
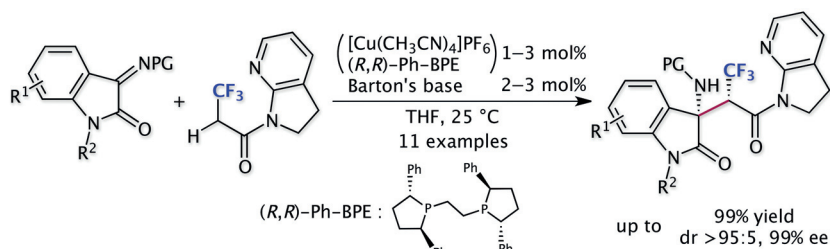


Direct Catalytic Asymmetric Mannich-Type Reaction of an α -CF₃ Amide to Isatin Imines

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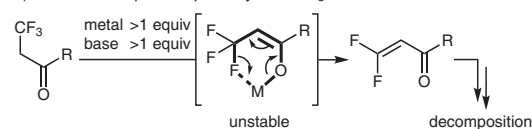
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Abstract An α -CF₃ amide underwent direct asymmetric Mannich-type reaction to isatin imines in the presence of a chiral catalyst comprising a soft Lewis acid Cu(I), a chiral bisphosphine ligand, and Barton's base. The Mannich adduct was converted in one step into a unique tricycle bearing a trifluoromethylated chiral center and an α -tertiary amine moiety.

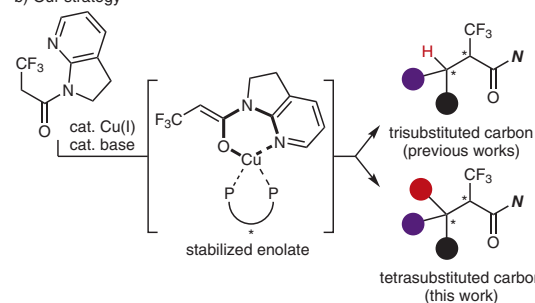
Key words asymmetric catalysis, copper catalysis, fluorine, Mannich reaction, heterocycle

Organofluorine compounds generally exhibit distinctive chemical properties compared to their corresponding non-fluorinated analogues owing to the strong C–F bond and high electronegativity of fluorine.¹ The altered attributes are often beneficial for medicinal and agrochemical applications.² Therefore, the incorporation of fluorine and perfluoroalkyl groups such as CF₃ into organic molecules has been a topic of the intensive research.³ In addition to fluorinated aromatics, recent effort has also been dedicated to the preparation of fluorine-containing aliphatic compounds in enantioenriched form.⁴ Two strategies exist for this purpose: fluorination/fluoroalkylation and building block approaches. Given the broad utility of enolate-based chemical transformations, α -CF₃ enolates would seem one of the most ideal building blocks for the construction of a trifluoromethylated stereogenic carbon. Nevertheless, only limited chemistry has been explored with this class of nucleophiles due to their notorious instability associated with the high aptitude for β -fluoride elimination from the corresponding metal enolates (Scheme 1, a).^{5,6}

a) Known decomposition pathway for α -CF₃ metal enolates



b) Our strategy



Scheme 1 (a) Known decomposition pathway for α -CF₃ metal enolates. (b) Our chelated amide strategy.

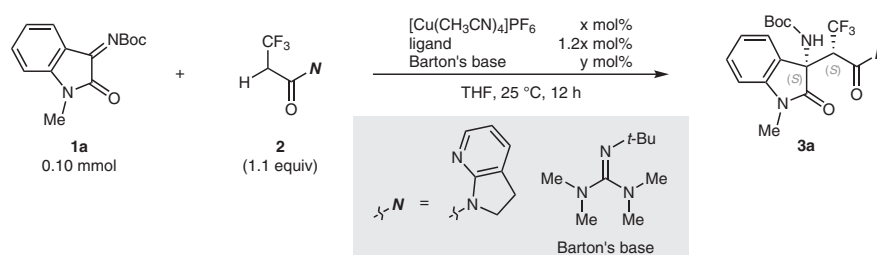
As a part of our research program in direct enolization chemistry,⁷ we have recently devised a chelated enolate strategy to tame otherwise unstable α -CF₃ metal enolates (Scheme 1, b).⁸ The designed pronucleophile⁹ contains a 7-azaindoline amide as a bidentate chelating unit that prevents unfavorable metal–fluorine interactions. The thus generated α -CF₃ enolate has proven effective in the construction of CF₃-containing stereogenic carbons in a wide range of Cu(I)-catalyzed asymmetric transformations.¹⁰ The applications have, however, been limited to the construction of trisubstituted stereocenters at the β -position of the amide carbonyl group.^{11,12} Facile Mannich addition of the α -CF₃ amide to Boc-aldimines⁸ prompted us to examine activated ketimines as potential reaction partners. Herein, we report the successful implementation of this strategy for

the preparation of tetrasubstituted carbons by means of a direct catalytic asymmetric Mannich-type reaction to isatin imines.¹³

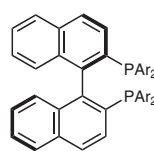
Our experience with 7-azaindoline amides has established a combined soft Lewis acid/Brønsted base system comprising Cu(I)/chiral bisphosphine ligand/Barton's base as a particularly effective catalyst for direct enolization chemistry.^{8,14} A recent systematic study has also found that the Ph-BPE ligand exhibits consistently high catalytic competency for a broad range of α -substituents of the amides including N₃, Cl, and alkyl groups, but not fluoroalkyl groups such as CF₃; biaryl-type phosphine ligands are preferred for the α -CF₃ amide.¹⁵ With these factors in mind,

our optimization studies for the Mannich-type reaction of amide **2** to isatin imine **1a** commenced with screening various biaryl-type ligands (Table 1). A quick examination revealed that the desired product was indeed formed in the presence of 5 mol% Cu(I)/chiral biaryl ligand complex, although the enantioselectivities were low to moderate (Table 1, entries 1–4). Hence, we turned our attention to different ligand backbones, and surprisingly, Ph-BPE (**L8**) was found to perform the best among the ligands evaluated (Table 1, entries 5–8). The catalyst loading was reduced to as little as 1 mol% without sacrificing the reactivity and selectivities (Table 1, entry 9).

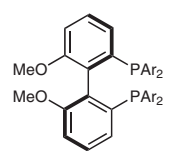
Table 1 Optimization Studies^a



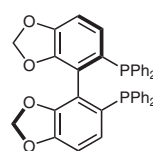
Entry	Ligand	x (mol%)	y (mol%)	Yield (%) ^b	dr ^b	ee (%) ^c
1	L1	5	5	93	91:9	-69
2	L2	5	5	70	60:40	21
3	L3	5	5	90	92:8	-49
4	L4	5	5	80	90:10	-23
5	L5	5	5	59	89:11	-95
6	L6	5	5	95	94:6	-70
7 ^d	L7	5	5	88	88:12	31
8 ^d	L8	5	5	98	>95:5	99
9 ^d	L8	1	2	98	>95:5	99



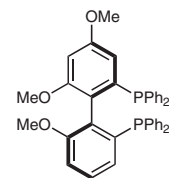
Ar = 4-Me-C₆H₄
L1: (*R*)-tol-BINAP



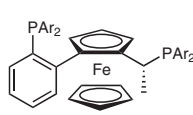
Ar = 3,4,5-(MeO)₃-C₆H₂
L2: (*R*)-BIPHEP-type



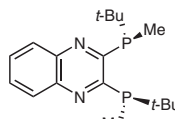
L3: (*R*)-Segphos



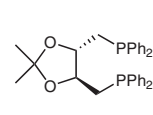
L4: (*R*)-Garphos



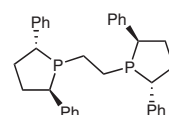
Ar = 3,5-Me₂-C₆H₃
L5: (*R,R_p*)-Walphos-type



L6: (*R,R*)-QuinoxP*



L7: (*S,S*)-DIOP



L8: (*R,R*)-Ph-BPE

^a Reaction conditions: **1a** (0.10 mmol), **2** (0.11 mmol), THF (0.1 M).

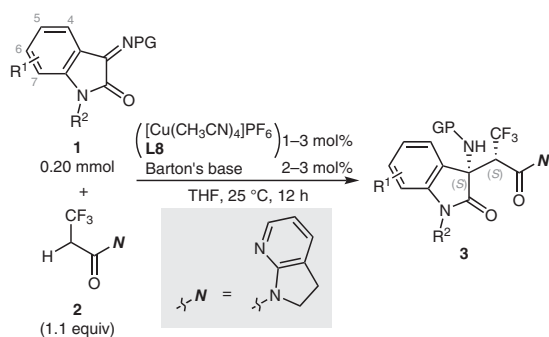
^b Yield and diastereomeric ratio were determined by ¹H NMR analysis of the unpurified reaction mixture using 3,4,5-trichloropyridine as an internal standard.

^c Enantiomeric excess of (*S,S*)-isomer was determined with normal-phase HPLC on a chiral support.

^d The reaction was performed on a 0.2 mmol scale in THF (0.2 M), and isolated yield was reported.

After the identification of a highly selective ligand for this transformation, a series of isatin imines **1** was evaluated with either 1 mol% or 3 mol% Cu catalyst (Table 2). The Cbz-protected imine also proved suitable for this catalytic system, affording the corresponding product with almost the same level of selectivities (Table 2, entries 1, 2). Both electron-donating and electron-withdrawing substituents at the 5-position were tolerated (Table 2, entries 3–7). Positional isomers of **3d** bearing a chlorine atom at different positions were obtained in comparable diastereo- and enantioselectivities (Table 2, entries 8, 9). Substituents on the oxindole nitrogen other than Me were also examined. While the PMB-protected substrate exhibited slightly lower reactivity and selectivities (Table 2, entry 10), the allyl-protected compound afforded results close to those of the Me-substituted one (Table 2, entry 11). The relative and absolute configurations of **3e** were determined by X-ray diffraction, and those of the other compounds were assigned by analogy.¹⁶

Table 2 Substrate Scope of the Mannich-Type Reaction of α -CF₃ Amide **2**^a



Entry	R ¹	R ²	PG	Product	Yield (%) ^b	er ^c	ee (%) ^d
1	H	Me	Boc	3a	98	>95:5	99
2	H	Me	Cbz	3b	91	>95:5	99
3	5-F	Me	Boc	3c	86	94:6	99
4	5-Cl	Me	Boc	3d	89	92:8	99
5	5-Br	Me	Boc	3e	90	>95:5	99
6	5-Me	Me	Boc	3f	99	>95:5	98
7	5-MeO	Me	Boc	3g	81	>95:5	99
8	6-Cl	Me	Boc	3h	86	>95:5	99
9	7-Cl	Me	Boc	3i	90	>95:5	96
10	H	PMB	Boc	3j	66	86:14	92
11	H	Allyl	Boc	3k	97	>95:5	97

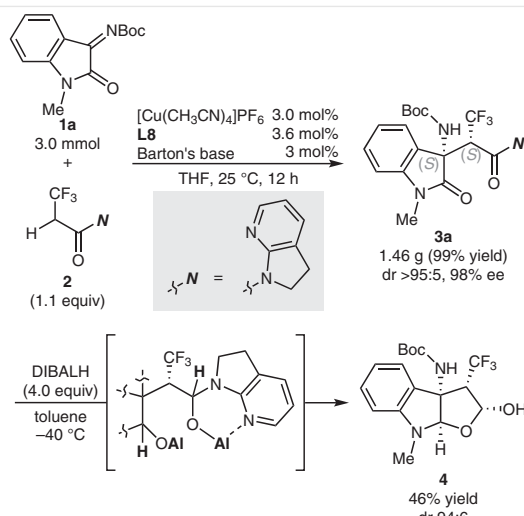
^a Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol), THF (0.2 M). For entries 1–4, [Cu(CH₃CN)₄]PF₆ (1.0 mol%), L8 (1.2 mol%), Barton's base (2.0 mol%). For entries 5–11, [Cu(CH₃CN)₄]PF₆ (3.0 mol%), L8 (3.6 mol%), Barton's base (3.0 mol%).

^b Yield values refer to isolated yield.

^c Diastereomer ratio was determined by ¹H NMR and ¹⁹F NMR analysis of the unpurified reaction mixture.

^d Enantiomeric excess of (S,S)-isomer was determined with normal-phase HPLC on a chiral support.

The reaction proceeded smoothly on a 3.0 mmol scale, producing 1.46 g of Mannich adduct **3a** with almost perfect stereoselectivities, albeit a slightly higher catalyst loading was necessary for full consumption of the substrates (Scheme 2).^{17,18} We have previously shown that 7-azaindoline amides can provide an in situ chelating group when treated with an organometallic reagent in a manner similar to Weinreb amides, and thus prevent further sequential addition of the reagent.^{8b,9,11b,14b} Mannich adduct **3a** was reduced by the action of DIBALH to form a masked aldehyde accompanied by the formation of an aluminum alkoxide derived from reduction of the oxindole moiety, which cyclized presumably during the workup. This triple-bond-forming process (two reductions and one cyclization) furnished highly decorated tricycle **4** in 46% yield with excellent diastereoselectivity.¹⁹



Scheme 2 A large scale reaction and the transformation of its product into a tricyclic skeleton.

In summary, we developed the direct catalytic Mannich-type reaction of an α -CF₃ amide to isatin imines. Enolization was promoted without decomposition by a proficient soft Lewis acidic Cu(I)/bisphosphine/Barton's base catalytic system, and the generated enolate underwent a highly stereoselective addition, producing an α -tertiary amine with an adjacent trifluoromethylated stereogenic carbon. The Mannich adduct was smoothly transformed into a tricyclic framework by harnessing a unique property of the 7-azaindoline as a chelating unit in the reduction step.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611642>.

References and Notes

- (1) (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 38.
- (2) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (e) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (f) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822.
- (3) (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2012**, *473*, 470. (d) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612. (e) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073.
- (4) (a) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891. (b) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (d) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (e) Noda, H.; Kumagai, N.; Shibasaki, M. *Asian J. Org. Chem.* **2018**, *7*, 599. (f) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. *Chem. Rev.* **2018**, *118*, 3887.
- (5) (a) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817. For early contributions, see: (b) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987. (c) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3991. (d) Yokozawa, T.; Ishikawa, N.; Nakai, T. *Chem. Lett.* **1987**, *16*, 1971.
- (6) Aldol reactions: (a) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807. (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174. (c) Franck, X.; Meniel, B. S.; Figadère, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5174. (d) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Org. Lett.* **2006**, *8*, 1129. (e) Ramachandran, P. V.; Parthasarathy, G.; Gagare, P. D. *Org. Lett.* **2010**, *12*, 4474. Allylic alkylations: (f) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369. (g) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037. Conjugate additions: (h) Wang, Q.; Huan, F.; Shen, H.; Xiao, J.-C.; Gao, M.; Yang, X.; Murahashi, S.-I.; Chen, Q.-Y.; Guo, Y. *J. Org. Chem.* **2013**, *78*, 12525. (i) Foster, R. W.; Lenz, E. N.; Simpkins, N. S.; Stead, D. *Chem. Eur. J.* **2017**, *23*, 8810. α -Sulfonylation: (j) Yuan, T.; Yin, L.; Xu, Y. *Tetrahedron Lett.* **2017**, *58*, 2521.
- (7) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
- (8) (a) Yin, L.; Brewitz, L.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2014**, *136*, 17958. (b) Brewitz, L.; Arteaga, F. A.; Yin, L.; Alagiri, K.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2015**, *137*, 15929.
- (9) Weidner, K.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6150.
- (10) (a) Saito, A.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 5551. (b) Sun, Z.; Sun, B.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2018**, *20*, 3070.
- (11) In Cu(I)-catalyzed aldol reactions, the reactivity of the α -CF₃ enolate is somewhat lower than those with other substituents: While α -alkyl, vinyl, and N₃ 7-azaindoline amides smoothly undergo aldol additions to simple aldehydes, α -CF₃ amide **2** only reacts with activated arylglyoxal hydrates. (a) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6236. (b) Liu, Z.; Takeuchi, T.; Pluta, R.; Arteaga, F. A.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2017**, *19*, 710. (c) Takeuchi, T.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2018**, *83*, 5851. (d) Matsuzawa, A.; Noda, H.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2017**, *82*, 8304.
- (12) For the construction of a tetrasubstituted carbon by aldol reaction of an α -N₃ amide to CF₃ ketones, see: Noda, H.; Amemiya, F.; Weidner, K.; Kumagai, N.; Shibasaki, M. *Chem. Sci.* **2017**, *8*, 3260.
- (13) For recent reviews on the use of isatin imines in asymmetric catalysis, see: (a) Pellissier, H. *Beilstein J. Org. Chem.* **2018**, *14*, 1349. (b) Kaur, J.; Chimni, S. S. *Org. Biomol. Chem.* **2018**, *16*, 3328.
- (14) (a) Sun, Z.; Weidner, K.; Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2015**, *21*, 17574. (b) Arteaga, F. A.; Liu, Z.; Brewitz, L.; Chen, J.; Sun, B.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2016**, *18*, 2391.
- (15) Li, Z.; Noda, H.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2018**, *74*, 3301.
- (16) See the Supporting Information for details. CCDC 1874483 contains the supplementary crystallographic data for **3e**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
- (17) With 1 mol% catalyst, **3a** was obtained in 55% yield with the high selectivities retained (dr >95:5, 98% ee).
- (18) **Compound 3a**
A flame-dried 30 mL flask equipped with a magnetic stirring bar and 3-way glass stopcock were charged with imine **1a** (781 mg, 3.0 mmol, 1.0 equiv), and α -CF₃ amide **2** (760 mg, 3.3 mmol, 1.1 equiv), followed by the addition of anhydrous THF (9.6 mL, 0.2 M) via syringe with a stainless steel needle under an Ar atmosphere. After being stirred at 25 °C for 5 min, a solution of the catalyst in THF (4.5 mL) containing a chiral copper(I) complex (0.090 mmol, 3.0 mol%), which was prepared from [Cu(CH₃CN)₄]PF₆ (33.5 mg, 0.090 mmol) and (R,R)-Ph-BPE L8 (54.7 mg, 0.11 mmol, 3.6 mol%), and a solution of Barton's base (0.1 M in THF, 0.90 mL, 0.09 mmol, 3.0 mol%) were sequentially added via a syringe with a stainless steel needle. After stirring at 25 °C for 12 h, the reaction mixture was filtered through a pad of silica gel and washed with EtOAc, then concentrated *in vacuo* to afford the crude residue. ¹H NMR analysis of the crude

residue showed that the dr was >95:5. The combined crude residue was then purified by silica gel column chromatography (5% to 80% EtOAc in hexane) to afford product **3a** (1.46 g, 99% yield). IR (thin film): $\nu = 3371, 2943, 1721, 1653, 1426, 1256, 1164, 754 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.93\text{--}7.92$ (m, 1 H), 7.51–7.49 (m, 1 H), 7.44 (d, $J = 7.2 \text{ Hz}$, 1 H), 7.35–7.31 (m, 1 H), 7.08–7.04 (m, 2 H), 6.91 (dd, $J = 7.6 \text{ Hz}, 5.2 \text{ Hz}$, 1 H), 6.84 (d, $J = 7.6 \text{ Hz}$, 1 H), 6.31 (q, $J = 8.8 \text{ Hz}$, 1 H), 4.31–4.10 (m, 2 H), 3.15–2.99 (m, 2 H), 2.96 (s, 3 H), 1.20 (s, 9 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 174.6, 163.4, 154.8, 153.8, 145.2, 143.2, 134.3, 129.3, 127.2, 126.8, 125.4$ (d, $J = 2.5 \text{ Hz}$), 124.3 (q, $J = 281.1 \text{ Hz}$), 122.2,

119.0, 108.1, 80.0, 61.2, 48.9 (q, $J = 26.1 \text{ Hz}$), 46.0, 27.9, 26.1, 23.7. $^{19}\text{F NMR}$ (376 MHz, CDCl_3): $\delta = -57.98$ (d, $J = 8.5 \text{ Hz}$). HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{25}\text{O}_4\text{N}_4\text{F}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 513.1720; found: 513.1724. $[\alpha]_{\text{D}}^{24} -48.0$ ($c = 1.00, \text{CHCl}_3$). Enantiomeric excess of the product was determined to be 98% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (ϕ 0.46 cm \times 25 cm), 2-propanol/*n*-hexane = 1:4, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 5.9 \text{ min}$ (major), 13.2 min (minor)).

(19) The stereochemistry of **4** was assigned by NOE analysis. See the Supporting Information for details.