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Enantioselective Fluorination of α-Branched β-Ynone Esters Using a Cinchona-Based Phase-Transfer Catalyst

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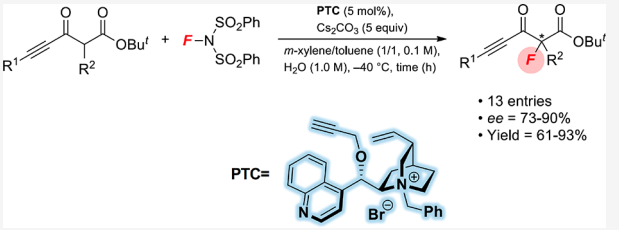
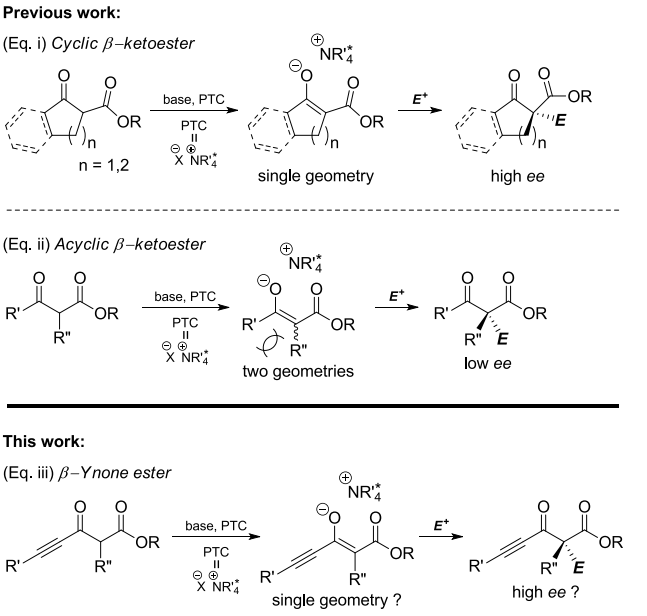
ABSTRACT: Herein, we report the fluorination of α-branched β-ynone esters to afford their corresponding quaternary fluorinated products with good enantioselectivity (ee = 73−90%) using a cinchona-based phase-transfer catalyst. α-Branched β-ynone esters possess a highly acidic α-proton and form their corresponding enolate as a single isomer, which allows the enantioselective fluorination reaction to occur under standard cinchona-based phase-transfer catalyst conditions. Moreover, the obtained α-fluorinated product can be treated with [(SPhos)AuNTf$_2$] (1 mol %) to afford a fluorinated 3,5-diketo carboxylic acid.



Asymmetric reactions using a phase-transfer catalyst (PTC) are one of the most important organocatalytic reactions reported to date because a wide variety of these reactions can be conducted under environmentally friendly conditions.[1] Activated methylene compounds are suitable nucleophiles in PTC reactions because their highly acidic α-proton can be easily removed using common bases to readily generate their corresponding enolate intermediate. For this reason, β-ketoesters have often been applied in asymmetric reactions catalyzed by PTCs, which can proceed with a broad spectrum of electrophiles even for the construction of quaternary carbon centers.[2] The resulting enantiomeric, multisubstituted β-ketoester products are attractive and versatile chemical synthons that can be further transformed into valuable compounds, such as natural products and pharmaceuticals.

Among all of the structural patterns observed for β-ketoesters, cyclic β-ketoesters have been frequently used in many types of asymmetric reactions catalyzed by PTCs and numerous reactions exhibiting high enantioselectivity have been reported to date (eq i, Scheme 1). However, α-branched acyclic β-ketoesters often result in very low enantioselectivity.[3] The fundamental reason behind this difference in the enantioselective outcomes partially depends on the geometry of the enolate. Thus, the geometry of the enolate can be controlled by a relatively weak ionic interaction in the transition state of a PTC-catalyzed reaction as compared to the strong interaction observed using transition-metal catalysts. Therefore, it is difficult to facilitate the formation of a single enolate isomer from α-branched acyclic β-ketoesters due to the steric repulsion, whereas the enolate of cyclic β-ketoesters can always be formed as a single isomer. Hence, highly enantioselective reactions using α-branched acyclic β-ketoesters have remained a challenging issue in PTC catalyzed reactions because both the geometry and the facial selectivity of the enolate need to be controlled (eq ii, Scheme 1).

Scheme 1. Phase-Transfer-Catalyzed Reaction Using β-Ketoesters



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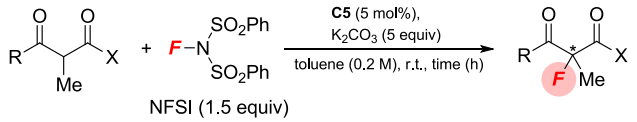
Recently, the alkynyl ketone motif—also known as an ynone—has received considerable attention as a useful synthetic substrate.[4] For instance, Trost et al. shed light on the utility of ynones as nucleophiles and developed many asymmetric reactions using the Zn-ProPhenol catalyst.[5,6] This research revealed that the increased acidity of the α-proton in ynones due to the higher *s*-character of the triple bond is beneficial for the deprotonation step to form their enolate intermediate. More importantly, the rigid and rodlike structure of the triple bond will ease steric repulsion and help form a single enolate isomer. In addition, the metallophilic nature of the triple bond provides a new synthetic approach toward the synthesis of heterocyclic compounds.[7] On the basis of these precedents, the enolate chemistry of α-branched β-ynone esters can be expected to proceed a similar manner. However, to the best of our knowledge, there are no reports using α-branched β-ynone esters as nucleophiles to construct asymmetric quaternary stereocenters at the α-position (eq iii, Scheme 1).[8] In this context, we wish to report the asymmetric fluorination of α-branched β-ynone esters using a cinchona-based phase-transfer catalyst.[9] It is worth mentioning that the synthesis of acyclic tetrasubstituted fluorine stereocenters has remained a significant challenge to date.[10]

Prior to carrying out a detailed optimization study, a control experiment was conducted to prove the effects of the substituents in the ynone and carbonyl moiety (Table 1).

Table 1. Control Experiment



entry	R	X	enol[a] (%)	time[b] (h)	yield[c] (%)	ee[d] (%)
1	Ph−C≡C	NMe_2	0	48	7	6
2	Ph−C≡C	OBu^t	54	2	47	48
3	Ph−C≡C	SBu^t	71	2	37	18
4	Ph	OBu^t	0.7	48	14	13

[a]Determined by ^{1}H NMR in $CDCl_3$ at room temperature. [b]Determined by monitoring the consumption of a dicarbonyl starting material by TLC. [c]Isolated yield. [d]Determined by HPLC equipped with a chiral stationary phase.

Thus, a series of β-keto carbonyl derivatives were treated with *N*-fluorobenzenesulfonimide (NFSI, 1.5 equiv) under standard PTC conditions using catalyst **C5** (Table 2). Initially, three sets of β-ynone carbonyl compounds were prepared in order to see the effect of a carbonyl moiety (entries 1−3, Table 1). Although the β-ynone amide gave a trace amount of product after 48 h (entry 1, Table 1), a striking contrast was observed using the β-ynone ester and thioester derivatives, in which their reactions were completed after 2 h, giving their corresponding products in moderate yield. Among the β-ynone carbonyl compounds studied, only the β-ynone ester gave moderate enantioselectivity (entries 2 and 3, Table 1). Moreover, the importance of the ynone moiety was confirmed by comparing the result obtained using the phenyl ketone substituted β-keto ester, which gave a trace amount of the desired product with low enantioselectivity (entries 2 and 4, Table 1). The difference in the reactivity can be attributed to the enolizability of the β-keto carbonyl compound (Table 1). ^{1}H NMR spectroscopy revealed that the enolizability was strongly influenced by the substituent, and as expected, the ynone moiety enhanced the acidity of the α-proton to ensure facile enolization (see the Supporting Information for the comparison of ^{1}H NMR). However, this high tendency for enolization also caused a background reaction, which deteriorated the enantioselectivity, especially in the case of the thioester derivative. In addition, careful analysis of the ^{1}H NMR spectra recorded for the β-ynone ester and thioester also suggests that their enolates exist as a single isomer. These results imply that high enantioinduction may be possible by controlling only the facial selectivity of the enolate as long as the background reaction was sufficiently suppressed.

After the substrate effect was confirmed, we commenced the optimization of the reaction by screening the structure of the cinchona-based PTC. The basic structure of PTC was determined in cinchonine-derived PTC by the comparison of quinidine-derived PTC (entries 1 and 2, Table 2). The substituent effect on the OH group of the PTC was then studied (entries 3−7, Table 2), and the highest enantioselectivity was obtained using a propargyl-substituted PTC (entry 5, Table 2). Unfortunately, modification of the substituent on the nitrogen atom of the quinuclidine moiety did not show any positive results in terms of enantioselectivity of the reaction (entries 8−10, Table 2). To attain better selectivity, the reaction was conducted at −40 °C, which drastically improved the enantioselectivity by suppressing the background reaction even though the reaction rate was significantly reduced and the reaction did not go to completion (entry 11, Table 2).

Other conditions were investigated to reduce the reaction time (see the Supporting Information for details of the screening study; such as base, solvent, and concentration). Using less water in the reaction led to a slight increase in both the yield and enantioselectivity (entry 12, Table 2). The use of a stronger base, Cs_2CO_3, resulted in an improved product yield while maintaining the enantioselectivity (entry 13, Table 2). Gratefully, a lower concentration of substrates led to the completion of the reaction (entry 14, Table 2), and the use of a mixture of *m*-xylene/toluene (v/v = 1/1) gave the product in 83% yield along with the highest enantioselectivity (ee = 83%) (entry 15, Table 2).[11]

After the optimal reaction conditions were determined, we examined the scope of the reaction with respect to the R^1 substituent on the ynone moiety. Generally, aromatic rings bearing electron-withdrawing or electron-donating groups did not influence the yield and enantioselectivity, giving their corresponding products in good yield (78−91%) with good enantioselectivity (ee = 77−83%) (**2a**−**2f**, Scheme 2).

Aromatic groups bearing sterically hindered substituents were well tolerated in the reaction and gave similar outcomes (**2g** and **2h**, Scheme 2). In fact, the highest enantioselectivity was attained in product **2h** (ee = 90%). A heteroaromatic ring, such as 3-thiophene, gave the product with a slightly lower enantioselectivity and yield (**2i**, Scheme 2). An aliphatic group also gave the desired product in good yield and enantioselectivity (ee = 80%), but required a shorter reaction time (**2j**, Scheme 2). Importantly, bulky substituents at R^2 on the α-position were also well tolerated in the reaction with no noticeable reduction in the reactivity and enantioselectivity (**2k**−**2m**, Scheme 2).

After establishing the substrate scope in the reaction, we further investigated the synthetic application of the fluorinated product (**2**) utilizing the unique reactivity of the alkyne. Thus,

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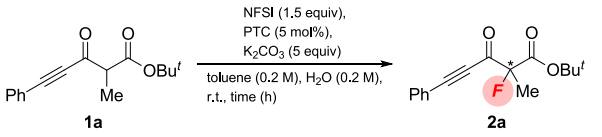
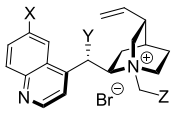
Table 2. Optimization of Reaction Conditions[a]



Phase-transfer catalyst



C1	X = OMe	Y = OH	Z = C_6H_5
C2	X = H	Y = OH	Z = C_6H_5
C3	X = H	Y = $OCH_2CH{=}CH_2$	Z = C_6H_5
C4	X = H	Y = $OCH_2CH{=}CHPh$	Z = C_6H_5
C5	X = H	Y = $OCH_2C{\equiv}CH$	Z = C_6H_5
C6	X = H	Y = OCH_2Ph	Z = C_6H_5
C7	X = H	Y = $OC(O)CH_3$	Z = C_6H_5
C8	X = H	Y = $OCH_2CH{=}CH_2$	Z = 9-anthryl
C9	X = H	Y = $OCH_2CH{=}CH_2$	Z = 3,5-F_2-C_6H_3
C10	X = H	Y = $OCH_2CH{=}CH_2$	Z = 3,5-$(CF_3)_2$-C_6H_3

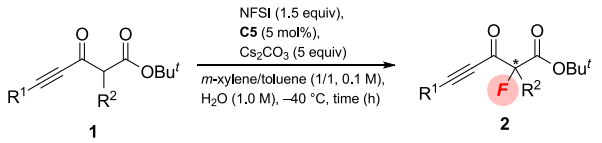
entry	PTC	base	time[b] (h)	yield[c] (%)	ee[d] (%)
1	**C1**	K_2CO_3	3	77	30
2	**C2**	K_2CO_3	5	99	37
3	**C3**	K_2CO_3	7	88	47
4	**C4**	K_2CO_3	5	86	33
5	**C5**	K_2CO_3	6	95	51
6	**C6**	K_2CO_3	24	63	31
7	**C7**	K_2CO_3	7	70	46
8	**C8**	K_2CO_3	2	72	22
9	**C9**	K_2CO_3	7	68	47
10	**C10**	K_2CO_3	7	73	24
11[e]	**C5**	K_2CO_3	48[f]	33	72
12[e,f]	**C5**	K_2CO_3	48[f]	45	77
13[e,f]	**C5**	Cs_2CO_3	48[f]	66	78
14[e,f,g]	**C5**	Cs_2CO_3	48	94	81
15[e,g,h,i]	**C5**	Cs_2CO_3	48	93(83)	83

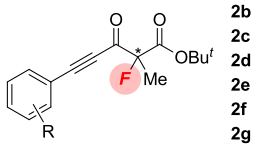
[a]Unless otherwise specified, the reaction was conducted in the mixture of toluene (0.2 M) and water (0.2 M) at room temperature. [b]Determined by monitoring the consumption of β-keto ester **1a** by TLC. [c]Determined by ^{19}F NMR of the crude reaction mixture using fluorobenzene as an internal standard, and the values in the parentheses are the isolated yields. [d]Determined by HPLC equipped with Daicel Chiralpak, IC-3. [e]At −40 °C. [f]The reaction did not completed. [g]1.0 M of water. [h]0.1 M of toluene. [i]A mixture of *m*-xylene/toluene (v/v = 1/1).

using the reaction conditions reported by Fürstner et al. (eq 1, Scheme 3),[12] fluorinated product **2a** was reacted in the presence of [(SPhos)AuNTf$_2$] (1 mol %) in AcOH (0.2 M) at room temperature for 24 h. As an interesting contrast to Fürstner's result, the reaction gave the 3,5-diketo carboxylic acid[13] rather than the expected heterocyclic product as a sole product of the reaction in good yield while maintaining its enantiopurity (ee = 82%). It is important to note that such a synthesis of 1,3,5-tricarbonyl compounds has not been reported in the literature,[14] and the regioselective hydration of the alkyne moiety was also intriguing.[15] Therefore, further investigations are currently ongoing in our laboratory.[16]

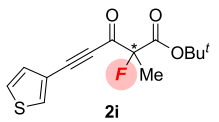
In conclusion, this research has demonstrated that the β-ynone moiety can alter the nature of the α-branched acyclic β-keto esters; it can enhance reactivity by increasing the acidity of the α-proton and provide a single geometry of the enolate by reducing the steric repulsion. These features allow the enantioselective fluorination of α-branched β-ynone esters under standard PTC conditions using a cinchona-based PTC. In addition, the α-fluorinated α-branched β-ynone ester product (**2a**) can be transformed into its corresponding 3,5-diketo carboxylic acid (**3a**) bearing a quaternary fluorinated stereocenter at the C2-position using gold catalysis. In principle, we believe that this PTC-mediated reaction will be compatible with other types of electrophiles, providing a new class of acyclic compounds bearing a quaternary stereocenter.

Scheme 2. Scope of Substrate[a]

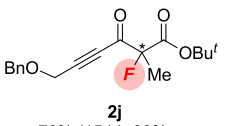




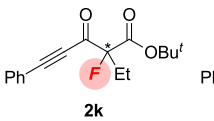
2a	R = H	83% (48 h), 83% *ee*
2b	R = 4-F	78% (48 h), 80% *ee*
2c	R = 4-Cl	91% (48 h), 80% *ee*
2d	R = 4-Br	81% (48 h), 77% *ee*
2e	R = 4-*n*-Bu	84% (48 h), 82% *ee*
2f	R = 4-EtO	75% (48 h), 80% *ee*
2g	R = 3-Me	83% (48 h), 77% *ee*
2h	R = 2,4,6-$(Me_2)_3$	78% (72 h), 90% *ee*



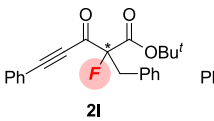
2i
61% (48 h), 73% *ee*



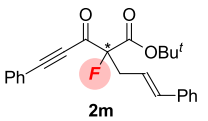
2j
76% (15 h), 80% *ee*



2k
75% (48 h), 82% *ee*



2l
83% (48 h), 80% *ee*

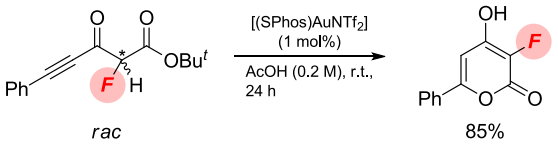


2m
93% (72 h), 78% *ee*

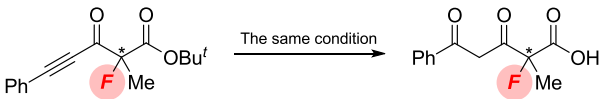
[a]Isolated yield. [b]The reaction time was determined by monitoring the consumption of β-ketoester **1** by TLC. [d]The value of enantioselectivity was determined by HPLC equipped with a chiral stationary phase.

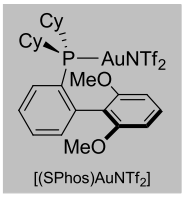
Scheme 3. Synthetic Application

(Eq. 1) Fürstner's reaction



(Eq. 2) Our reaction





[a]Isolated yield. [b]The value of enantioselectivity was determined by HPLC equipped with a chiral stationary phase after transformed to its methyl ester.

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EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were measured on a Bruker (400 or 500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on Bruker (100 or 125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. ^{19}F NMR spectra were measured on Bruker (376 or 470 MHz) spectrometer. ^{19}F NMR yield in the mixture was obtained using fluorobenzene as the internal reference. High-resolution mass spectra (HRMS) were recorded on Q-TOF mass spectrometry by SYNAPT, Waters. For thin-layer chromatography (TLC) analysis, TLC plates (silica gel 60 F_{254}) were used. The products were purified by flash column chromatography silica gel 60 (KANTO, spherical, neutral, 40−50 μm). High-performance liquid chromatography (HPLC) was performed on JASCO PU-41810 and UV-4075 instruments using 4.6 × 250 nm Daicel Chiralpak and Chiralcel. Optical rotations were measured on JASCO P-1010 digital polarimeter. Melting points were measured on ATM-02, AS ONE.

General Procedure for α-Branched β-Ynone Esters 1. α-Branched β-ynone esters **1** were prepared by the modified procedure of Fürstner's method.[12a]

Step i: Preparation of 3-Substituted Propiolate. To a stirred solution of terminal alkyne (1.0 equiv) in anhydrous THF (0.1 M) was added *n*-BuLi (1.2 equiv, 1.6 M in hexane) at −78 °C under an argon atmosphere, and the whole solution was stirred for 30 min at −78 °C. Then methyl chloroformate (1.1 equiv) was added to the reaction mixture at −78 °C, and whole reaction mixture was stirred at −78 °C until TLC showed that the terminal alkyne was totally consumed. The reaction was quenched with satd NH_4Cl at −78 °C, and the reaction mixture was then warmed to room temperature. The resulting mixture was extracted with EtOAc, and the combined organic phase was washed with brine and dried over $MgSO_4$. The organic layer was filtered and concentrated with the rotary evaporator. The residue was purified by a silica gel flash chromatography to afford the corresponding propiolate.

*Step ii: Preparation of α-Branched β-Ynone Ester **1**.* A solution of diisopropylamine (1.44 equiv) in anhydrous THF (0.33 M) was carefully treated with *n*-BuLi (1.2 equiv) at 0 °C under an argon atmosphere, and the resulting solution was stirred for 30 min at 0 °C to prepare for lithium diisopropylamide (LDA). *tert*-Butyl ester (1.2 equiv) was added to a prepared LDA solution at −78 °C. After 30 min, the propiolate prepared by step i (1.0 equiv) was added to the solution at this temperature, and the resulting reaction mixture was stirred until TLC showed that the propiolate was totally consumed. The reaction was quenched with satd NH_4Cl at −78 °C, and the reaction mixture was then warmed to room temperature. The resulting mixture was extracted with EtOAc, and the combined organic phase was washed with brine and dried over $MgSO_4$. The organic layer was filtered and concentrated with the rotary evaporator. The residue was purified by a silica gel flash chromatography to afford the corresponding α-branched β-ynone ester **1**.

*tert-Butyl 2-Methyl-3-oxo-5-phenylpent-4-ynoate (**1a**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 40/1) to give the title compound as a yellow oil (0.78 g, 61% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 46%] δ 7.59−7.33 (5H, m), 3.58 (1H, q, J = 7.2 Hz), 1.48 (9H, s), 1.45 (3H, d, J = 7.2 Hz); [enol form, 54%] δ 12.35 (1H, s), 7.59−7.33 (5H, m), 1.95 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.3, 172.7, 168.7, 151.3, 133.9, 131.1, 130.9, 129.5, 128.7, 128.4, 121.4, 119.7, 105.5, 97.2, 92.7, 86.5, 83.1, 82.03, 82.01, 56.0, 28.2, 27.9, 13.7, 13.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{19}O_3$ 259.1329, found 259.1322.

*tert-Butyl 5-(4-Fluorophenyl)-2-methyl-3-oxopent-4-ynoate (**1b**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a pale yellow solid (0.24 g, 43% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 27%] δ 7.49−7.42 (2H, m), 7.01−6.95 (2H, m), 3.49 (1H, q, J = 7.2 Hz), 1.39 (9H, s), 1.35 (3H, d, J = 7.2 Hz); [enol form, 73%] δ 12.26 (1H, s), 7.49−7.42 (2H, m), 7.01−6.95 (2H, m), 1.84 (3H, s), 1.44 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.1, 172.6, 168.6, 164.0 (d, J = 254.1 Hz), 163.2 (d, J = 251.6 Hz), 151.2, 135.4 (d, J = 8.9 Hz), 133.9 (d, J = 8.6 Hz), 117.5 (d, J = 3.4 Hz), 116.2 (d, J = 22.4 Hz), 115.80 (d, J = 22.2 Hz), 115.75 (d, J = 3.8 Hz), 105.5, 96.0, 91.5, 86.4 (d, J = 1.3 Hz), 82.9 (d, J = 1.1 Hz), 82.01, 81.96, 55.9, 28.1, 27.8, 13.5, 12.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{18}O_3F$ 277.1234, found 277.1227; mp 66−68 °C.

*tert-Butyl 5-(4-Chlorophenyl)-2-methyl-3-oxopent-4-ynoate (**1c**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a pale yellow solid (0.61 g, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [enol form, 100%] δ 12.32 (1H, s), 7.46 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.4 Hz), 1.93 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) [enol form, 100%] δ 172.6, 151.0, 135.7, 133.1, 128.9, 119.9, 105.9, 95.8, 84.0, 82.2, 28.2, 13.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{17}ClNaO_3$ 315.0764, found 315.0760; mp 103−105 °C.

*tert-Butyl 5-(4-Bromophenyl)-2-methyl-3-oxopent-4-ynoate (**1d**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a pale yellow solid (0.16 g, 33% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 21%] δ 7.53 (2H, d, J = 8.5 Hz), 7.42 (2H, d, J = 8.5 Hz), 3.58 (1H, q, J = 7.2 Hz), 1.47 (9H, s), 1.44 (3H, d, J = 7.2 Hz); [enol form, 79%] δ 12.32 (1H, s), 7.49 (2H, d, J = 8.4 Hz), 7.38 (2H, d, J = 8.6 Hz), 1.93 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.1, 172.6, 168.6, 151.0, 134.3, 133.3, 133.1, 132.1, 131.9, 131.8, 120.3, 118.6, 105.9, 95.9, 91.2, 87.2, 84.1, 82.13, 82.08, 55.9, 28.2, 27.9, 13.6, 12.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{17}BrNaO_3$ 359.0259, found 359.0245; mp 99−101 °C.

*tert-Butyl 5-(4-Butylphenyl)-2-methyl-3-oxopent-4-ynoate (**1e**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a yellow oil (0.53 g, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 32%] δ 7.38 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 8.1 Hz), 3.47 (1H, q, J = 7.1 Hz), 2.54−2.48 (2H, m), 1.52−1.44 (2H, m), 1.37 (9H, s), 1.34 (3H, d, J = 7.3 Hz), 1.28−1.19 (2H, m), 0.82 (3H, t, J = 7.3 Hz); [enol form, 68%] δ 12.28 (1H, s), 7.33 (2H, d, J = 8.1 Hz), 7.05 (2H, d, J = 8.1 Hz), 2.54−2.48 (2H, m), 1.85 (3H, s), 1.52−1.44 (2H, m), 1.42 (9H, s), 1.28−1.19 (2H, m), 0.82 (3H, t, J = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.1, 172.7, 168.6, 151.6, 146.5, 144.8, 133.1, 131.8, 128.7, 128.5, 118.4, 116.6, 105.0, 97.6, 93.3, 86.3, 82.6, 81.74, 81.72, 55.8, 35.6, 35.5, 33.2, 33.0, 28.0, 27.7, 22.1 (1C overlap), 13.74, 13.73, 13.4, 12.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{27}O_3$ 315.1955, found 315.1947.

*tert-Butyl 5-(4-Ethoxyphenyl)-2-methyl-3-oxopent-4-ynoate (**1f**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow oil (0.35 g, 55% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 67%] δ 7.42 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 4.00−3.93 (2H, m), 3.48 (1H, q, J = 7.0 Hz), 1.39 (9H, s), 1.35 (3H, d, J = 7.2 Hz), 1.36−1.31 (3H, m); [enol form, 33%] δ 12.29 (1H, s), 7.36 (2H, d, J = 8.7 Hz), 6.77 (2H, d, J = 9.1 Hz), 4.00−3.93 (2H, m), 1.85 (3H, s), 1.44 (9H, s), 1.36−1.31 (3H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.3, 172.8, 168.9, 161.3, 160.0, 151.9, 135.2, 133.6, 114.9,

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114.6, 113.2, 111.2, 104.7, 97.8, 94.3, 86.5, 82.2, 81.9 (1C overlap), 63.7, 63.6, 55.9, 28.2, 27.9, 14.7, 14.6, 13.5, 12.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{23}O_4$ 303.1591, found 303.1586.

*tert-Butyl 2-Methyl-5-(3-methylphenyl)-3-oxopent-4-ynoate (**1g**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a pale yellow solid (0.41 g, 67% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [keto form, 44%] δ 7.39−7.18 (4H, m), 3.58 (1H, q, J = 7.1 Hz), 2.33 (3H, s), 1.48 (9H, s), 1.45 (3H, d, J = 7.2 Hz); [enol form, 56%] δ 12.34 (1H, s), 7.39−7.18 (4H, m), 2.35 (3H, s), 1.94 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.3, 172.7, 168.7, 151.5, 138.5, 138.2, 133.6, 132.4, 131.9, 130.4, 130.2, 129.0, 128.5, 128.3, 121.2, 119.4, 105.4, 97.4, 93.1, 86.2, 82.8, 81.95, 81.93, 55.9, 28.2, 27.8, 21.12, 21.09, 13.5, 12.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{21}O_3$ 273.1485, found 273.1477; mp 52−54 °C.

*tert-Butyl 2-Methyl-3-oxo-5-(2,4,6-trimethylphenyl)pent-4-ynoate (**1h**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a pale yellow solid (0.40 g, 58% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [keto form, 50%] δ 6.89 (2H, s), 3.60 (1H, q, J = 7.1 Hz), 2.44 (6H, s), 2.29 (3H, s), 1.48 (3H, d, J = 7.1 Hz), 1.45 (9H, s); [enol form, 50%] δ 12.35 (1H, s), 6.90 (2H, s), 2.44 (6H, s), 2.30 (3H, s), 1.96 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.3, 172.8, 168.8, 152.2, 142.7, 141.2, 141.0, 139.3, 128.0, 127.8, 118.4, 116.5, 104.6, 95.6, 94.4, 91.4, 90.8, 81.9, 81.8, 56.1, 28.2, 27.9, 21.5, 21.4, 21.0, 20.9, 13.6, 13.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{24}NaO_3$ 323.1623, found 323.1578; mp 73−76 °C.

*tert-Butyl 2-Methyl-3-oxo-5-(thiophene-3-yl)pent-4-ynoate (**1i**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 50/1) to give the title compound as a yellow oil (0.26 g, 40% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [keto form, 38%] δ 7.76 (1H, s), 7.35−7.34 (1H, m), 7.23−7.21 (1H, m), 3.56 (1H, q, J = 7.1 Hz), 1.48 (9H, s), 1.43 (3H, d, J = 7.2 Hz); [enol form, 62%] δ 12.33 (1H, s), 7.76 (1H, s), 7.32−7.30 (1H, m), 7.20−7.19 (1H, m), 1.92 (3H, s), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 183.2, 172.7, 168.7, 151.4, 134.2, 130.7, 130.2, 129.7, 126.3, 125.7, 120.6, 119.0, 105.3, 92.4, 88.0, 86.8, 82.9, 82.0 (1C overlap), 55.8, 28.2, 27.9, 13.5, 12.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{17}O_3S$ 265.0893, found 265.0885.

*tert-Butyl 6-(Benzyloxy)-2-methyl-3-oxohex-4-ynoate (**1j**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 30/1) to give the title compound as a yellow oil (0.55 g, 55% yield): ^{1}H NMR (400 MHz, $CDCl_3$) [keto form, 15%] δ 7.36−7.29 (5H, m), 4.61 (2H, s), 4.33 (2H, s), 3.50 (1H, q, J = 7.1 Hz), 1.47 (9H, s), 1.40 (3H, d, J = 7.2 Hz); [enol form, 85%] δ 12.25 (1H, s), 7.36−7.29 (5H, m), 4.63 (2H, s), 4.38 (2H, s), 1.88 (3H, s), 1.51 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 182.7, 172.6, 168.4, 150.6, 137.0, 136.6, 128.5, 128.4 (1C overlap), 128.1 (1C overlap), 128.0, 105.8, 93.4, 89.6, 84.0, 82.14, 82.10, 80.3, 72.0, 71.8, 57.4, 56.8, 55.7, 28.1, 27.8, 13.5, 12.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{23}O_4$ 303.1591, found 303.1582.

*tert-Butyl 2-Ethyl-3-oxo-5-phenylpent-4-ynoate (**1k**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow oil (0.19 g, 57% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [keto form, 44%] δ 7.58−7.34 (5H, m), 3.41 (1H, t, J = 7.4 Hz), 2.05−1.95 (2H, m), 1.48 (9H, s), 1.01 (3H, t, J = 7.5 Hz); [enol form, 56%] δ 12.35 (1H, s), 7.58−7.34 (5H, m), 2.40 (2H, q, J = 7.4 Hz), 1.54 (9H, s), 1.08 (3H, t, J = 7.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 182.9, 172.5, 168.0, 151.5, 133.2, 132.0, 130.9, 129.5, 128.6, 128.4, 121.5, 119.7, 111.9, 96.5, 92.5, 86.7, 82.9, 82.0, 81.9, 63.5, 28.2, 27.9, 21.7, 21.6, 14.2, 11.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{21}O_3$ 273.1485, found 273.1481.

*tert-Butyl 2-Benzyl-3-oxo-5-phenylpent-4-ynoate (**1l**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel treated Et_3N (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a white solid (0.45 g, 54% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [enol form, 100%] δ 12.55 (1H, s), 7.52−7.18 (5H, m), 3.74 (2H, s), 1.39 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [enol form, 100%] δ 172.3, 152.8, 140.9, 132.1, 129.7, 128.5, 128.3, 128.1, 125.9, 121.2, 109.7, 96.9, 83.4, 82.4, 34.1, 28.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{23}O_3$ 335.1642, found 335.1633; mp 67−69 °C.

*tert-Butyl 2-[(2Z)-3-Phenylprop-2-en-1-yl]-3-oxo-5-phenylpent-4-ynoate (**1m**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel treated Et_3N (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a yellow oil (0.31 g, 56% yield): ^{1}H NMR (500 MHz, $CDCl_3$) [keto form, 38%] δ 7.59−7.18 (5H, m), 6.51 (1H, d, J = 15.7 Hz), 6.23−6.15 (1H, m), 3.67 (1H, t, J = 7.3 Hz), 2.92−2.81 (2H, m), 1.47 (9H, s); [enol form, 62%] δ 12.47 (1H, s), 7.59−7.18 (5H, m), 6.45 (1H, d, J = 15.7 Hz), 6.23−6.15 (1H, m), 3.29 (2H, d, J = 6.4 Hz), 1.53 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) [keto and enol form] δ 182.0, 172.3, 167.5, 152.6, 137.7, 137.1, 133.2, 132.8, 132.0, 131.0, 130.5, 129.7 (1C overlap), 128.7, 128.5, 128.0 (1C overlap), 127.3, 127.0, 126.2, 126.0, 125.5, 121.3, 119.6, 108.1, 97.3, 93.1, 86.8, 82.9, 82.3 (1C overlap), 61.8, 31.7, 31.6, 28.2, 27.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{24}NaO_3$ 383.1623, found 383.1637.

General Procedure for Enantioselective Fluorination of α-Branched β-Ynone Esters. To a solution of α-branched β-ynone ester **1** (0.1 mmol, 1.0 equiv) in a mixture of 1/1 m-xylene/toluene (0.1 M) and water (1.0 M) were added PTC **C5** (5 mol %) and Cs_2CO_3 (5.0 equiv) at room temperature. The reaction mixture was then cooled at −40 °C. After 20 min, NFSI (1.5 equiv) was added to the reaction mixture, and the resulting reaction mixture was stirred until TLC showed that the ester **1** was totally consumed. After Me_2S was added to quench the reaction at −40 °C, the solution was stirred for 20 min at room temperature. The resulting mixture was mixed with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic layer was filtered and concentrated with the rotary evaporator. The residue was purified by a silica gel flash chromatography to afford the desired fluorinated product **2**.

*tert-Butyl 2-Fluoro-2-methyl-3-oxo-5-phenylpent-4-ynoate (**2a**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow oil (20.4 mg, 83% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 245 nm, retention time; 7.0 min (minor) and 6.2 min (major): $[\alpha]^{28}_D$ = −13.7 (c = 1.0, $CHCl_3$; 83% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.60 (2H, m), 7.52−7.48 (1H, m), 7.43−7.39 (2H, m), 1.78 (3H, d, J = 24.6 Hz), 1.50 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0 (d, J = 29.4 Hz), 165.2 (d, J = 25.4 Hz), 133.3, 131.4, 128.7, 119.1, 96.73, 96.68 (d, J = 195.6 Hz), 84.5, 84.0, 27.6, 19.6 (d, J = 23.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.44 (1F, q, J = 21.5 Hz); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{17}FNaO_3$ 299.1059, found 299.1045.

Procedure for 1.0 mmol scale reaction of **2a**: To a solution of **1a** (259.1 mg, 1.0 mmol, 1.0 equiv) in a mixture of 1/1 m-xylene/toluene (10 mL, 0.1 M) and water (1.0 mL, 1.0 M) was added PTC **C5** (25.1 mg, 5 mol %) and Cs_2CO_3 (1.632 g, 5.0 equiv) at room temperature. The reaction mixture was then cooled at −40 °C. After 20 min, NFSI (0.474 g, 1.5 equiv) was added portionwise to the reaction mixture, and the resulting reaction mixture was stirred vigorously until TLC showed that the ester **1a** was totally consumed (note that the efficiency of stirring is very important). After Me2S was added to

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quench the reaction at −40 °C, the solution was stirred for 20 min at room temperature. The resulting mixture was mixed with saturated NaHCO3 and extracted with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic layer was filtered and concentrated with the rotary evaporator. The residue was purified by a silica gel flash chromatography to afford the desired fluorinated product **2a** (222.3 mg, 80%, 82% ee) as a yellow oil.

*tert-butyl 2-fluoro-5-(4-fluorophenyl)-2-methyl-3-oxopent-4-ynoate (**2b**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 50/1) to give the title compound as a pale yellow oil (17.9 mg, 78% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 0.75 mL/min, wavelength = 254 nm, retention time; 8.9 min (minor) and 7.9 min (major). [α]27D = −22.3 (*c* = 1.0, $CHCl_3$; 80% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64−7.62 (2H, m), 7.11 (2H, t, *J* = 8.5 Hz), 1.77 (3H, d, *J* = 21.7 Hz), 1.50 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0 (d, *J* = 29.7 Hz), 165.3 (d, *J* = 25.4 Hz), 164.4. (d, *J* = 255.2 Hz), 135.9 (d, *J* = 9.2 Hz), 116.4 (d, *J* = 22.2 Hz), 115.4 (d, *J* = 3.5 Hz), 96.8 (d, *J* = 195.5 Hz), 95.76, 84.6, 84.2, 27.7, 19.7 (d, *J* = 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.39 (1F, q, *J* = 21.7 Hz), −104.63 to −104.71 (1F, m); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}F_2NaO_3$ 317.0965, found 317.0950.

*tert-Butyl 5-(4-Chlorophenyl)-2-fluoro-2-methyl-3-oxopent-4-ynoate (**2c**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 50/1) to give the title compound as a yellow oil (28.2 mg, 91% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 6.4 min (minor) and 5.8 min (major): $[\alpha]^{28}_D$ = −29.0 (*c* = 1.0, $CHCl_3$; 80% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55(2H, d, *J* = 8.8 Hz), 7.40 (2H, d, *J* = 8.5 Hz), 1.77 (3H, d, *J* = 21.5 Hz), 1.50 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0 (d, *J* = 29.7 Hz), 165.2 (d, *J* = 25.3 Hz), 138.0, 134.6, 129.2, 117.7, 96.8 (d, *J* = 195.9 Hz), 95.3, 85.3, 84.2, 27.7, 19.7 (d, *J* = 22.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.35 (1F, q, *J* = 20.7 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}ClFO_3$ 311.0845, found 311.0833.

*tert-Butyl 5-(4-Bromophenyl)-2-fluoro-2-methyl-3-oxopent-4-ynoate (**2d**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 50/1) to give the title compound as a pale yellow oil (28.8 mg, 81% yield). The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 6.5 min (minor) and 5.9 min (major): $[\alpha]^{28}_D$ = −20.3 (*c* = 1.0, $CHCl_3$; 77% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.5 Hz), 7.48 (2H, d, *J* = 8.7 Hz), 1.77 (3H, d, *J* = 22.0 Hz), 1.50 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0 (d, *J* = 29.8 Hz), 165.2 (d, *J* = 25.6 Hz), 134.7, 132.2, 126.4, 118.1, 96.7 (d, *J* = 195.5 Hz), 95.3, 85.3, 84.2, 27.7, 19.7 (d, *J* = 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.37 (1F, q, *J* = 21.5 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}BrFO_3$ 355.0340, found 355.0326.

*tert-Butyl 5-(4-Butylphenyl)-2-fluoro-2-methyl-3-oxopent-4-ynoate (**2e**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a yellow oil (27.9 mg, 84% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 0.75 mL/min, wavelength = 245 nm, retention time; 8.9 min (minor) and 8.0 min (major): $[\alpha]^{27}_D$ = −25.6 (*c* = 1.0, $CHCl_3$; 82% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 8.2 Hz), 7.22 (2H, d, *J* = 8.2 Hz), 2.65 (2H, t, *J* = 7.7 Hz), 1.77 (3H, d, *J* = 21.6 Hz), 1.60 (2H, m), 1.50 (9H, s), 1.35 (2H, dt, *J* = 22.4 Hz, *J* = 7.3 Hz), 0.93 (3H, t, *J* = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.1 (d, *J* = 29.4 Hz), 165.4 (d, *J* = 25.5 Hz), 147.3, 133.6, 128.9, 116.3, 97.76, 96.8 (d, *J* = 198.1 Hz), 84.6, 84.1, 35.8, 33.1, 27.7, 22.3, 19.7 (d, *J* = 23.5 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.41 (1F, q, *J* = 21.6 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}FO_3$ 333.1860, found 333.1852.

*tert-Butyl 5-(4-Ethoxyphenyl)-2-fluoro-2-methyl-3-oxopent-4-ynoate (**2f**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a pale yellow solid (19.2 mg, 75% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 245 nm, retention time; 6.0 min (minor) and 7.2 min (major): $[\alpha]^{28}_D$ = −28.5 (*c* = 1.0, $CHCl_3$; 80% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 4.07 (2H, q, *J* = 8.7 Hz), 1.77 (3H, d, *J* = 21.7 Hz), 1.50 (9H, s), 1.43 (3H, t, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0 (d, *J* = 29.6 Hz), 165.5 (d, *J* = 25.5 Hz), 161.7, 135.7, 114.9, 110.7, 98.6, 97.2 (d, *J* = 195.6 Hz), 84.9, 84.0, 63.8, 27.7, 19.8 (d, *J* = 23.4 Hz), 14.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.33 (1F, q, *J* = 21.8 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}FO_4$ 321.1497, found 321.1492; mp 61−63 °C.

*tert-Butyl 2-Fluoro-2-methyl-5-(3-methylphenyl)-3-oxopent-4-ynoate (**2g**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a yellow oil (24.1 mg, 83% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 7.0 min (minor) and 6.2 min (major): $[\alpha]^{22}_D$ = −19.2 (*c* = 1.0, $CHCl_3$; 77% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.19 (4H, m), 2.29 (3H, s), 1.70 (3H, d, *J* = 21.6 Hz), 1.43 (9H, s); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.1 (d, *J* = 29.6 Hz), 165.3 (d, *J* = 25.5 Hz), 138.6, 133.9, 132.4, 130.6, 128.6, 119.0, 97.3, 96.8 (d, *J* = 196.3 Hz), 84.4, 84.1, 27.7, 21.1, 19.7 (d, *J* = 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.41 (1F, q, *J* = 21.7 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}FO_3$ 291.1391, found 291.1383.

*tert-Butyl 2-Fluoro-2-methyl-3-oxo-5-(2,4,6-trimethylphenyl)-pent-4-ynoate (**2h**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 80/1) to give the title compound as a yellow oil (24.9 mg, 78% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 245 nm, retention time; 6.5 min (minor) and 5.8 min (major): $[\alpha]^{22}_D$ = −46.6 (*c* = 1.0, $CHCl_3$; 90% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (2H, s), 2.46 (6H, s), 2.31 (3H, s), 1.78 (3H, d, *J* = 21.5 Hz), 1.49 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.2 (d, *J* = 29.9 Hz), 165.5 (d, *J* = 25.4 Hz), 143.5, 141.9, 128.1, 116.2, 97.0 (d, *J* = 195.5 Hz), 95.9 (d, *J* = 1.8 Hz), 92.5, 83.9, 27.8, 21.6, 20.8, 19.9 (d, *J* = 23.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −154.50 (1F, q, *J* = 21.1 Hz); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{23}FNaO_3$ 341.1529, found 341.1529.

*tert-Butyl 2-Fluoro-2-methyl-3-oxo-5-(thiophene-3-yl)pent-4-ynoate (**2i**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow solid (17.2 mg, 61% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 8.3 min (minor) and 7.1 min (major): $[\alpha]^{28}_D$ = −29.9 (*c* = 0.5, $CHCl_3$; 73% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, bs), 7.36 (1H, bs), 7.26 (1H, bs), 1.77 (3H, d, *J* = 21.5 Hz), 1.50 (9H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.1 (d, *J* = 29.5 Hz), 165.3 (d, *J* = 25.4 Hz), 135.3, 130.3, 126.4, 118.6, 96.7 (d, *J* = 195.1 Hz), 92.2, 85.1, 84.1, 27.7, 19.7 (d, *J* = 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.36 (1F, q, *J* = 21.9 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}FO_3S$ 283.0799, found 283.0789; mp 44−46 °C.

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*tert-Butyl 6-(Benzyloxy)-2-fluoro-2-methyl-3-oxohex-4-ynoate (**2j**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 40/1) to give the title compound as a yellow oil (24.5 mg, 76% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 8.3 min (minor) and 6.9 min (major). $[\alpha]^{28}_{D}$ = −29.9 (*c* = 0.5, $CHCl_3$; 80% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (5H, m), 4.64 (2H, s), 4.37 (2H, s), 1.73 (3H, d, *J* = 21.6 Hz), 1.50 (9H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.7 (d, *J* = 30.5 Hz), 165.0 (d, *J* = 25.8 Hz), 136.5, 128.5, 128.23, 128.19, 96.6 (d, *J* = 195.6 Hz), 93.9 (d, *J* = 1.6 Hz), 84.4, 82.0 (d, *J* = 1.5 Hz), 72.0, 56.8, 27.7, 19.6 (d, *J* = 23.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.56 (1F, q, *J* = 21.7 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}FO_4$ 321.1497, found 321.1487.

*tert-Butyl 2-Ethyl-2-fluoro-3-oxo-5-phenylpent-4-ynoate (**2k**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow oil (21.8 mg, 75% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 7.3 min (minor) and 6.6 min (major): $[\alpha]^{29}_{D}$ = −23.9 (*c* = 0.5, $CHCl_3$; 82% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.49 (2H, m), 7.44−7.41 (1H, m), 7.34−7.31 (2H, m), 2.27−2.05 (2H, m), 1.50 (9H, s), 1.03 (3H, t, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.1 (d, *J* = 29.9 Hz), 164.7 (d, *J* = 26.0 Hz), 133.5, 131.5, 128.7, 119.3, 99.7 (d, *J* = 198.7 Hz), 96.7, 85.1, 84.1, 27.8, 27.2 (d, *J* = 22.2 Hz), 7.0 (d, *J* = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −167.47 (1F, dd, *J* = 24.5 Hz, *J* = 21.8 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}FO_3$ 291.1391, found 291.1387.

*tert-Butyl 2-Benzyl-2-fluoro-3-oxo-5-phenylpent-4-ynoate (**2l**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow oil (29.4 mg, 83% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OJ-3, hexane/2-propanol = 40/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 12.3 min (minor) and 26.7 min (major): $[\alpha]^{28}_{D}$ = −41.2 (*c* = 1.0, $CHCl_3$; 80% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.61−7.59 (2H, m), 7.51−7.48 (1H, m), 7.41−7.38 (2H, m), 7.31−7.23 (5H, m), 3.55 (1H, dd, *J* = 27.8 Hz, *J* = 14.9 Hz), 3.45 (1H, dd, *J* = 22.5 Hz, *J* = 14.9 Hz), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5 (d, *J* = 30.2 Hz), 163.9 (d, *J* = 26.1 Hz), 133.5, 133.0, 131.5, 130.5, 128.7, 128.3, 127.4, 119.2, 98.9 (d, *J* = 201.2 Hz), 97.3, 85.0, 84.3, 39.5 (d, *J* = 20.8 Hz), 27.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −161.56 (1F, dd, *J* = 27.8 Hz, *J* = 22.5 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}FO_3$ 353.1547, found 353.1539.

*tert-Butyl 2-Fluoro-2-[(2Z)-3-phenylprop-2-en-1-yl]-3-oxo-5-phenylpent-4-ynoate (**2m**).* The title compound was prepared according to the general procedure as described above. The crude material was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 60/1) to give the title compound as a yellow solid (35.3 mg, 93% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3, hexane/2-propanol = 40/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 10.8 min (minor) and 10.3 min (major): $[\alpha]^{22}_{D}$ = −20.5 (*c* = 1.0, $CHCl_3$; 78% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.61 (2H, m), 7.51−7.48 (1H, m), 7.42−7.39 (2H, m), 7.35−7.21 (5H, m), 6.58 (1H, d, *J* = 15.8 Hz), 6.20−6.14 (1H, m), 3.18−3.01 (2H, m), 1.48 (9H, s); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.3 (d, *J* = 29.9 Hz), 164.2 (d, *J* = 26.1 Hz), 136.7, 135.6, 133.5, 131.5, 128.7, 128.5, 127.7, 126.4, 120.4, 119.2, 98.5 (d, *J* = 199.9 Hz), 97.2, 85.0, 84.4, 37.5 (d, *J* = 21.6 Hz), 27.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −163.39 (1F, dd, *J* = 25.9 Hz, *J* = 20.8 Hz); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{23}FNaO_3$ 401.1529, found 401.1552; mp 65−68 °C.

General Procedure for 3,5-Diketo Carboxylic Acid. To a solution of **2a** (1.0 equiv) in anhydrous AcOH (0.2 M) was added [(SPhos)AuNTf$_2$] (1 mol %) at room temperature under an argon atmosphere. After 24 h, the excess AcOH was removed by the rotary evaporator. The residue was purified by a silica gel flash chromatography (eluting with DCM/MeOH = 50/1 to MeOH only) to afford the desired carboxylic acid as a colorless oil (19.5 mg, 82% yield): $[\alpha]^{22}_{D}$ = −42.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.4 (1H, s), 7.94−7.93 (2H, m), 7.60−7.57 (1H, m), 7.50−7.47 (2H, m), 6.68 (1H, d, *J* = 3.1 Hz), 1.88 (3H, d, *J* = 22.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.1 (d, *J* = 25.9 Hz), 182.3 (d, *J* = 1.9 Hz), 171.3 (d, *J* = 25.8 Hz), 133.3, 133.0, 128.8, 127.3, 94.7 (d, *J* = 195.0 Hz), 91.7 (d, *J* = 6.7 Hz), 21.5 (d, *J* = 22.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −159.48 (1F, q, *J* = 21.9 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}FO_4$ 239.0720, found 239.0721.

Next, in order to determined enantioselectivity, the carboxylic acid was transformed to the corresponding methyl ester: The afforded carboxylic acid was dissolved in MeOH (0.5 M). To the solution was added a catalytic amount of H_2SO_4 (2 mol %), and the resulting solution was heated at 70 °C for 4 h. After the completion of the reaction, water was added to the reaction mixture, and the reaction mixture was extracted with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic layer was filtered and concentrated with the rotary evaporator. The residue was purified by a silica gel flash chromatography (eluting with hexane/ethyl acetate = 40/1 to 20/1) to afford the desired 3,5-diketo methyl ester as a colorless oil (15.8 mg, 63% yield). Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID-3, hexane/2-propanol = 40/1, flow rate = 1.0 mL/min, wavelength = 254 nm, retention time; 8.7 min (minor) and 7.6 min (major): $[\alpha]^{22}_{D}$ = −82.4 (c = 1.0, $CHCl_3$; 82% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.5 (1H, s), 7.93−7.92 (2H, m), 7.58−7.55 (1H, m), 7.49−7.46 (2H, m), 6.62 (1H, d, *J* = 3.2 Hz), 3.84 (3H, s), 1.84 (3H, d, *J* = 22.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.9 (d, *J* = 26.2 Hz), 182.5 (d, *J* = 2.0 Hz), 167.8 (d, *J* = 25.6 Hz), 133.3, 133.0, 128.8, 127.2, 95.3 (d, *J* = 193.5 Hz), 91.6 (d, *J* = 6.7 Hz), 53.4, 21.0 (d, *J* = 22.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −158.53 (1F, dq = *J* = 23.2 Hz, 3.01 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}FO_4$ 253.0876, found 253.0882.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01997.

Experimental part including, additional information on screening, characterization data, NMR spectra, HPLC data for all new compounds (**1**, **2**, and **3a**) (PDF)

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Notes

The authors declare no competing financial interest.

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