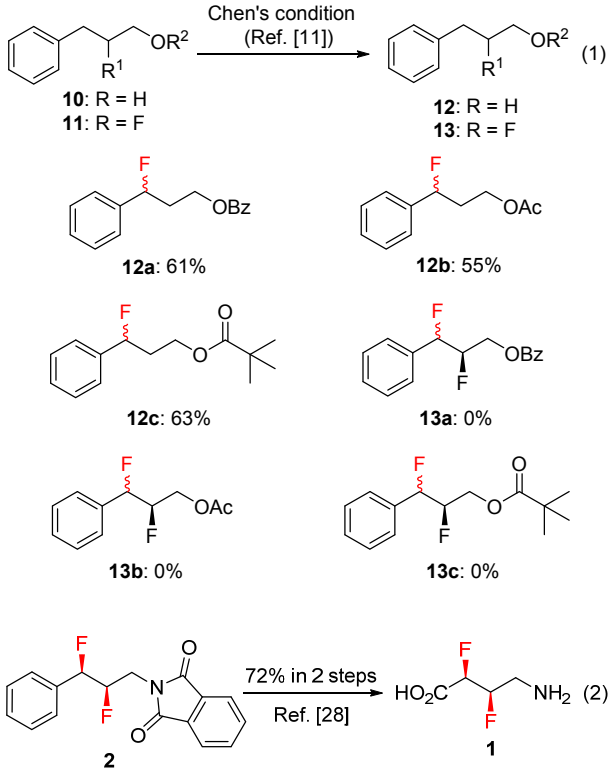


Entry	Conditions[a]	Yield[b]/%	Molar ratio[b] of **2**∶**14**
1	9-Fluorenone (5 mol%),[11] Selectfluor (2 equiv), CFL, 2 ℃, 48 h	0	NA
2	$Fe(acac)_2$ (10 mol%),[5] Selectfluor (2.2 equiv.), 50 ℃, 24 h	＜1	NA
3	NDHPI (2.5 mol%),[8] Selectfluor (1.2 equiv.), 50 ℃, 24 h	＜1	NA
4	Xanthone (5 mol%), Selectfluor (1.2 equiv.), Black-light lamp, 25 ℃, 24 h[11,14]	0	NA
5	9-Fluorenone (5 mol%), Selectfluor (2 equiv.), CFL, 40 ℃, 48 h	4	1.1∶1
6	9-Fluorenone (5 mol%), Selectfluor (2 equiv.), CFL, 60 ℃, 48 h	3	1.1∶1
7	Xanthone (5 mol%), Selectfluor (1.2 equiv.), Black-light lamp, 40 ℃, 24 h[11,14]	38	1.76∶1
8	Xanthone (5 mol%), Selectfluor (1.2 equiv.), Black-light lamp, 60 ℃, 24 h	38	1.19∶1
9	Xanthone (50 mol%), Selectfluor (5.0 equiv.), Black-light lamp, 60 ℃, 24 h	68	1.58∶1
10	Xanthone (50 mol%), Selectfluor (5.0 equiv.), Black-light lamp, 70 ℃, 24 h	56	1.42∶1
11	Xanthone (50 mol%), Selectfluor (5.0 equiv.), Black-light lamp, 80 ℃, 24 h	43	1.32∶1
12	Xanthone (50 mol%), Selectfluor (5.0 equiv.), Black-light lamp, 60 ℃, 24 h	79[c], 71[d]	1.52∶1[b], 1.53∶1[c]

[a] Reactions were conducted on 0.07 mmol scale; [b] yields and ratio were calculated based on the integration of ^{19}F NMR; [c] yield on 500 mini-gram scale; [d] yield on 1 gram scale.

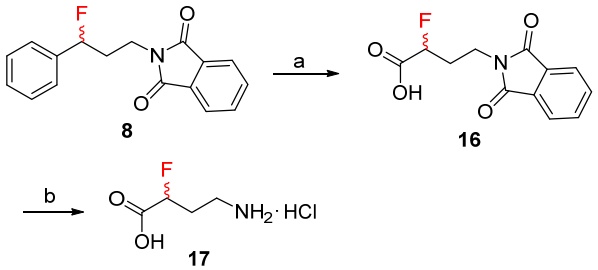
68% yield with 1.58∶1 of *syn*/*anti* ratio, when a large amount of photocatalyst and fluorinating reagent were used at 60 ℃ (Entries 8～9). Further optimization proved that a high temperature was not good for this reaction. With the optimized conditions in hand (Entry 9, Table 2), the remaining tasks were to scale the reaction up and separate the desired *syn*-isomer **2** from *anti*-isomer **14**. To our delight, when the reaction was conducted on a 500 mini-gram and one gram scale, the yields were even better than that on small scale. However, the formation of ketone **15** was unavoidable, which was isolated in about 5% yield. As expected, the purification of **2** was not a trivial job, because compounds **2**, **14** and **15** have almost the same polarity. At last, we managed to solve the problem by running two successive column purifications, first with *V*(*n*-hexane)∶*V*(CH_2Cl_2)∶*V*(ethyl acetate)＝35∶2∶2 to isolate pure **2** and ketone **15**, then with *V*(*n*-hexane)∶*V*(dioxane)＝15∶1 to get **14**. Thus, 450 mini-gram of difluorinated **2** could be readily obtained from one gram of **3**.

Conversion of compound **2** to the difluorinated amino acid **1** is a well-established chemistry (Eq. 2).[21b] Based on this fact, this formal synthesis of *α*,*β*-difluoro-*γ*-amino acid **1** requires 7 steps from commercial available reagents and has an overall yield of 18%. This result is significant as the previous synthesis of **1** requires 8 steps with overall yield around 5%. Moreover, no toxic and corrosive nucleophilic



fluorinating reagents is used. Thus, the successful utilization of benzylic C—H fluorination has enabled a practical synthesis of a challenged target, *α*,*β*-difluoro-*γ*-amino acid **1**.

α-Fluoro-*γ*-amino acid **17** is a useful component for prodrug development.[31] Previous synthesis also requires nucleophilic fluorinating reagents. In this work, *α*-fluoro-*γ*-amino acid **17** was obtained readily from **8** in an overall yield of 79%, thus offering additional benefit to our work (Scheme 3).



Conditions: (a) $NaIO_4$, $RuCl_3$, CH_2Cl_2/MeCN/H_2O, r.t., 80%; (b) NH_2NH_2•$3H_2O$, EtOH, reflux, 99%

Scheme 3 Synthesis of *α*-fluoro-*γ*-amino acid from **8**

3 Conclusions

In conclusion, benzylic C—H fluorination has been successfully utilized as the key step for the formal synthesis of *syn*-*α*,*β*-difluoro-*γ*-amino acid **1**, a very challenging but useful target. Because no corrosive and toxic nucleophilic fluorinating reagents are used and the overall yield is 18% (the previous approach is about 5%), the approach developed in this work could be viewed as more practical than the previous one. The key benzylic C—H reaction developed by Chen and co-workers[11,14] was scaled up to one gram without decreasing its original efficiency. A striking fluorine effect was observed: a carbon with one fluorine atom on the adjacent carbon is much less reactive than an ordinary carbon for the benzylic C—H fluorination. We believe that the evaluation and optimization of different methods for benzylic C—H fluorination would provide valuable information for chemists who want to use them for target synthesis in future.

4 Experimental section

4.1 Instruments and reagents

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a JEOL FT-NMR spectrometer (^{1}H NMR, 400 MHz; ^{2}H NMR, 61 MHz; ^{13}C NMR, 100 MHz; ^{19}F NMR, 377 MHz). ^{1}H NMR chemical shifts were determined relative to Me_4Si (*δ* 0.0) as an internal standard. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ (*δ* 77.0). ^{19}F NMR chemical shifts were determined relative to $PhCF_3$ (*δ* —62.7) as an external standard. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR Spectrometer. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System. All reactions were carried out under nitrogen. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or aluminum oxide (Merck, 90 active stage I, 0.063～0.200 mm). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel glass plates (Merck silica gel 60 F254, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

4.2 Benzylic C—H fluorination procedure on gram-scale

A 250 mL of round-bottom flask equipped with a magnetic stir bar was charged with Selectfluor (6.25 g, 17.65 mmol), xanthone (346.3 mg, 1.76 mmol) and (*S*)-2-(2-fluoro-3-phenylpropyl)isoindoline-1,3-dione (**3**) (1.0 g, 3.53 mmol). Then anhydrous acetonitrile (120 mL) was added. The reaction mixture was degassed five times by freeze-pump-thaw cycles, and irradiated with a 26 W of black light bulb at 60 ℃ for 24 h. The reaction was quenched with H_2O (20 mL) and extracted three times with EtOAc, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel [*V*(*n*-hexane) ∶ *V*(CH_2Cl_2) ∶ *V*(ethyl acetate)＝35 ∶ 2 ∶ 2] to afford **2** as a white solid (457 mg, 43%), **15** as a colorless oil (50 mg, 5%) and a mixture of **14** (major) and **3** (minor). Then the mixture of **14** and **3** was purified by flash column chromatography with silica gel [*V*(*n*-he-

xane)∶*V*(dioxane) =15∶1] to afford **14** as a white solid (297 mg, 28%) and recovered starting material **3** (100 mg).[11,14]

2-((2*R*,3*R*)-2,3-Difluoro-3-phenylpropyl)isoindoline-1,3-dione (**2**):[21a] ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.85 (dd, *J*=3.1, 5.4 Hz, 2H), 7.73 (dd, *J*=3.0, 5.4 Hz, 2H), 7.45～7.35 (m, 5H), 5.56 (ddd, *J*=4.6, 19.3, 46.1 Hz, 1H), 5.11 (ddddd, *J*=3.6, 4.5, 9.1, 19.3, 48.3 Hz, 1H), 4.16 (ddd, *J*=9.1, 11.9, 21.2 Hz, 1H), 3.73 (ddd, *J*=3.6, 14.7, 29.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 134.2, 131.8, 129.4 (d, *J*=1.9 Hz), 128.8, 126.6, 126.5, 123.5, 92.4 (dd, *J*=19.8, 180.5 Hz), 90.1 (dd, *J*=23.0, 185.4 Hz), 38.3 (dd, *J*=6.4, 23.8 Hz); ^{19}F NMR (367 MHz, $CDCl_3$) *δ*: −188.42 (ddd, *J*=12.7, 19.7, 46.4 Hz, 1F), −199.91 (m, 1F); ^{19}F {^{1}H} NMR (367 MHz, $CDCl_3$) *δ*: −188.42 (d, *J*=12.3 Hz, 1F), −199.90 (d, *J*=12.9 Hz, 1F).

2-((2*S*,3*R*)-2,3-Difluoro-3-phenylpropyl)isoindoline-1,3-dione (**14**):[21a] ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.81 (dd, *J*=3.1, 5.6 Hz, 2H), 7.70 (dd, *J*=3.1, 5.5 Hz, 2H), 7.44～7.31 (m, 5H), 5.68 (ddd, *J*=4.3, 12.9, 46.4 Hz, 1H), 5.11 (ddddd, *J*=3.9, 3.9, 8.5, 16.5, 47.8 Hz, 1H), 4.16 (ddd, *J*=8.8, 13.3, 14.4 Hz, 1H), 3.87 (ddd, *J*=3.4, 14.4, 29.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 134.1, 131.8, 129.4 (d, *J*=1.9 Hz), 128.7, 126.1, 126.0, 123.4, 92.3 (dd, *J*=23.0, 177.2 Hz), 90.2 (dd, *J*=25.6, 181.7 Hz), 37.4 (dd, *J*=6.6, 23.6 Hz); ^{19}F NMR (367 MHz, $CDCl_3$) *δ*: −193.10 (ddd, *J*=16.5, 16.5, 46.5 Hz, 1F), −195.16 (m, 1F); ^{19}F {^{1}H} NMR (367 MHz, $CDCl_3$) *δ*: −193.10 (d, *J*=16.5 Hz, 1F), −195.16 (d, *J*=16.9 Hz, 1F).

(*R*)-2-(2-Fluoro-3-*oxo*-3-phenylpropyl)isoindoline-1,3-dione (**15**): $[\alpha]_D^{25}$ −2.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.08 (d, *J*=7.6 Hz, 2H), 7.88 (dd, *J*=3.1, 5.4 Hz, 2H), 7.75 (dd, *J*=3.0, 5.5 Hz, 2H), 7.66～7.60 (m, 1H), 7.55～7.40 (m, 2H), 5.99 (ddd, *J*=3.4, 9.0, 49.3 Hz, 1H), 4.35 (ddd, *J*=8.9, 14.6, 14.6, Hz, 1H), 4.18 (ddd, *J*=3.5, 14.8, 30.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 193.7 (d, *J*=17.3 Hz), 167.8, 134.3, 133.9, 131.8, 129.1, 129.0, 128.9, 123.5, 89.5 (d, *J*=188.0 Hz), 39.4 (d, *J*=23.1 Hz); ^{19}F NMR (367 MHz, $CDCl_3$) *δ*: −194.0 (ddd, *J*=14.6, 29.09, 49.4 Hz, 1F); ^{19}F {^{1}H} NMR (367 MHz, $CDCl_3$) *δ*: −194.05 (s, 1F); IR (neat) ν_{max}: 2928, 2855, 1772, 1717, 1486, 1467, 1457, 1419, 1395, 1363, 1279, 1223, 1188, 1080, 971, 888, 758, 720, 700, 647, 530 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}FNO_3(M+H)^+$ 298.0874, found 298.0875.

Supporting Information The Supporting Information (PDF file of synthetic procedures, characterization data and NMR spectra) is available free of charge via the Internet at http://sioc-journal.cn/.

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