JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Construction of Furan Derivatives with a Trifluoromethyl Stereogenic Center: Enantioselective Friedel–Crafts Alkylations via Formal Trienamine Catalysis

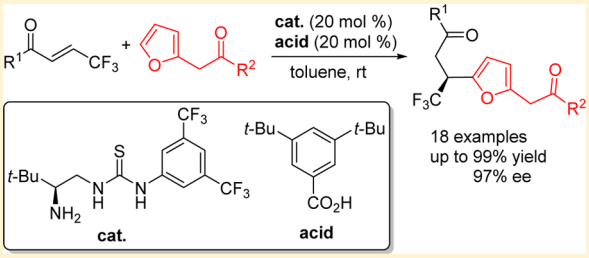
Guang-Jun Yang,[†] Wei Du,[†] and Ying-Chun Chen*[,†,‡]

[†]Key Laboratory of Drug-Targeting and Drug Delivery System of the Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

[‡]College of Pharmacy, Third Military Medical University, Shapingba, Chongqing 400038, China

Supporting Information

ABSTRACT: An asymmetric Friedel–Crafts alkylation reaction of 2-furfuryl ketones with β-trifluoromethyl enones has been developed via formal trienamine catalysis of a bifunctional primary amine-thiourea substance derived from *L-tert*-leucine, delivering the furan derivatives incorporating a stereogenic trifluoromethyl (CF_3) group in good to high yields with excellent enantioselectivity.



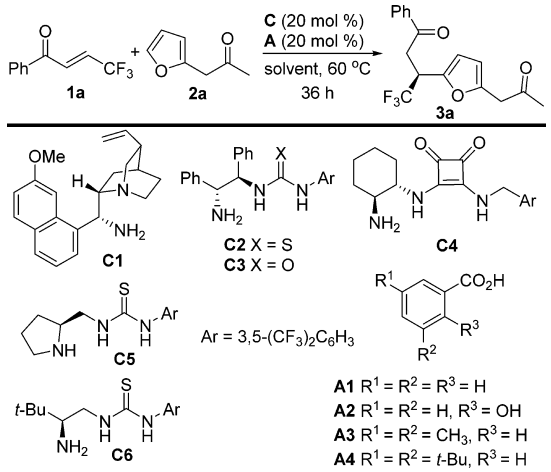
The enantioselective introduction of a trifluoromethyl group into organic molecules has attracted great attention in material and medicinal chemistry, because of the unique properties of the perfluoroalkyl group.[1] In particular, asymmetric catalysis starting from prochiral trifluoromethylated substrates seems to be a convenient and efficient strategy for the construction of the target compounds with a CF_3 stereogenic center, and fruitful results have been achieved.[2] On the other hand, asymmetric Friedel–Crafts alkylation of electron-rich arenes or heteroarenes with unsaturated substances provides a straightforward protocol to access compounds with a benzylic stereogenic center.[3] As a powerful and atom-economical method for the construction of chiral building blocks, previous strategy mainly relies on the LUMO activation of the electrophilic partners.[4] In contrast, an alternative activation mode, increasing the nucleophilicity of the aromatic compounds by raising the HOMO energy, has rarely been explored. Since the HOMO activation of carbonyl compounds via the in situ formation of enamine species has been well developed,[5] recently chemists further found that the energy transfer to aromatic systems could be effectively achieved by generating the conjugated enamine intermediates with arene substances.[6] Based on such an inspiration, our group first reported the remote enantioselective Friedel–Crafts alkylations of 2-furfuryl ketones with alkylidenemalononitriles by forming the formal trienamine intermediates,[7] giving the desired chiral products with excellent regio- and enantioselectivity.[8,9] Nevertheless, it was found that the limited substrate scope was observed, as the other tested activated alkenes generally suffered from low reactivity or poor enantioselectivity. While many natural products possessing the furan units with chiral benzylic centers exhibit antimalarial, antifeedant, or other bioactivities,[10] it would be desirable to expand our newly developed catalytic method, by incorporating the stereogenic trifluoromethyl group to furan derivatives from the highly electrophilic β-CF_3 substituted enones and 2-furfuryl ketones.

The enantioselective Friedel–Crafts alkylation was first investigated with readily available (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (**1a**) and 1-(furan-2-yl)propan-2-one (**2a**) under the catalysis of 9-amino-9-deoxyepiquinidine (**C1**) and benzoic acid (**A1**) in toluene at 60 °C (Table 1, entry 1).[11] To our delight, the desired product **3a** was obtained in 40% yield, while the enantioselectivity was poor (Table 1, entry 1). Bifunctional primary amine catalysts **C2**–**C4** significantly improved the ee values (entries 2–4), indicating that the H-bonding donor was crucial for the stereocontrol, in a concerted activation pattern as previously observed.[8] Interestingly, the *L*-proline derived secondary amine **C5**, which is usually employed for the activation of aldehydes or cyclic ketones,[12] also provided the product with good enantioselectivity (entry 5). Lowering down the temperature enhanced enantioselectivity to 91%, while a longer reaction time was needed for a better conversion (entry 6). Subsequently, the solvent effects were evaluated. 1,2-Dichloroethane (DCE), dioxane, and trifluoromethylbenzene ($PhCF_3$) only gave moderate results (entries 7–9), while mesitylene provide the best ee value with a moderate yield (entry 10). Thus, toluene was chosen with a compromise between reactivity and enantioselectivity. The acid additives were screened as well, and **A4** with a bulky substituent at *meta*-position afforded a better yield than those of others (entries 11–13). Pleasingly, a new primary amine-thiourea catalyst derived from L-*tert*-leucine (**C6**) greatly improved the reactivity of the reaction, affording an almost quantitative yield in 12 h

Received: August 8, 2016
Published: September 26, 2016

DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056–10061

Table 1. Condition Optimization of Friedel–Crafts Alkylation[a]



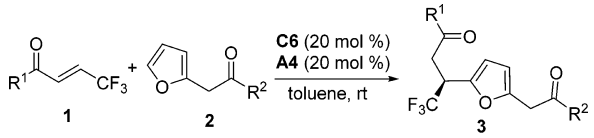
entry	cat.	acid	solvent	yield (%)[b]	ee (%)[c]
1	**C1**	**A1**	toluene	40	7
2	**C2**	**A1**	toluene	58	67
3	**C3**	**A1**	toluene	65	65
4	**C4**	**A1**	toluene	37	−41
5	**C5**	**A1**	toluene	60	73
6[d]	**C5**	**A1**	toluene	52	91
7[d]	**C5**	**A1**	DCE	38	65
8[d]	**C5**	**A1**	dioxane	41	65
9[d]	**C5**	**A1**	$PhCF_3$	41	59
10[d]	**C5**	**A1**	mesitylene	41	93
11[d]	**C5**	**A2**	toluene	14	14
12[d]	**C5**	**A3**	toluene	41	87
13[d]	**C5**	**A4**	toluene	61	91
14[e]	**C6**	**A4**	toluene	99	91
15[d,f]	**C6**	**A4**	toluene	64	86
16[d,g]	**C6**	**A4**	toluene		

[a]Unless noted otherwise, reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst **C** (0.02 mmol), acid **A** (0.02 mmol) in solvent at 60 °C for 36 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis using a chiral stationary phase. [d]At rt for 96 h. [e]At rt for 12 h. [f]With 0.04 mmol acid. [g]Without acid.

with excellent enantioselectivity (entry 14). The acid additive also played an important role in the reaction, as higher loadings resulted in decreased reactivity and enantioselectivity (entry 15), while no product was formed in the absence of the acid (entry 16).

With the optimized conditions in hand, the substrate scope was examined as shown in Table 2. At first, a variety of β-trifluoromethyl enones,[13] with a different aryl substituent at the α'-position, were applied to the Friedel–Crafts alkylations with **2a**. The substrates with an electron-deficient aryl group seemed to be more reactive than those with an electron-rich one, and all of them, as well as the one with a 2-naphthyl group, afforded the corresponding products **3b–i** in excellent yields and enantioselectivity (entries 2–9). The enones with a heteroaryl group also provided the desired products with good to excellent ee values (entries 10–12). The one possessing a styrene group showed lower reactivity, but still with high enantiocontrol (entry 13). Nevertheless, enones with an α'-alkyl group or the unsaturated ester analogues failed to participate in the reaction due to the lower electrophilicity.[14] On the other hand, a few 2-furfuryl ketones were tested with **1a**. The ketones with a larger

Table 2. Substrate Scope for the Asymmetric Friedel–Crafts Reactions of 2-Furfuryl Ketones (2) and β-Trifluoromethyl Enones (1)[a]



entry	R^1	R^2	t (h)	yield (%)[b]	ee (%)[c]
1	Ph	Me	12	**3a**, 99	91
2	2-MeC_6H_4	Me	36	**3b**, 96	93
3	3-MeC_6H_4	Me	12	**3c**, 93	93
4	4-MeC_6H_4	Me	18	**3d**, 98	97
5	2-ClC_6H_4	Me	12	**3e**,97	90
6	3-ClC_6H_4	Me	12	**3f**, 91	95
7	4-ClC_6H_4	Me	12	**3g**, 95	91
8[d]	4-$NO_2C_6H_4$	Me	48	**3h**, 97	94
9	2-naphthy	Me	12	**3i**, 97	97
10	2-pyridyl	Me	12	**3j**, 91	82
11	2-furyl	Me	12	**3k**, 91	94
12	2-thienyl	Me	19	**3l**, 98	95
13[e]	PhCH=CH	Me	24	**3m**, 74	90
14	Ph	Et	45	**3n**, 80	97
15	Ph	n-$C_{10}H_{21}$	96	**3o**, 63	96
16	Ph	$(CH_2)_2CH=CH_2$	96	**3p**, 76	95
17	Ph	Bn	96	**3q**, 62	93
18	Ph	t-$BuOCH_2$	24	**3r**, 97	87

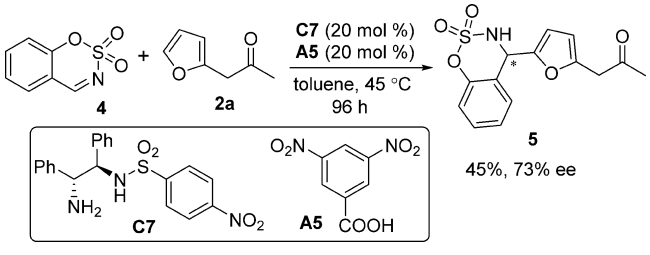
[a]Unless noted otherwise, reactions were conducted with **1** (0.1 mmol), **2** (0.15 mmol), catalyst **C6** (0.02 mmol), **A4** (0.02 mmol) in toluene at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis using a chiral stationary phase. [d]At 0 °C. [e]The absolute configuration of **3m** was determined by X-ray analysis.[14] The other products were assigned by analogy.

group, such as ethyl, or an even longer liner alkyl chain, showed decreased reactivity but with comparable enantioselectivity (entries 14–16). Other α'-substituted ketones bearing a functional group, including a benzyl or ether moiety were also compatible for the transformation, generating **3q** and **3r** in good results (entries 17 and 18).

To further expand the substrate scope, a cyclic *N*-sulfonyl ketimine **4** was also employed as the electrophile for the Mannich-type Friedel–Crafts alkylation with **2a**. In this case, the combination of a bifunctional catalyst **C7** and acid **A5** showed better catalytic efficacy after extensive screenings, while the product **5** was obtained with a fair yield with moderate enantioselectivity (Scheme 1).

In conclusion, we have developed an efficient and enantioselective Friedel–Crafts alkylation reaction between β-

Scheme 1. Asymmetric Friedel–Crafts Reactions of 2a with Cyclic *N*-Sulfonyl Ketimine 4



DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056–10061

trifluoromethyl enones and 2-furfuryl ketones in the presence of a bifunctional primary amine-thiourea via HOMO activation strategy. A variety of highly enantioenriched furan derivatives containing a trifluoromethyl stereogenic center were produced in good to excellent yields. Such an activation strategy for aromatic systems might be further applied in organic synthesis in the future.

EXPERIMENTAL SECTION

General Procedures. NMR data were obtained for ^{1}H NMR at 400 or 600 MHz and for ^{13}C NMR at 100 or 150 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. Mass spectra were recorded using ESI as the method of ionization. ESI-HRMS spectra were measured with a QTOF instrument. In each case, enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase in comparison with authentic racemate, UV detection was monitored at 220 or 254 nm. Optical rotation data were examined at 589 nm in $CHCl_3$ solution at 20 °C. Column chromatography was performed on silica gel (200−300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and I_2 were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted.

β-Trifluoromethyl enones **1**,[15] 2-furfuryl ketones **2**,[8] and imine **4**[16] were prepared according to the literature procedures.

Procedure for the Synthesis of (*S*)-1-(2-Amino-3,3-dimethylbutyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (C6). To a solution of (*S*)-2-amino-3,3-dimethylbutan-1-ol[17] (4.5 g, 43.7 mmol) and triethylamine (18 mL, 130.1 mmol) in CH_2Cl_2 (50 mL) was added $(Boc)_2O$ (10.5 g, 48.1 mmol) at 0 °C. The mixture was stirred at room temperature until the consumption of (*S*)-2-amino-3,3-dimethylbutan-1-ol (monitored by TLC analysis). Then the mixture was concentrated in vacuo and purified through flash chromatography on silica gel. According to the reported procedure,[18] the *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate was obtained. Isothiocyanato-3,5-bis(trifluoromethyl)benzene (2.70 g, 10.0 mmol) was added to a stirred solution of the chiral amine (2.2 g, 10.2 mmol) in CH_2Cl_2 (25 mL) for 30 min at 0 °C and for 2 h at room temperature. The solvent was removed and the residue was dissolved in CF_3COOH:CH_2Cl_2 = 1:1 (5 mL:5 mL), and the mixture was stirred until the reaction was completed (monitored by TLC analysis). The mixture was diluted with CH_2Cl_2 (20 mL) and adjusted pH to 8 with saturated sodium bicarbonate solution. The organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:MeOH = 30:1) gave product **C6** in 57% yield (for two steps), 2.2 g, light yellow solid, mp 52−55 °C, $[\alpha]_D^{20}$ = −14.3 (*c* = 10.45 in $CHCl_3$), ^{1}H NMR (400 MHz, CD_3OD) *δ* 8.22 (s, 2H), 7.60 (s, 1H), 3.99 (bs, 1H), 3.33−3.27 (m, 1H), 2.74, 2.72 (d, *J* = 7.2 Hz, 1H), 0.97 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD_3OD) *δ* 185.2, 145.5, 134.8 (q, $J_{(C-F)}$ = 33.3 Hz), 126.9 (q, $J_{(C-F)}$ = 270.4 Hz), 125.9, 119.9, 63.3, 49.9, 37.0, 28.8 ppm; IR (CH_2Cl_2) *ν* 3262, 2964, 2873, 1602, 1538, 1472, 1275, 1229, 1173, 1131 (cm^{-1}); ESI HRMS: calcd. For $[C_{15}H_{19}F_6N_3S + H^+]$ 388.1277, found 388.1275.

General Procedure for Asymmetric Friedel−Crafts Alkylations. The reaction was carried out with trifluoromethyl-containing electrophile **1** or **4** (0.1 mmol) and 2-furfuryl ketone **2** (0.15 mmol) in toluene (1.0 mL) in the presence of primary amine catalyst **C6** (7.74 mg, 0.02 mmol), 3,5-di-*tert*-butylenzoic acid **A4** (4.68 mg, 0.02 mmol) at room temperature or 0 °C for 12 to 96 h. After completion, the solution was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 30:1 to 10:1) to afford the chiral product **3** or **4**.

The racemic products were prepared following the general procedure, using a racemic 1-(2-amino-1,2-diphenylethyl)-3-(4-fluorophenyl)thiourea compound as the catalyst.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-phenylbutan-1-one (**3a**).* R_f = 0.31 (petroleum ether:ethyl acetate = 10:1), 99% yield, 16.0 mg, light yellow oil, $[\alpha]_D^{20}$ = −20.2 (*c* = 4.65 in $CHCl_3$), 91% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{major} = 10.92 min, t_{minor} = 15.51 min); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 6.30 (d, *J* = 3.0 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 4.39−4.36 (m, 1H), 3.74 (dd, *J* = 17.4 Hz, *J* = 9.6 Hz, 1H), 3.63 (s, 2H), 3.45 (dd, *J* = 18.0 Hz, *J* = 4.2 Hz, 1H), 2.06 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 203.9, 194.9, 148.6, 147.1, 136.1, 133.7, 128.8, 128.1, 125.6 (q, $J_{(C-F)}$ = 278.2 Hz), 110.5, 119.4, 43.2, 39.1 (q, $J_{(C-F)}$ = 28.9 Hz), 35.8, 28.9 ppm; IR (CH_2Cl_2) *ν* 2920, 2850, 1716, 1691, 1597, 1463, 1106, 1154, 1262 (cm^{-1}); ESI HRMS: calcd. For $[C_{17}H_{15}F_3O_3 + Na^+]$ 347.0866, found 347.0872.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-(o-tolyl)butan-1-one (**3b**).* R_f = 0.35 (petroleum ether:ethyl acetate = 8:1), 96% yield, 32.4 mg, light yellow oil, $[\alpha]_D^{20}$ = −7.2 (*c* = 6.55 in $CHCl_3$), 93% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{major} = 9.30 min, t_{minor} = 11.03 min); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31−7.24 (m, 2H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 4.36−4.30 (m, 1H), 3.66−3.59 (m, 3H), 3.40 (dd, *J* = 17.6 Hz, *J* = 4.0 Hz, 1H), 2.41 (s, 3H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 203.9, 198.6, 148.6, 147.2, 138.6, 136.8, 132.1, 131.9, 128.4, 125.9, 125.6 (q, $J_{(C-F)}$ = 278.2 Hz), 110.5, 109.4, 43.2, 39.3 (q, $J_{(C-F)}$ = 29.2 Hz), 38.5, 29.0, 21.2 ppm; IR (CH_2Cl_2) *ν* 2923, 2853, 1719,1689, 1590, 1459, 1421, 1263, 1156, 1110, 758 (cm^{-1}); ESI HRMS: calcd. for $[C_{18}H_{17}F_3O_3 + Na^+]$ 361.1022, found 361.1033.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-(m-tolyl)-butan-1-one (**3c**).* R_f = 0.35 (petroleum ether:ethyl acetate = 8:1), 93% yield, 31.2 mg, light yellow oil, $[\alpha]_D^{20}$ = −17.9 (*c* = 8.00 in $CHCl_3$), 93% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 5.59 min, t_{minor} = 6.76 min); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.75 (m, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 6.30 (d, *J* = 3.0 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 4.39−4.35 (m, 1H), 3.72 (dd, *J* = 17.4 Hz, *J* = 9.6 Hz, 1H), 3.63 (s, 2H), 3.43 (dd, *J* = 17.4 Hz, *J* = 3.6 Hz, 1H), 2.42 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 203.9, 195.1, 148.6, 147.2, 138.6, 136.1, 134.5, 128.6, 128.6, 125.7 (q, $J_{(C-F)}$ = 278.6 Hz), 125.3, 110.5, 109.3, 43.2, 39.1 (q, $J_{(C-F)}$ = 29.1 Hz), 35.9, 28.9, 21.3 ppm; IR (CH_2Cl_2) *ν* 2921, 2850, 1717, 1687, 1604, 1422, 1262, 1152, 1105, 888, 789, 694 (cm^{-1}); ESI HRMS: calcd. for $[C_{18}H_{17}F_3O_3 + Na^+]$ 361.1022, found 361.1039.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-(p-tolyl)butan-1-one (**3d**).* R_f = 0.16 (petroleum ether:ethyl acetate = 10:1), 98% yield, 34.0 mg, yellow oil, $[\alpha]_D^{20}$ = −35.3 (*c* = 4.70 in $CHCl_3$), 97% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, UV 220 nm, t_{major} = 7.38 min, t_{minor} = 9.08 min); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.86 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 4.41−4.32 (m, 1H), 3.72 (dd, *J* = 17.6 Hz, *J* = 9.6 Hz, 1H), 3.62 (s, 2H), 3.42 (dd, *J* = 17.6 Hz, *J* = 3.2 Hz, 1H), 2.42 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 204.0, 194.5, 148.5, 147.2, 144.6, 133.6, 129.4, 128.2 125.7 (q, $J_{(C-F)}$ = 277.8 Hz), 110.5, 109.4, 43.2, 39.1 (q, $J_{(C-F)}$ = 29.6 Hz), 35.6, 28.9, 21.7 ppm; IR (CH_2Cl_2) *ν* 3033, 2924, 1717, 1686, 1607, 1512, 1418, 1263, 1156, 1107, 817 (cm^{-1}); ESI HRMS: calcd. for $[C_{18}H_{17}F_3O_3 + Na^+]$ 361.1022, found 361.1021.

*(S)-1-(2-Chlorophenyl)-4,4,4-trifluoro-3-(5-(2-oxopropyl)furan-2-yl)butan-1-one (**3e**).* R_f = 0.18 (petroleum ether:ethyl acetate = 10:1), 97% yield, 34.6 mg, light yellow oil, $[\alpha]_D^{20}$ = +0.4 (*c* = 8.45 in $CHCl_3$), 90% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, UV 220 nm, t_{major} = 8.47 min, t_{minor} = 9.42 min); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.43−7.40 (m, 3H), 7.36−7.31 (m, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 4.36−4.26 (m, 1H), 3.71−3.65 (m, 3H), 3.50 (dd, *J* = 17.6 Hz, *J* = 4.0 Hz, 1H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 203.8, 198.0, 148.7, 146.7, 138.2, 132.4, 131.0, 130.7, 129.2, 127.1, 125.4 (q, $J_{(C-F)}$ = 278.2 Hz), 110.7, 109.4, 43.2, 40.2, 39.4 (q, $J_{(C-F)}$ = 29.4 Hz),

DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056−10061

29.0 ppm; IR (CH_2Cl_2) ν 2921, 2851, 1713, 1590, 1470, 1262, 1153, 1107,759 (cm^{-1}); ESI HRMS: calcd. for [$C_{17}H_{14}{}^{35}ClF_3O_3$ + Na^+] 381.0476, found 381.0494.

*(S)-1-(3-Chlorophenyl)-4,4,4-trifluoro-3-(5-(2-oxopropyl)furan-2-yl)butan-1-one (**3f**).* R_f = 0.22 (petroleum ether:ethyl acetate = 10:1), 91% yield, 32.7 mg, colorless oil, $[\alpha]_D{}^{20}$ = −19.2 (*c* = 8.70 in $CHCl_3$), 95% ee,determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 6.79 min, t_{minor} = 9.60 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 4.40−4.30 (m, 1H), 3.71 (dd, *J* = 17.6 Hz, *J* = 9.6 Hz, 1H), 3.64 (s, 2H), 3.43 (dd, *J* = 17.6 Hz, *J* = 4.0 Hz, 1H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 193.8, 148.7, 146.9, 137.6, 135.2, 133.6, 130.1, 128.2, 126.2, 125.5 (q, $J_{(C-F)}$ = 278.2 Hz), 110.6, 109.4, 43.2, 39.1(q, $J_{(C-F)}$ = 29.3 Hz), 36.0, 29.0 ppm; IR (CH_2Cl_2) ν 3071, 2925, 2854, 1717, 1693, 1570,1519, 1422, 1264, 1159, 1111, 888, 792, 682 (cm^{-1}); ESI HRMS: calcd. for [$C_{17}H_{14}{}^{35}ClF_3O_3$ + Na^+] 381.0476, found 381.0473.

*(S)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-(5-(2-oxopropyl)furan-2-yl)butan-1-one (**3g**).* R_f = 0.22 (petroleum ether:ethyl acetate = 10:1), 95% yield, 17.0 mg, light yellow oil, $[\alpha]_D{}^{20}$ = −39.0 (*c* = 3.90 in $CHCl_3$), 91% ee, determined by HPLC analysis (Daicel Chiralpak IE, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{minor} = 12.85 min, t_{major} = 17.31 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 4.40−4.30 (m, 1H), 3.70 (dd, *J* = 17.6 Hz, *J* = 9.6 Hz, 1H), 3.64 (s, 2H), 3.42 (dd, *J* = 17.6 Hz, *J* = 3.6 Hz, 1H), 2.08 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8, 193.8, 148.6, 146.9, 140.3, 134.4, 129.5, 129.1, 125.7 (q, $J_{(C-F)}$ = 278.3 Hz), 110.6, 109.4, 43.2, 39,1 (q, $J_{(C-F)}$ = 29.0 Hz), 35.8, 28.9 ppm; IR (CH_2Cl_2) ν 2923, 2852, 1717, 1687, 1590, 1518, 1261, 1155, 1107, 831 (cm^{-1}); ESI HRMS: calcd. for [$C_{17}H_{14}{}^{35}ClF_3O_3$ + Na^+] 381.0476, found 381.0489.

*(S)-4,4,4-Trifluoro-1-(4-nitrophenyl)-3-(5-(2-oxopropyl)furan-2-yl)butan-1-one (**3h**).* R_f = 0.13 (petroleum ether:ethyl acetate = 10:1), 97% yield, 35.7 mg, light yellow oil, $[\alpha]_D{}^{20}$ = −15.8 (*c* = 6.65 in $CHCl_3$), 94% ee, determined by HPLC analysis (Daicel Chiralpak IE, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{minor} = 13.37 min, t_{major} = 15.19 min), ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 2H), 6.33 (d, *J* = 3.2 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 4.39−4.32 (m, 1H), 3.77 (dd, *J* = 18.0 Hz, *J* = 9.6 Hz, 1H), 3.65 (s, 2H), 3.50 (dd, *J* = 18.0 Hz, *J* = 3.6 Hz, 1H), 2.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 193.7, 150.6, 148.8, 146.5, 140.3, 129.2, 125.4 (q, $J_{(C-F)}$ = 278.2 Hz), 124.0, 110.8, 109.5, 43.1, 39.1 (q, $J_{(C-F)}$ = 29.4 Hz), 36.5, 29.0 ppm; IR (CH_2Cl_2) ν 2921, 2851, 1737, 1701, 1527, 1492, 1463, 1362, 1261, 1157, 1107, 854 (cm^{-1}); ESI HRMS: calcd. for [$C_{17}H_{14}F_3NO_5$ + Na^+] 392.0716, found 392.0721.

*(S)-4,4,4-Trifluoro-1-naphthalen-2-yl)-3-(5-(2-oxopropyl)furan-2-yl)butan-1-one (**3i**).* R_f = 0.33 (petroleum ether:ethyl acetate = 10:1), 97% yield, 18.2 mg, light yellow oil, $[\alpha]_D{}^{20}$ = −59.0 (*c* = 7.70 in $CHCl_3$), 97% ee, determined by HPLC analysis (Daicel Chiralpak IE, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{minor} = 8.33 min, t_{major} = 9.78 min); ^1H NMR (600 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.00−7.98 (m, 2H), 7.91−7.87 (m, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 4.47−4.40 (m, 1H), 3.89 (dd, *J* = 17.4 Hz, *J* = 9.6 Hz, 1H), 3.62 (s, 2H), 3.58 (dd, *J* = 17.4 Hz, *J* = 3.6 Hz, 1H), 2.05 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.9, 194.9, 148.6, 147.2, 135.8, 133.4, 132.4, 130.0, 129.6, 128.8, 128.7, 127.8, 127.0, 125.7 (q, $J_{(C-F)}$ = 278.1 Hz), 123.5, 110.6, 109.4, 43.2, 39.2 (q, $J_{(C-F)}$ = 29.3 Hz), 35.9, 28.9 ppm; IR (CH_2Cl_2) ν 3062, 2924, 2853, 1719, 1684, 1627, 1518, 1467, 1263, 1158, 1109 (cm^{-1}); ESI HRMS: calcd. for [$C_{21}H_{17}F_3O_3$ + Na^+] 397.1022, found 397.1030.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-(pyridin-2-yl)-butan-1-one (**3j**).* R_f = 0.08 (petroleum ether:ethyl acetate = 10:1), 91% yield, 29.2 mg, brown oil, $[\alpha]_D{}^{20}$ = −37.6 (*c* = 9.25 in $CHCl_3$), 82% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{major} = 11.65 min, t_{minor} = 13.23 min); ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.4 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 4.4 Hz, 1H), 6.31 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 4.41−4.31 (m, 1H), 4.08 (dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), 3.69 (dd, *J* = 18.4 Hz, *J* = 4.0 Hz, 1H), 3.63 (s, 2H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 197.0, 152.5, 149.1, 148.5, 147.6, 137.0, 127.6, 125.6 (q, $J_{(C-F)}$ = 278.1 Hz), 122.0, 110.3, 109.3, 43.2, 39.0 (q, $J_{(C-F)}$ = 29.2 Hz), 35.4, 28.9 ppm; IR (CH_2Cl_2) ν 2922, 2852, 1704, 1682, 1584, 1518, 1439, 1260, 1178, 1109 (cm^{-1}); ESI HRMS: calcd. for [$C_{16}H_{14}F_3NO_3$ + Na^+] 348.0818, found 348.0818.

*(S)-4,4,4-Trifluoro-1-(furan-2-yl)-3-(5-(2-oxopropyl)furan-2-yl)-butan-1-one (**3k**).* R_f = 0.20 (petroleum ether:ethyl acetate = 10:1), 91% yield, 28.7 mg, colorless oil, $[\alpha]_D{}^{20}$ = −41.7 (*c* = 7.10 in $CHCl_3$), 94% ee, determined by HPLC analysis (Daicel Chiralpak IE, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{minor} = 8.25 min, t_{major} = 9.33 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.25 (d, *J* = 3.2 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 4.37−4.27 (m, 1H), 3.64−3.56 (m, 3H), 3.32 (dd, *J* = 17.2 Hz, *J* = 4.0 Hz, 1H), 2.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 184.0, 152.0, 148.7, 146.9, 125.5 (q, $J_{(C-F)}$ = 278.1 Hz), 117.8, 112.6, 110.6, 109.3, 43.2, 38.7 (q, $J_{(C-F)}$ = 29.5 Hz), 35.6, 28.9 ppm; IR (CH_2Cl_2) ν 2922, 2852, 1717, 1665, 1517, 1463, 1261, 1156, 1108 (cm^{-1}); ESI HRMS: calcd. for [$C_{15}H_{13}F_3O_4$ + Na^+] 337.0658, found 337.0661.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxopropyl)furan-2-yl)-1-(thiophen-2-yl)butan-1-one (**3l**).* R_f = 0.23 (petroleum ether:ethyl acetate = 8:1), 98% yield, 32.3 mg, light yellow oil, $[\alpha]_D{}^{20}$ = −28.7 (*c* = 9.10 in $CHCl_3$), 95% ee, determined by HPLC analysis (Daicel Chiralpak IE, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{minor} = 8.04 min, t_{major} = 9.42 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 3.2 Hz, 1H), 7.69 (d, *J* = 4.8 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 6.31 (d, *J* = 2.8 Hz, 1H), 6.15 (d, *J* = 2.8 Hz, 1H), 4.39−4.29 (m, 1H), 3.69−3.63 (m, 3H), 3.39 (dd, *J* = 16.8 Hz, *J* = 3.6 Hz, 1H), 2.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 187.8, 148.7, 146.8, 143.1, 134.6, 132.5, 128.3, 125.9, 125.5 (q, $J_{(C-F)}$ = 278.3 Hz), 110.7, 109.4, 43.2, 39.2 (q, $J_{(C-F)}$ = 29.4 Hz), 36.3, 28.9 ppm; IR (CH_2Cl_2) ν 2920, 2851, 1716, 1664, 1518, 1463, 1262, 1156, 1108 (cm^{-1}); ESI HRMS: calcd. for [$C_{15}H_{13}F_3O_3S$ + Na^+] 353.0430, found 353.0435.

*(S,E)-6,6,6-Trifluoro-5-(5-(2-oxopropyl)furan-2-yl)-1-phenylhex-1-en-3-one (**3m**).* R_f = 0.18 (petroleum ether:ethyl acetate = 10:1), 74% yield, 26.0 mg, white solid, mp 66−68 °C, $[\alpha]_D{}^{20}$ = −59.3 (*c* = 11.15 in $CHCl_3$), 90% ee, determined by HPLC analysis (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{major} = 15.24 min, t_{minor} = 18.77 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.58−7.55 (m, 2H), 7.42−7.41 (m, 3H), 6.74 (d, *J* = 16.4 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 4.33−4.23 (m, 1H), 3.65 (s, 2H), 3.41 (dd, *J* = 17.6 Hz, *J* = 9.6 Hz, 1H), 3.19 (dd, *J* = 17.6 Hz, *J* = 3.6 Hz, 1H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 194.7, 148.6, 147.1, 143.9, 133.9, 130.9, 129.0, 128.4, 125.6 (q, $J_{(C-F)}$ = 278.2 Hz), 125.3, 110.5, 109.3, 43.2, 39.0 (q, $J_{(C-F)}$ = 29.2 Hz), 37.7, 29.0 ppm; IR (CH_2Cl_2) ν 3060, 2925, 2855, 1719, 1613, 1495, 1450, 1264, 1158, 1108, 978 (cm^{-1}); ESI HRMS: calcd. for [$C_{19}H_{17}F_3O_3$ + Na^+] 373.1022, found 373.1035.

*(S)-4,4,4-Trifluoro-3-(5-(2-oxobutyl)furan-2-yl)-1-phenylbutan-1-one (**3n**).* R_f = 0.16 (petroleum ether:ethyl acetate = 10:1), 80% yield, 27.0 mg, yellow oil, $[\alpha]_D{}^{20}$ = −29.9 (*c* = 5.65 in $CHCl_3$), 97% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, UV 220 nm, t_{major} = 8.79 min, t_{minor} = 12.05 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 4.42−4.32 (m, 1H), 3.76 (dd, *J* = 18.0 Hz, *J* = 10.0 Hz, 1H), 3.63 (s, 2H), 3.44 (dd, *J* = 18.0 Hz, *J* = 3.6 Hz, 1H), 2.40−2.32 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 195.0, 148.7, 147.0, 136.0, 133.7, 128.8, 128.1, 125.7 (q, $J_{(C-F)}$ = 278.0 Hz),, 110.5, 109.3, 42.2, 39.1 (q, $J_{(C-F)}$ = 29.2 Hz), 35.8, 34.9, 7.5 ppm; IR (CH_2Cl_2) ν 2958, 2925, 2854, 1731, 1688, 1493, 1460, 1262, 1183 (cm^{-1}); ESI HRMS: calcd. for [$C_{18}H_{17}F_3O_3$ + Na^+] 361.1022, found 361.1024.

*(S)-1-(5-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl)furan-2-yl)-dodecan-2-one (**3o**).* R_f = 0.38 (petroleum ether:ethyl acetate = 10:1), 63% yield, 28.7 mg, colorless oil, $[\alpha]_D{}^{20}$ = −15.3 (*c* = 12.45 in $CHCl_3$), 96% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-

DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056−10061

hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 4.76 min, t_{minor} = 5.67 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 6.30 (d, J = 3.2 Hz, 1H), 6.14 (d, J = 3.2 Hz, 1H), 4.42−4.32 (m, 1H), 3.74 (dd, J = 17.6 Hz, J = 9.6 Hz, 1H), 3.62 (s, 2H), 3.45 (dd, J = 17.6 Hz, J = 3.6 Hz, 1H), 2.33 (td, J = 7.2 Hz, J = 3.2 Hz, 2H), 1.50−1.43 (m, 2H), 1.23 (bs, 16H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 194.9, 148.7, 147.0, 136.1, 133.7, 128.8, 128.1, 125.7 (q, $J_{(C-F)}$ = 278.0 Hz), 110.5, 109.3, 42.5, 41.7, 39.1 (q, $J_{(C-F)}$ = 29.2 Hz), 35.8, 31.9, 29.5, 29.4, 29.3, 29.3, 29.0, 23.5, 22.7, 14.1 ppm; IR (CH_2Cl_2) ν 2923, 2853, 1736, 1687, 1589, 1495, 1448, 1262, 1162, 1111 (cm^{-1}); ESI HRMS: calcd. for [$C_{26}H_{33}F_3O_3$ + Na^+] 473.2274, found 473.2279.

(S)-1-(5-(1,1,1-Trifluoro-4-oxo-4-phenylbutan-2-yl)furan-2-yl)-hex-5-en-2-one (**3p**). R_f = 0.17 (petroleum ether:ethyl acetate = 10:1), 76% yield, 27.7 mg, colorless oil, $[\alpha]_D^{20}$ = −18.8 (c = 11.35 in $CHCl_3$), 95% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 5.73 min, t_{minor} = 7.03 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 6.30 (d, J = 3.2 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 5.75−5.65 (m, 1H), 4.97−4.91 (m, 1H), 4.40−4.32 (m, 1H), 3.74 (dd, J = 18.0 Hz, J = 10.0 Hz, 1H), 3.63 (s, 2H), 3.45 (dd, J = 18.0 Hz, J = 3.6 Hz, 1H), 2.45 (td, J = 7.6 Hz, J = 4.0 Hz 2H), 2.23 (q, J = 6.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 194.9, 148.5, 147.1, 136.7, 136.0, 133.7, 128.8, 128.1, 125.7 (q, $J_{(C-F)}$ = 278.1 Hz), 115.2, 110.5, 109.4, 42.6, 40.6, 39.1 (q, $J_{(C-F)}$ = 29.1 Hz), 35.8, 27.4 ppm; IR (CH_2Cl_2) ν 2922, 2852, 1736, 1685, 1597, 1518, 1450, 1260, 1159, 1111, 963, 909 (cm^{-1}); ESI HRMS: calcd. for [$C_{20}H_{19}F_3O_3$ + Na^+] 387.1179, found 387.1181.

(S)-4,4,4-Trifluoro-3-(5-(2-oxo-3-phenylpropyl)furan-2-yl)-1-phenylbutan-1-one (**3q**). R_f = 0.25 (petroleum ether:ethyl acetate = 10:1), 62% yield, 24.6 mg, light yellow oil, $[\alpha]_D^{20}$ = −13.8 (c = 6.90 in $CHCl_3$), 93% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 11.27 min, t_{minor} = 14.22 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.30−7.22 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 6.31 (d, J = 3.2 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 4.43−4.33 (m, 1H), 3.76−3.68 (m, 3H), 3.65 (s, 2H), 3.46 (dd, J = 18.0 Hz, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 194.9, 148.2, 147.1, 136.0, 133.7, 129.4, 128.8, 128.6, 128.1, 127.1, 123.1 (q, $J_{(C-F)}$ = 229.2 Hz), 110.5, 109.6, 48.6, 41.7, 39.1 (q, $J_{(C-F)}$ = 29.0 Hz), 35.8 ppm; IR (CH_2Cl_2) ν 2922, 2852, 1724, 1691, 1597, 1495, 1450, 1262, 1157, 1108 (cm^{-1}); ESI HRMS: calcd. for [$C_{23}H_{19}F_3O_3$ + Na^+] 423.1179, found 423.1177.

(S)-3-(5-(3-(tert-Butoxy)-2-oxopropyl)furan-2-yl)-4,4,4-trifluoro-1-phenylbutan-1-one (**3r**). R_f = 0.16 (petroleum ether:ethyl acetate = 10:1), 97% yield, 38.4 mg, colorless oil, $[\alpha]_D^{20}$ = −14.8 (c = 13.10 in $CHCl_3$), 87% ee, determined by HPLC analysis (Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{major} = 6.91 min, t_{minor} = 8.65 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 6.30 (d, J = 3.2 Hz, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.40−4.34 (m, 1H), 3. 98 (s, 2H), 3.79 (s, 2H), 3.72 (dd, J = 17.6 Hz, J = 9.2 Hz, 1H), 3.46 (dd, J = 17.6 Hz, J = 4.0 Hz, 1H), 1.16 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 194.9, 148.1, 146.9, 136.1, 133.7, 128.7, 128.1, 125.7 (q, $J_{(C-F)}$ = 278.1 Hz), 110.5, 109.4, 74.2, 67.6, 39.0 (q, $J_{(C-F)}$ = 29.2 Hz), 39.0, 35.9, 27.1 ppm; IR (CH_2Cl_2) ν 2920, 2851, 1733, 1689, 1597, 1450, 1261, 1155, 1106, 1021, (cm^{-1}); ESI HRMS: calcd. for [$C_{21}H_{23}F_3O_4$ + Na^+] 419.1141, found 419.1142.

1-(5-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)-furan-2-yl)propan-2-one (**5**). R_f = 0.18 (petroleum ether:ethyl acetate = 10:1), 45% yield, 13.7 mg, yellow oil, $[\alpha]_D^{20}$ = +27.1 (c = 14.20 in $CHCl_3$), 73% ee, determined by HPLC analysis (Daicel Chiralpak AD, *n*-hexane/*i*-PrOH = 80/20, 1 mL/min, UV 220 nm, t_{minor} = 15.71 min, t_{major} = 18.00 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 6.26 (d, J = 2.8 Hz, 1H), 5.96 (d, J = 8.0 Hz, 1H), 5.27 (bs, 1H), 3.71 (s, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 151.2, 149.9, 148.2, 130.1, 127.5, 125.2, 119.5, 118.9, 112.1, 109.5, 55.2, 42.9, 29.3 ppm; IR (CH_2Cl_2) ν 2922, 2852, 1711, 1581, 1452, 1326, 1166, 1205, 1099, (cm^{-1}); ESI HRMS: calcd. for [$C_{14}H_{13}NO_5S$ + Na^+] 330.0407, found 330.0411.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01950.

Characterization data (including ^{1}H and ^{13}C NMR spectra and HPLC chromatograms) for catalyst **C6**, products **3** and **5** (PDF)

Single crystal data of product **3m** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*ycchen@scu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the NSFC (21125206, 21372160, and 21321061).

■ REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Hoboken, NJ, 2008. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (e) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (g) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009. (h) Lin, G.-Q.; You, Q.-D.; Cheng, J.-F. *Chiral Drugs: Chemistry and Biological Action*; Wiley-VCH: Hoboken, 2011. (i) 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.

(2) For selected reviews, see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (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) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Synthesis* **2012**, 1591. (e) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135.

(3) For selected examples of asymmetric Friedel−Crafts alkylations for the construction of trifluromethylated stereogenic centers, see: (a) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086. (b) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127. (c) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983. (d) Wu, H.; Liu, R.-R.; Shen, C.; Zhang, M.-D.; Gao, J.; Jia, Y.-X. *Org. Chem. Front.* **2015**, *2*, 124. (e) Xiang, B.; Xu, T.-F.; Wu, L.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *J. Org. Chem.* **2016**, *81*, 3929.

(4) (a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (b) Bandini, M.; Umani-Bonchi, A. *Catalytic Asymmetric Friedel−Crafts Alkylations*; Wiley-VCH: Weinheim, 2009. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (d) Terrasson, V.; Marcia de Figueiredo, R.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, *2010*, 2635. (e) Scheffler, U.; Mahrwald, R. *Chem. - Eur. J.* **2013**, *19*, 14346.

(5) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860.

(6) (a) Jiang, H.; Rodríguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10271. (b) Rodríguez-Escrich, C.; Davis, R. L.; Jiang, H.; Stiller, J.; Johansen, T. K.; Jørgensen, K. A. *Chem. - Eur. J.* **2013**, *19*, 2932. (c) Xiao, Y.-C.; Yue, C.-Z.; Chen, P.-Q.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 3208.

DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056−10061

(7) For selected reviews, see: (a) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491. (b) Arceo, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5290. (c) Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (d) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709.
(8) Li, J.-L.; Yue, C.-Z.; Chen, P.-Q.; Xiao, Y.-C.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5449.
(9) Skrzyńska, A.; Przydacz, A.; Albrecht, Ł. *Org. Lett.* **2015**, *17*, 5682.
(10) (a) Thomas, A. F.; Dubini, R. *Helv. Chim. Acta* **1974**, *57*, 2066. (b) Itokawa, H.; Morita, H.; Kobayashi, T.; Watanabe, K.; Iitaka, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2860. (c) Rueda, A.; Zubía, E.; Ortega, M. J.; Carballo, J. L.; Salvá, J. *J. Org. Chem.* **1997**, *62*, 1481. (d) Posner, G. H.; Parker, M. H.; Northrop, J.; Elias, J. S.; Ploypradith, P.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 300. (e) Qiu, Y.; Deng, Z.; Pei, Y.; Fu, H.; Li, J.; Proksch, P.; Lin, W. *J. Nat. Prod.* **2004**, *67*, 921.
(11) Please see the Supporting Information for more screening conditions.
(12) (a) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (b) Cao, C.-L.; Zhou, Y.-Y.; Zhou, J.; Sun, X.-L.; Tang, Y.; Li, Y.-X.; Li, G.-Y.; Sun, J. *Chem. - Eur. J.* **2009**, *15*, 11384. (c) Xiao, W.; Yin, X.; Zhou, Z.; Du, W.; Chen, Y.-C. *Org. Lett.* **2016**, *18*, 116.
(13) (a) Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Chem. - Eur. J.* **2010**, *16*, 9117. (b) Marrec, O.; Christophe, C.; Billard, T.; Langlois, B.; Vors, J.-P.; Pazenok, S. *Adv. Synth. Catal.* **2010**, *352*, 2825. (c) Kawai, H.; Kitayama, T.; Tokunaga, E.; Matsumoto, T.; Sato, H.; Shiro, M.; Shibata, N. *Chem. Commun.* **2012**, *48*, 4067. (d) Kawai, H.; Sugita, Y.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Chem. Commun.* **2012**, *48*, 3632. (e) Davies, A. T.; Taylor, J. E.; Douglas, J.; Collett, C. J.; Morrill, L. C.; Fallan, C.; Slawin, A. M.; Churchill, G.; Smith, A. D. *J. Org. Chem.* **2013**, *78*, 9243. (f) Morigaki, A.; Tanaka, T.; Miyabe, T.; Ishihara, T.; Konno, T. *Org. Biomol. Chem.* **2013**, *11*, 586. (g) Morigaki, A.; Tsukade, K.; Arimitsu, S.; Konno, T.; Kubota, T. *Tetrahedron* **2013**, *69*, 1521. (h) Sanz-Marco, A.; García-Ortiz, A.; Blay, G.; Pedro, J. R. *Chem. Commun.* **2014**, *50*, 2275.
(14) For more details, see the Supporting Information.
(15) Marrec, O.; Borrini, J.; Billard, T.; Langlois, B. R. *Synlett* **2009**, 1241.
(16) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762.
(17) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362.
(18) Busacca, C. A.; Grossbach, D.; Spinelli, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1907.

DOI: 10.1021/acs.joc.6b01950
J. Org. Chem. 2016, 81, 10056−10061