Substrate-Controlled Product Divergence: Silver-Catalyzed Reaction of Trifluoromethyl Ketones with Terminal Alkynes

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ABSTRACT: A distinct dichotomy in product distribution was initially observed in the silver-catalyzed reaction of trifluoromethyl (CF₃) ketones with terminal alkynes having two different types of electronic natures. The domino reaction smoothly proceeded almost exclusively with high stereoselectivity with terminal alkynes containing ester groups, whereas alkynylation occurred in good yield when terminal alkynes containing aryl or alkyl groups were present. The results indicated that the electronic nature of terminal alkynes can act as a switch that enables either the domino reaction or alkynylation between terminal alkynes and CF₃ ketones.

INTRODUCTION

Introduction of fluorine into organic molecules often significantly affects their properties through strong polar interactions because of the small size and high electronegativity of the fluorine atoms. In particular, the incorporation of the trifluoromethyl (CF₃) group in pharmaceutical molecules makes them more bioavailable, lipophilic, and metabolically stable. However, naturally occurring fluorinated compounds are virtually absent from the natural world. As a result, tremendous effort has been exerted to introduce CF₃ groups into organic molecules.

CF₃-containing 1,3-dioxolane derivatives exhibit unique properties in the field of functional materials. For example, when CF₃ groups were introduced into polymers, such as the copolymers of 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole, the frictional and hydrophobic properties of polymers were dramatically improved. Despite the importance of CF₃-containing 1,3-dioxolane compounds, the development of more efficient and higher stereoselective synthetic methods continues to be a challenge. The initial route for the construction of the 1,3-dioxolane ring containing a single CF₃ group developed by Ishihara needs functionalized trimethyl-silane agents. Later, Hung and Resnick reported a method for the synthesis of multi-CF₃-containing 1,3-dioxolane derivatives through a three-step synthetic procedure using a reactive fluorinating reagent, SF₆. However, both of these methods have not reported the stereoselectivity of the product.

Jeong et al. developed a highly stereoselective synthesis of (Z)-isomer products from starting materials in a three-step procedure. Recently, Larichev and Petrov used (E)-trimethyl (perfluoroprop-1-enyl) silane as a starting material to produce (E)-isomers (Scheme 1, route b). However, diastereoselectivity of the 1,3-dioxolane ring is not controlled in these two methods. Unlike the above-mentioned methods starting from highly functionalized agents, de Armas and co-workers first employed easily available propiolic esters to synthesize these fluorinated 1,3-dioxolane compounds through the triethylamine (Et₃N)-catalyzed domino reaction (Scheme 1, route c). Although the method is efficient and useful, it might suffer from limitations such as harsh reaction conditions (−78 °C) and relatively low stereoselectivity.

Recently, Coates and co-workers reveal that the stereocomplex exhibits significantly improved thermal properties in comparison to those of the enantiopure parent polymers. The CF₃-containing 1,3-dioxolane skeleton is an important monomer for the synthesis of a perfluorinated polymer. Thus, the development of practical and higher stereoselective methods to construct this skeleton would open a door for screening fluorinated 1,3-dioxolane-based polymer materials. Herein, we report a mild and efficient silver-catalyzed domino reaction between CF₃ ketones and propiolic esters that allows highly stereoselective access to a variety of CF₃-containing 1,3-dioxolane compounds (Scheme 1). Importantly, in the catalytic system developed by us, the reaction pathway can also be tuned by the electronic nature of the terminal alkyne. The reaction terminated in alkynylation instead of the domino reaction when the ester group on the terminal alkyne was replaced with an aryl or alkyl group.

RESULTS AND DISCUSSION

At the outset, ethyl propiolate 1a and trifluoroacetoephone 2a were chosen as the model substrates for condition optimization. Various conditions, including solvent, base, Ag catalyst, and temperature, were investigated (Table 1).

An initial test using 1a and 2a led to the desired product, 3a, in 93% yield but a low dr value when 10 mol % AgCl was used as a catalyst, 20 mol % NaOH as a base, and DMF as a solvent at 50 °C for 24 h (Table 1, entry 1). To improve the stereoselectivity of the desired products, various solvents were screened, and the
best results were obtained when DMC was used (Table 1, entry 6). Using the optimal solvent DMC, the base and Ag source parameters were next explored (Table 1). Among the tested Ag sources, AgCl was the most effective catalyst for this transformation (Table 1, entry 9). The effect of the anion of bases was investigated. Switching the base to KOTBu resulted in an evident improvement in the yield and selectivity (Table 1, entry 9). The result suggested that the anion of bases played an important role in the efficiency and selectivity of the silver-catalyzed domino reaction, which is consistent with previous reports.12

Et3N, DIPEA, and DABCO were examined as organic bases, but only Et3N and DABCO were moderately effective for the transformation and provided a lower product yield (Table 1, entries 12−14). It is worth noting that the target product was obtained with 96:4 dr when using DABCO as an organic base (Table 1, entry 14). Control experiments were designed with the absence of AgCl to probe the main function of the silver catalyst, using the catalyst system reported by de Armas (Table 1, entries 15 and 16). The control experiment showed that the addition of AgCl promoted greatly the reaction stereoselectivity (Table 1, entries 15 vs 16).

Control reactions confirmed that the transformation did not occur in the absence of base (Table 1, entry 23). The collaboration between Ag salts and base is required for substrate conversion and increasing selectivity (Table 1, entries 9 and 24), and catalytic amount of 20 mol % base is enough to fully convert all materials (Table 1, entry 1). A higher temperature gave a relatively higher conversion, with slightly decreasing stereoselectivity (Table 1, entries 9, 25, and 26).

Having the optimized reaction conditions, we examined the scope of CF3 ketones (Table 2). The reactions of CF3 ketones with electron-withdrawing substituents, such as chloride and bromide at the para-position of the aryl ring, proceeded smoothly to provide the coupling products in good yield with >90:10 dr (3ca, 3da, and 3ia). The electron-donating groups at the para-position of the aryl ring slightly decreased the yield, presumably because of the decreased electrophilicity of the carbonyl group, which slows the addition of the silver acetylide intermediate to the carbon-bearing carbonyl group (3ba and 3ha).

Importantly, the successful synthesis of 3ca, 3da, 3ea, 3fa, 3ia−3ka, and 3oa, 3pa with a halogen tolerance provides a good opportunity for further C−C or C−heteroatom bond-forming reactions through the transition-metal-catalyzed approach. The CF3 ketones bearing meta-, -bromo, or -chloro substitutions afforded the desired product in good yield with >90:10 dr (3ea, 3fa, 3ja, 3ka, and 3oa, 3pa).

Next, we investigated the scope of the alkynes (Table 2). The product yield is not affected by the alkyl substituents bearing propiolic esters. The reaction of methyl-, ethyl-, and tert-butylpropiolate gave moderate to good yield (3aa, 3ga, and 3ma).

The scope and limitations of the terminal alkynes were investigated (Table 3). Interestingly, replacing the ester group on the terminal alkyne with an aryl or alkyl group resulted in a switch in the silver-catalyzed paths and the reaction terminated in the alkylation process instead of the domino reaction.13 The electronic effect of para substituents bearing the aromatic ring of alkynes was observed. The terminal alkyne bearing electron-donating and electron-neutral groups provided higher yields than...
those from the alkynes containing electron-withdrawing groups (Table 3, 4a—4e vs 4f—4h). The reaction of aryl acetylene bearing a fluoro group at the meta position on the aryl ring proceeded well, whereas that with a methyl group at the ortho position on the aryl ring showed a relatively low reactivity (Table 3, 4i vs 4j).

To extend the scope of alkylation, the reactions of alicyclic, aliphatic, and sulfur heterocyclic alkynes were tested. The alicyclic, aliphatic, and sulfur heterocyclic alkynes were also compatible with this reaction, generating the corresponding products (Table 3, 4k—4o).

The scope of CF₃ ketones was explored. CF₃ ketones having electron-withdrawing and electron-donating groups were successfully converted to the desired products in good yields (Table 3, 4p—4r).

We performed an ethyl propiolate H/D exchange experiment to gain insight into the mechanism of these reactions. Generally, the bond energy of the C—D bond can be evidently higher than that of the C—H bond, suggesting that the C—H bond is easier to cleave than the C—D bond. As shown in Figure 1, we found that the use of deuterated ethyl propiolate instead of ethyl propiolate resulted in a significant increase in the reaction rate, but the stereoselectivity of the deuterated product dramatic decreased (dr decreased from 99:1 to 56:44). The reverse kinetic isotope effect indicates that the C(sp)−H(D) bond cleavage was not involved the rate-determining step.

To gain further insight into the reaction mechanism, an isotope labeling experiment was carried out (Scheme 2). The reaction of 2a with alkyne 1a-d labeled with deuterium at the terminal position of the alkylnyl group was examined. The deuterium shifted to the vinylc position in product 3aa-d.

On the basis of previous reports and our experimental results, a possible mechanism is illustrated in Scheme 3. The reaction of propiolic esters with AgCl in the presence of a base of KOtBu generates the key silver acetylide, A1. Intermediate B1 was formed through a ligand association process between A1 and CF₃ ketones. A subsequent nucleophilic attack of intermediate B1 on the oxygen atom of CF₃ ketones then occurs to form intermediate C1. The nucleophilic attack of intermediate C1 on other CF₃ ketones generates intermediate D1, which undergoes intramolecular nucleophilic addition to form intermediate E1. The final protonolysis between E1 and propiolic esters affords product F1, and the active intermediate, A1, was regenerated.

When we changed the electronic nature of the substituents by replacing the electron-deficient ester group with the electron-rich aryl or alkyl group, we discovered a remarkable electronically
controllable product divergence in the silver-catalyzed alkynylation and domino reaction. As shown in Scheme 3, the process of nucleophilic attack of CF₃ ketones on C₁ requires a strong electron-defi cient triple bond. A strong electron-withdrawing group such as ester should speed up the reaction rate of intramolecular attack on D₁. By contrast, electron-donating groups like aryl and alkyl groups will slow down this step, so the reaction terminated the alkynylation.

**CONCLUSIONS**

In summary, we discovered a remarkable electronically controllable product divergence in the silver-catalyzed alkynylation and domino reaction. As shown in Scheme 3, the process of nucleophilic attack of CF₃ ketones on C₁ requires a strong electron-deficient triple bond. A strong electron-withdrawing group such as ester should speed up the reaction rate of intramolecular attack on D₁. By contrast, electron-donating groups like aryl and alkyl groups will slow down this step, so the reaction terminated the alkynylation.

**EXPERIMENTAL SECTION**

**General Experimental Methods.** All reactions were performed in Schlenk tubes under an atmosphere of nitrogen. All reagents and solvents were purchased from commercial sources and were used without additional purification. ¹H NMR spectra were recorded at 400 MHz using tetramethylsilane (TMS) as internal standard. ¹³C NMR spectra were recorded at 100 MHz using TMS as internal standard. ¹⁹F NMR spectra were recorded at 376 MHz. The mass data of the compounds were collected on a time-of-flight mass spectrometer equipped with electron ionization (EI) instrument. The molecular weights of high-resolution mass spectrometry (HRMS) were calculated for the following isotopes: ³⁵Cl and ⁷⁹Br. GC−MS analyses were conducted on a gas chromatograph spectrometer using EI mode.

**General Procedure for Domino Reaction.** Ag catalyst (0.05 mmol, 10 mol %), base (0.1 mmol, 20 mol %), propiolic esters (0.5 mmol), CF₃ ketones (1.0 mmol), and solvent (1 mL) were successively added to the Schlenk tubes under a nitrogen atmosphere. The reaction mixture was stirred at the required temperature for 6 h. After the reaction, the reaction mixture was added to brine (15 mL) and extracted three times with dichloromethane (3 × 15 mL). The solvent was concentrated under vacuum. The cis or trans isomers were separated by short chromatography on a silica gel (300−400 mesh) column using a
petroleum ether/ethyl acetate (EtOAc) (100/1, v/v) mixture as an eluent.

(Z)-Ethyl 2-((2S,5S)-2,5-diphenyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3aa).

Purification by flash chromatography (petroleum ether/EtOAc = 100:1): a colorless oil (185 mg, 83%); 1H NMR (400 MHz, DMSO-d$_6$): Zsyn $\delta$ 7.62-7.57 (m, 4H), 7.42-7.27 (m, 6H), 5.91 (s, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.27 (t, $J = 7.2$ Hz, 3H), ppm; 13C NMR (100 MHz, DMSO-d$_6$).

Table 3. Scope of Substrates in Alkynylation$^a$

| entry | substrate, 1 | R$_2$ | product | yield (%) |
|-------|--------------|-------|---------|-----------|
| 1     | H            | H     | 4a      | 98        |
| 2     | Me           | H     | 4b      | 95        |
| 3     | MeO          | H     | 4c      | 92        |
| 4     | Ph           | H     | 4d      | 89        |
| 5     | Et           | H     | 4e      | 93        |
| 6     | F            | H     | 4f      | 75        |
| 7     | Cl           | H     | 4g      | 69        |
| 8     | Br           | H     | 4h      | 71        |
| 9     | H            | H     | 4i      | 94        |
| 10    | Me           | H     | 4j      | 78        |
| 11    | H            | H     | 4k      | 73        |
| 12    | H            | H     | 4l      | 76        |
| 13    | H            | H     | 4m      | 79        |
| 14    | H            | H     | 4n      | 77        |
| 15    | H            | H     | 4o      | 81        |
| 16    | H            | 4-Cl  | 4p      | 83        |
| 17    | H            | 4-Br  | 4q      | 86        |
| 18    | H            | 4-Me  | 4r      | 74        |

$^a$Reaction conditions: 1 (0.5 mmol), 2 (0.75 mmol), AgCl (7.16 mg, 10 mol %), K$_2$CO$_3$ (13.9 mg, 20 mol %), DMF (1 mL), 50 °C, 24 h, under N$_2$, isolated yield.
DMSO-d$_6$): $^{1}H$ NMR (400 MHz, DMSO-d$_6$): $^{13}C$ NMR (100 MHz, DMSO-d$_6$): 19F NMR (376 MHz, DMSO-d$_6$): HRMS (EI): m/z calcd for C$_{21}$H$_{16}$F$_6$O$_4$ [M + H]$^+$ 446.0953, found 446.0952.

(Z)-Ethyl 2-((2S,5R)-2,5-diphenyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3ab).

Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 100:1): a colorless oil; $^{1}H$ NMR (400 MHz, DMSO-d$_6$): $^{13}C$ NMR (100 MHz, DMSO-d$_6$): 19F NMR (376 MHz, DMSO-d$_6$): HRMS (EI): m/z calcd for C$_{21}$H$_{16}$F$_6$O$_4$ [M + H]$^+$ 446.0953, found 446.0957.

(Z)-Ethyl 2-((2S,5S)-2,5-di-p-tolyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3bb).

Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 100:1): a colorless oil (145 mg, 61%); $^{1}H$ NMR (400 MHz, DMSO-d$_6$): $^{13}C$ NMR (100 MHz, DMSO-d$_6$): 19F NMR (376 MHz, DMSO-d$_6$): HRMS (EI): m/z calcd for C$_{23}$H$_{20}$F$_6$O$_4$ [M + H]$^+$ 474.1266, found 474.1265.

(Z)-Ethyl 2-((2S,5R)-2,5-di-p-tolyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3ba).

Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 100:1): a colorless oil; $^{1}H$ NMR (400 MHz, DMSO-d$_6$): $^{13}C$ NMR (100 MHz, DMSO-d$_6$): 19F NMR (376 MHz, DMSO-d$_6$): HRMS (EI): m/z calcd for C$_{23}$H$_{20}$F$_6$O$_4$ [M + H]$^+$ 474.1265, found 474.1265.

Figure 1. Time course of the cycloaddition reaction. Reaction conditions: 1a (0.5 mmol, blue curve) or deuterated 1a (0.5 mmol, red curve), 2a (1.0 mmol), AgCl (10 mol %), KOtBu (20 mol %), DMC (1 mL), 30 °C.

Scheme 2. Isotope Labeling Experiments

Scheme 3. Proposed Mechanism
(2)-Ethyl 2-((25,5S)-2,5-bis-(4-bromophenyl)-2,5-bis-(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3ca). Purification by flash chromatography (petroleum ether/EtOAc = 100:1): a pale yellow solid (124 mg, 71%); 1H NMR (400 MHz, DMSO-d6): δ 7.72 (dt, J = 7.6, 2.0 Hz, 2H), 7.69 (dd, J = 2.0, 0.8 Hz, 1H), 7.67 (dd, J = 2.0, 0.8 Hz, 1H), 7.63 (dt, J = 8.0 Hz, 1H), 7.58 (dq, J = 8.0, 0.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 6.07 (s, 1H), 4.21 (q, J = 7.2, 1.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 162.4, 154.9, 134.5, 133.8, 132.4, 131.9, 131.1, 130.9, 129.6, 129.0, 126.1, 125.7, 121.9, 121.6, 121.4 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.58 (dq, J = 8.0, 0.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 6.07 (s, 1H), 4.21 (q, J = 7.2, 1.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), ppm; 19F NMR (376 MHz, DMSO-d6): δ −76.37, −81.39, ppm; HRMS (EI): m/z calc for C_{21}H_{14}Br_{2}F_{6}O_{4} [M + H]^+ 601.9163, found 601.9161.

(2)-Ethyl 2-((25,5R)-2,5-bis-(3-bromophenyl)-2,5-bis-(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3cb). Purification by flash chromatography (petroleum ether/EtOAc = 100:1): a pale yellow solid (148 mg, 77%); 1H NMR (400 MHz, DMSO-d6): δ 7.99 (s, 1H), 7.89 (m, J = 8.4 Hz, 1H), 7.85 (dd, J = 7.2, 0.8 Hz, 2H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 6.19 (s, 1H), 4.21 (q, J = 7.2, 1.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 162.4, 155.3, 134.5, 133.8, 132.6, 132.4, 131.4, 131.3, 132.6, 128.4, 125.3, 125.2, 122.3, 121.8 (q, J_C = 284.0 Hz), 120.1 (q, J_C = 286.7 Hz), 107.6 (q, J_C = 34.1 Hz), 97.7, 86.7 (q, J_C = 32.1 Hz), 60.6, 14.0, ppm; 19F NMR (376 MHz, DMSO-d6): δ −76.50, −81.41, ppm; HRMS (EI): m/z calc for C_{21}H_{14}Br_{2}F_{6}O_{4} [M + H]^+ 601.9163, found 601.9164.

(2)-Ethyl 2-((25,5S)-2,5-bis-(3-chlorophenyl)-2,5-bis-(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3da). Purification by flash chromatography (petroleum ether/ EtOAc = 100:1): a pale yellow solid (25 mg, 75%); 1H NMR (400 MHz, DMSO-d6): δ 7.65–7.58 (m, 4H), 7.56–7.53 (m, 1H), 7.48–7.43 (m, 2H), 7.36 (t, J = 8.4 Hz, 1H), 6.08 (s, 1H), 4.23 (q, J = 7.2, 1.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 162.4, 155.2, 136.4, 135.8, 129.1, 129.0, 128.8, 128.5, 128.4, 121.7 (q, J_C = 282.3 Hz), 120.5 (q, J_C = 284.7 Hz), 108.0 (q, J_C = 34.1 Hz), 96.8, 86.9 (q, J_C = 32.1 Hz), 60.6, 14.0, ppm; 19F NMR (376 MHz, DMSO-d6): δ −76.54, −81.52, ppm; HRMS (EI): m/z calc for C_{21}H_{14}Cl_{2}F_{6}O_{4} [M + H]^+ 514.0175, found 514.0173, 514.0174.

(2)-Ethyl 2-((25,5R)-2,5-bis-(3-chlorophenyl)-2,5-bis-(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3db). Purification by flash chromatography (petroleum ether/ EtOAc = 100:1): a pale yellow solid (28 mg, 76%); 1H NMR (400 MHz, DMSO-d6): δ 7.86 (d, J = 8.8 Hz, 2H), 7.69 (s, 4H), 7.64 (dt, J = 8.8, 2.8 Hz, 2H), 6.07 (s, 3H), 4.20 (qd, J = 7.2, 1.6 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 162.3, 155.8, 136.5, 135.8, 129.3, 129.2, 129.18, 129.0, 128.1, 127.8, 121.9 (q, J_C = 283.8 Hz), 120.6 (q, J_C = 286.9 Hz), 108.2 (q, J_C = 33.8 Hz), 97.1, 87.1 (q, J_C = 32.0 Hz), 60.5, 14.0, ppm; 19F NMR (376 MHz, DMSO-d6): δ −76.59, −81.56, ppm; HRMS (EI): m/z calc for C_{21}H_{14}Cl_{2}F_{6}O_{4} [M + H]^+ 514.0173, found 514.0178.

(2)-Ethyl 2-((25,5S)-2,5-bis-(3-bromophenyl)-2,5-bis-(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3ea). Purification by flash chromatography (petroleum ether/ EtOAc = 100:1): a pale yellow solid (147 mg, 68%); mp = 62.5–63.6 °C; 1H NMR (400 MHz, DMSO-d6): δ 7.59 (q, J = 7.2 Hz, 4H), 7.47–7.29 (m, 6H), 5.96 (s, 1H), 3.78 (s, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 162.9, 156.0, 131.2, 130.5, 130.2, 129.6, 128.7, 128.6, 126.9, 126.3, 121.9 (q, J_C = 282.0 Hz), 120.7 (q, J_C = 1110
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(Z)-Methyl 2-((2S,5S)-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3gb).

Purification by flash chromatography (petroleum ether/ EtOAc = 100:1): a pale yellow solid, mp = 60.9–61.7 °C; 1H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.65 (d, $J$ = 8.8 Hz, 2H), 5.70 (dt, $J$ = 8.8, 2.0 Hz, 2H), 7.45 (dt, $J$ = 8.8, 2.0 Hz, 2H), 6.02 (s, 1H), 3.77 (s, 3H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): $\delta$ 163.0, 156.9, 141.2, 140.3, 129.6, 129.5, 127.7, 127.4, 126.0, 125.8, 122.2 (q, $J_{CF}$ = 284.8 Hz), 120.9 (q, $J_{CF}$ = 286.7 Hz), 108.8 (q, $J_{CF}$ = 33.7 Hz), 96.9, 87.5 (q, $J_{CF}$ = 32.0 Hz), 51.7, 20.8, 20.6, ppm; 19F NMR (376 MHz, DMSO-d$_6$): $\delta$ 76.44, −81.41, ppm; HRMS (EI): $m/z$ calc'd for C$_{20}$H$_{12}$F$_6$O$_4$ [M + H$^+$] 587.9007, found 587.9004.

(2Z)-Methyl 2-((2S,5R)-2,5-di-4-chlorophenyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidene) Acetate (3ia).

Purification by flash chromatography (petroleum ether/ EtOAc = 100:1): a yellow solid (193 mg, 77%), mp = 70.4–71.9 °C; 1H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.86–7.85 (m, 2H), 7.76–7.67 (m, 5H), 7.62 (t, $J$ = 8.0, 1.0 Hz, 1H), 6.26 (s, 1H), 3.76 (s, 3H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): $\delta$ 162.8, 155.4, 153.9, 133.9, 133.8, 133.2, 132.2, 131.7, 131.3, 131.0, 129.5, 125.6, 125.0, 124.8, 121.8 (q, $J_{CF}$ = 283.8 Hz), 120.6 (q, $J_{CF}$ = 286.8 Hz), 107.8 (q, $J_{CF}$ = 34.0 Hz), 97.3, 86.8 (q, $J_{CF}$ = 32.7 Hz), 51.8, ppm; 19F NMR (376 MHz, DMSO-d$_6$): $\delta$ 76.51, −81.30, ppm; HRMS (EI): $m/z$ calc'd for C$_{20}$H$_{12}$Br$_2$F$_6$O$_4$ [M + H$^+$] 587.9007, found 587.9004.
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(Z)-tert-Butyl 2-((2S,5S)-2,5-diphenyl-2,5-bis(trifluoromethyl)-1,3-dioxolan-4-ylidine) Acetate (3ma). Purification by flash chromatography (petroleum ether/EtOAc = 100:1): a colorless oil (195 mg, 72%); 'H NMR (400 MHz, DMSO-d6): δ 7.62−7.55 (m, 3H), 7.51−7.45 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 5.94 (s, 1H), 1.52 (s, 9H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 161.7, 154.0, 133.7, 133.7, 123.5, 131.6, 131.3, 130.8, 130.8, 130.7, 126.8, 126.2, 125.7, 125.3, 121.6 (q, J = 282.0 Hz), 120.4 (q, J = 285.0 Hz), 107.2 (q, J = 34.3 Hz), 98.8, 86.5 (q, J = 32.5 Hz), 81.3, 27.7, ppm; 19F NMR (376 MHz, DMSO-d6): δ −6.57, −61.8, ppm; HRMS (EI): m/z calc'd for C21H18ClF4O4 [M + H]+ 424.0846, found 424.0846. **General Procedure for Alkylation.** A mixture of ketone (0.5 mmol), acryl acrylate (0.75 mmol), AgCl (7.16 mg, 0.05 mmol), and KCO3 (13.9 mg, 0.1 mmol) in DME (1 mL) was allowed to react in Schlenk tubes at 50 °C for 24 h under a nitrogen atmosphere. After the reaction, the mixture was added to brine (15 mL) and extracted three times with dichloromethane (3 × 15 mL). The solvent was concentrated under vacuum, and the product was isolated by short chromatography on a silica gel (300−400 mesh) column.

1,1,1-Trifluoro-2,4-diphenylbut-3-yn-2-ol (4a). Purification by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (135 mg, 98%); 'H NMR (400 MHz, DMSO-d6): δ 8.00 (d, J = 4.0 Hz, 1H), 7.84−7.82 (m, 2H, 7.60 (d, J = 3.2 Hz, 2H), 7.52−7.44 (m, 6H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 137.2, 132.1, 130.8, 129.7, 129.3, 128.6, 127.6, 122.8 (t, J = 284.0 Hz), 120.0, 86.9, 86.2, 72.4 (q, J = 31.0 Hz), ppm; 19F NMR (376 MHz, DMSO-d6): δ −0.86, ppm.

1,1,1-Trifluoro-2-phenyl-4-(p-tolyl)but-3-yn-2-ol (4b). Purification by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (138 mg, 95%); 'H NMR (400 MHz, DMSO-d6): δ 7.93 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 6.0 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H), 2.34 (s, 3H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 140.0, 137.2, 132.0, 129.9, 129.6, 128.7, 125.7, 122.8 (t, J = 284.0 Hz), 118.1, 87.1, 85.5, 72.6 (q, J = 31.0 Hz), 21.4, ppm; 19F NMR (376 MHz, DMSO-d6): δ −0.85, ppm.

1,1,1-Trifluoro-4-(4-methoxyphenyl)-2-phenylbut-3-yn-2-ol (4c). Purification by flash chromatography (petroleum ether/EtOAc = 10:1): a white solid (141 mg, 92%), mp = 94−95 °C; 'H NMR (400 MHz, DMSO-d6): δ 7.85 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 6.00 (s, 1H), 1.48 (s, 9H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 161.7, 154.5, 134.4, 133.7, 132.7, 132.5, 131.4, 131.3, 128.4, 125.2, 125.1, 122.3, 121.8 (q, J = 284.1 Hz), 120.6 (q, J = 287.1 Hz), 107.4 (q, J = 34.0 Hz), 99.2, 86.5 (q, J = 32.1 Hz), 81.2, 27.7, ppm; 19F NMR (376 MHz, DMSO-d6): δ −6.74, −81.4, ppm; HRMS (EI): m/z calc'd for C23H20BrF4O4 [M + H]+ 629.9476, found 629.9477.
Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (113 mg, 78%); 1H NMR (400 MHz, DMSO-d$_6$): δ 7.96 (s, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.52–7.44 (m, 3H), 7.42–7.27 (m, 4H), 2.33 (s, 3H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): δ 138.5, 136.9, 132.0, 129.4, 128.93, 128.91, 128.4, 127.3, 122.6 (t, J$_{CF}$ = 285.0 Hz), 120.7, 86.8, 85.5, 72.3 (q, J$_{CF}$ = 31.0 Hz), 20.8, ppm; 19F NMR (376 MHz, DMSO-d$_6$): δ −0.86, ppm.

4-Cyclopropyl-1,1,1-triﬂuoro-2-phenyl-3-yne-2-ol (4k). Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (88 mg, 73%); 1H NMR (400 MHz, DMSO-d$_6$): δ 7.65 (d, J = 8.0 Hz, 2H), 7.54 (s, 1H), 7.45–7.38 (m, 3H), 1.52–1.46 (m, 1H), 0.88 (dd, J = 8.2 Hz, 2H), 0.72–0.69 (m, 2H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): δ 138.2, 131.2, 129.0, 128.1, 123.4 (t, J$_{CF}$ = 284.0 Hz), 92.1, 72.8, 72.6 (q, J$_{CF}$ = 31.0 Hz), 9.19, 9.14, ppm; 19F NMR (376 MHz, DMSO-d$_6$): δ −1.08, ppm.

4-Cyclohexyl-1,1,1-triﬂuoro-2-phenyl-3-yne-2-ol (4l). Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (107 mg, 76%); 1H NMR (400 MHz, DMSO-d$_6$): δ 6.79 (d, J = 6.8 Hz, 2H), 7.54 (s, 1H), 7.46–7.39 (m, 3H), 2.64–2.60 (m, 1H), 1.76 (d, J = 8.4 Hz, 2H), 1.70–1.66 (m, 2H), 1.53–1.43 (m, 3H), 1.38–1.35 (m, 3H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): δ 137.7, 129.4, 128.4, 127.5, 122.9 (t, J$_{CF}$ = 284.0 Hz), 92.0, 77.6, 72.0 (q, J$_{CF}$ = 31.0 Hz), 32.0 (d, J = 3.7 Hz), 28.3, 25.7, 24.3, ppm; 19F NMR (376 MHz, DMSO-d$_6$): δ −1.25, ppm; HRMS (MALDI): m/z calcd for C$_{12}$H$_{12}$F$_2$O [M + H]$^+$ 282.1322, found 282.1284.

4-Cyclohex-1-en-1-yl-1,1,1-triﬂuoro-2-phenyl-3-yne-2-ol (4m). Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (111 mg, 79%); 1H NMR (400 MHz, DMSO-d$_6$): δ 7.70 (s, 2H), 7.68 (s, 1H), 7.47–7.40 (m, 3H), 6.24–6.24 (m, 1H), 1.62–1.54 (m, 4H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): δ 137.7, 137.4, 129.5, 128.5, 127.5, 122.8 (t, J$_{CF}$ = 284.0 Hz), 91.2, 88.7, 83.5, 72.4 (q, J$_{CF}$ = 31.0 Hz), 28.8, 25.6, 22.1, 21.3, ppm; 19F NMR (376 MHz, DMSO-d$_6$): δ −1.01, ppm; HRMS (MALDI): m/z calcd for C$_{12}$H$_{12}$F$_2$O [M + H]$^+$ 263.1042, found 263.1044.

Puriﬁcation by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (114 mg, 85%); 1H NMR (400 MHz, DMSO-d$_6$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.62–7.52 (m, 2H), 1.65–1.41 (m, 4H), ppm; 13C NMR (100 MHz, DMSO-d$_6$): δ 136.3, 134.4, 129.5, 128.8, 128.7, 127.5, 123.7, 122.7 (t, J$_{CF}$ = 284.0 Hz), 120.2, 87.2, 85.9, 72.6 (q, J$_{CF}$ = 31.0 Hz), ppm; 19F NMR (376 MHz, DMSO-d$_6$): δ −0.79, ppm; HRMS (MALDI): m/z calcd for C$_{16}$H$_{16}$BrF$_3$O [M + H]$^+$ 528.9600, found 528.9608.

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2-(4-Chlorophenyl)-4-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (4p). Purification by flash chromatography (petroleum ether/EtOAc = 10:1): a pale yellow oil (114 mg, 83%); 1H NMR (400 MHz, DMSO-d6): δ 7.71 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 1.53–1.47 (s, 1H), 0.93–0.87 (m, 2H), 0.76–0.69 (m, 2H), ppm; 13C NMR (100 MHz, DMSO-d6): δ 137.3, 135.1, 130.1, 129.2, 123.3 (t, JCF = 284.0 Hz), 92.6, 72.3, 72.3, (q, JCF = 31.0 Hz), 9.3, 9.2, ppm; 19F NMR (376 MHz, DMSO-d6): δ −1.12, ppm; HRMS (MALDI): m/z calc for C13H10ClF3O [M + H-H2O]+ 257.0339, found 257.0340.

Deuteration of Ethyl Propiolate.17 Ethyl propiolate 1a (0.5 mmol, 52 µL) was dissolved in dichloromethane (1 mL) in Schlenk tubes. Deuterium oxide (50 µL), deuterium oxide (50 µL) containing catalytic quantity of sodium deuterioxide (wt %, 30%), and tetrabutylammoniumfluoride (0.01 mmol, 3.70 mg) were successively added to Schlenk tubes. The mixture was stirred at room temperature. After stirring for 1 h, the reaction mixture was added with fresh deuterium oxide (50 µL). After the reaction, the reaction mixture was extracted three times with dichloromethane (3 × 5 mL). The solvent was concentrated at room temperature under vacuum and gave deuterated ethyl propiolate 1a-d. 1H NMR (400 MHz, CDCl3): δ 4.22 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 2.91 (s, 1H, <0.06), ppm (terminal hydrogen deuteration ratio of 99.9% D).

Preparation of Crystalline. The crystalline was prepared through the layer-to-layer diffusion method. The product, 3ga or 3gb, was added into the THF solution and layered with n-hexane. After 3 days, a crystal suitable for single-crystal X-ray diffraction was obtained. Crystallographic data of the structures have been deposited at the Cambridge Crystallographic Database Centre, Supplementary publication no.: CCDC 1503942 and CCDC 1503943 for product 3ga and 3gb.

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