

Visible-Light-Driven Organophotocatalyzed Multicomponent Approach for Tandem C(sp³)–H Activation and Alkylation Followed by Trifluoromethylthiolation

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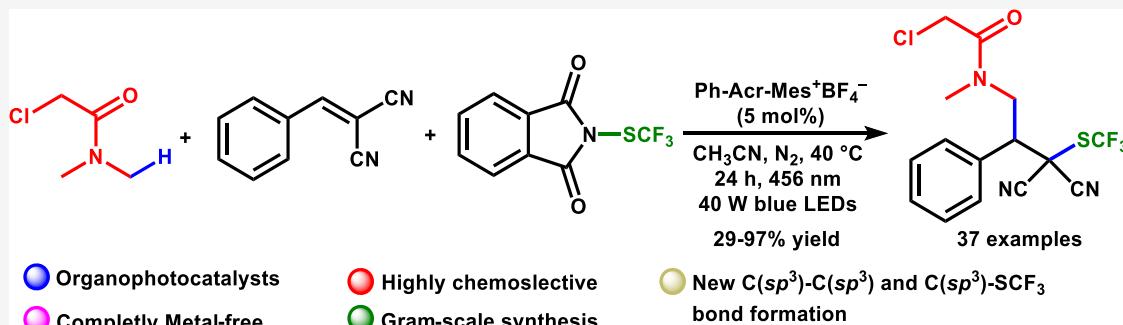
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ABSTRACT: A visible-light-driven organophotocatalyzed multicomponent approach has been developed for tandem direct C(sp³)–H activation and alkylation followed by trifluoromethylthiolation in a one-pot operation. We report a completely metal-free, tandem, three-component approach for the difunctionalization of activated alkenes via the photoinduced radical pathway. This protocol allows the formation of two new C(sp³)–C(sp³) and C(sp³)–SCF₃ bonds using a bench-stable, easy-to-handle trifluoromethylthiolating reagent under mild reaction conditions. The generosity of this reaction is shown with a library of C(sp³)–H donors and alkenes derivatives. The reaction conditions can tolerate a wide variety of functional groups. Gram-scale synthesis using environmentally benign and straightforward conditions highlights the synthetic advancement of the methodology. Further functionalization of the final product is also successfully demonstrated.

INTRODUCTION

Fluorine-containing organic molecules facilitate enhanced metabolic stability, lipophilicity, and greater bioavailability.¹ Given these advantages, the selective introduction of fluorinated groups (such as –F, –CF₃, –CF₂CO₂Et, and –SCF₃) into an organic architecture has garnered interest in pharmaceutical, agrochemical, and advanced functional material chemistry.² Among the fluorinated organic frameworks, the trifluoromethylthio group (–SCF₃) has strong electronegativity and high lipophilicity (Hansch parameter $\pi = 1.44$), which further increases the therapeutic potential of bioactive organic compounds.³ Due to this, several drugs containing the trifluoromethylthio group have been developed over the last few decades.⁴ Some representative examples of the drugs containing trifluoromethylthio groups are depicted in Figure 1.⁵

The difunctionalization of alkenes allows a diverse complex synthesis to enrich the stock of the library of organic compounds.⁶ Additionally, selective, direct functionalization of the most abundant C–H bond in organic compounds, particularly the C(sp³)–H bond, is desirable. To achieve this, photoredox catalysis can be utilized, and significant progress

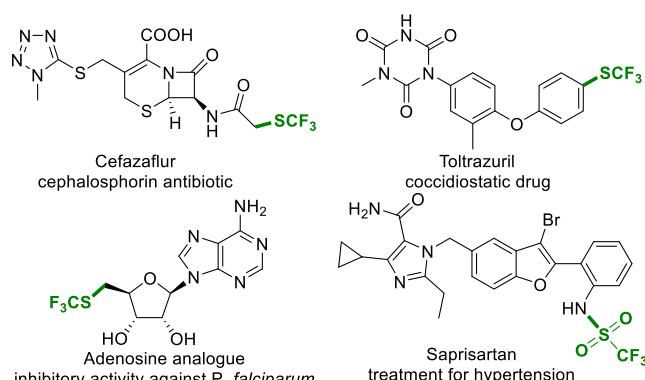


Figure 1. Representative example for biologically active trifluoromethylthio compounds.

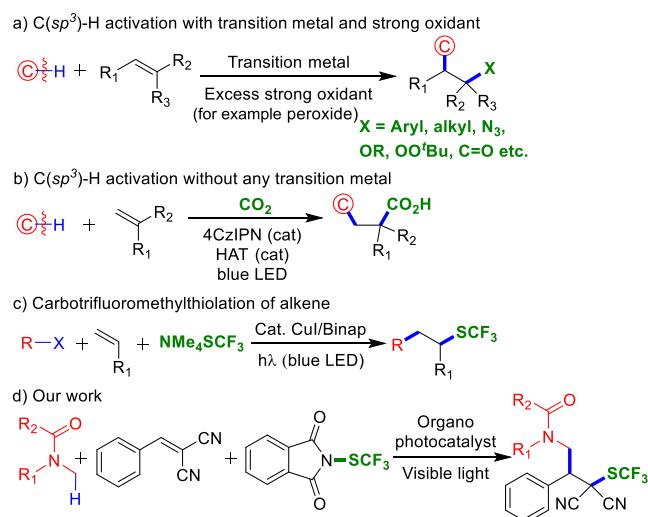
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has been made in this area.⁷ However, reports on multicomponent reactions involving direct C–H functionalization are still scarce. A few methods on multicomponent difunctionalization of alkenes via C(sp³)–H activation using transition metals catalysts with stoichiometric amounts of strong oxidants have been reported (Scheme 1a).⁸ Recently,

Scheme 1. Previous Report on Alkene Difunctionalization and Our Work



Wu's group reported three-component difunctionalization of alkenes via direct ubiquitous C(sp³)–H bond activations using visible-light photocatalysts without any transition metal or strong oxidant (Scheme 1b).⁹

The incorporation of the trifluoromethylthio (–SCF₃) group along with other functional groups into a double bond can lead to the synthesis of a diverse set of complex molecular frameworks in a multicomponent fashion.¹⁰ Hence, a number of methodologies for carbotrifluoromethylthiolation of alkene along with other functional groups such as cyanation, amidation, trifluoromethylation, fluorination, etherification, chlorination, phosphonization, selenylation, arylation and so forth have been developed predominantly with transition metals.¹⁰ Further, carbotrifluoromethylthiolation of a double bond that requires the simultaneous formation of C(sp³)–C and C(sp³)–SCF₃ is not well-explored.¹¹ Jonas C. Peters's group reported a visible-light-induced, copper-catalyzed carbotrifluoromethylthiolation of alkenes, where alkyl halide was used as the carbon source (Scheme 1c).^{11a} The carbotrifluoromethylthiolation of alkenes via direct C(sp³)–H activation has presumably not been known before. Given the importance of trifluoromethylthiolation and direct C(sp³)–H activation, we report a metal-free visible-light-induced methodology for the construction of carbotrifluoromethylthiolation of alkenes (Scheme 1d).

RESULTS AND DISCUSSION

The study began by optimizing the carbotrifluoromethylthiolation reaction using 5 equiv of 1a, 1 equiv of 2a, 1.5 equiv of "SCF₃" source 3, and 5 mol % acridinium photocatalyst PC-I in a dichloromethane (DCM) (2.0 mL) solvent. After irradiating the reaction mixture using a blue light-emitting diode (LED) (456 nm, 40 W) at 25 °C for 24 h, the expected product 4a was obtained in 30% yield along with C–H alkylated product 5a in 33% yield (Table 1, Entry 1). A better

yield of 42% of 4a was obtained when acridinium photocatalyst PC-II was used with 46% of 5a. Acridinium photocatalyst PC-III failed to produce better results than PC-II. No desired product was found when eosin Y (PC-IV) was used as a photocatalyst. Different pyrylium salts (PC-V, PC-VI, and PC-VII) were screened, but none of them improved the reaction yield (Table 1, entries 5–7). The reaction failed in the case of iridium photocatalyst PC-VIII (Table 1, entry 8). After careful screening of photocatalysts, we performed solvent screening. Different solvents such as DCE, chlorobenzene, benzene, EtOAc, acetone, and CH₃CN were tested, and CH₃CN gave the best results of 4a (56%) with 39% of 5a. Interestingly, by reducing the solvent amount from 2 mL to 1 mL, the yield of 4a was increased to 68%. Further reducing the solvent to 0.5 mL, the yield of 4a was improved to 79% with 6% of 5a. Increasing the temperature of the reaction from 25 to 40 °C, a yield of 91% of 4a was achieved along with 8% of 5a. The best result of 4a was obtained (97%) by using 2.5 equiv of "SCF₃" source 3, where no C–H alkylated product 5a was observed.

We expanded the scope of the developed methodology using various substrates with optimized reaction conditions, as shown in Scheme 2. Simple substituents on the aryl ring of alkenes gave products 4a–4c with excellent yields ranging from 87 to 97%. Electron-donating substituents on the aryl ring produced 4d and 4e with yields of 86% and 45%, respectively. Aryl ring-bearing halogen substituents delivered the expected products 4f–4j with 85–91% yields. Similarly, electron-deficient substituents on the phenyl ring furnished the anticipated products 4k–4o with good yields ranging from 85 to 93%. The Michael acceptor-bearing heteroaromatic ring also provided the desired products 4p and 4q with good yields of 66 and 57%, respectively. The aliphatic alkene delivered the desired products 4r and 4s in moderate yields of 36 and 44%, respectively. When we performed our reaction with the alkene derived from monoterpenoid aldehyde, citronellal, the trifluoromethylthiolated product 4t was obtained with a yield of 51%. Similarly, our reaction conditions could produce the anticipated product 4u in 59% yield. Here, the alkene was obtained from a bile acid (lithocholic acid). Our standard reaction conditions failed to produce products 4v–4x in good yields, but by adding 20 mol % of 2,6-lutidine to our standard conditions and extending the reaction time to 40 h, we were able to obtain products 4v–4x in good yields ranging from 36 to 78%. When the dialkene was subjected to the standard reaction conditions, product 4y was obtained with a yield of 59%, showcasing the broad scope of our methodology. However, when we used benzylidene malonate as a Michael acceptor, we failed to observe our desired product 4z, which shows the limitation of our developed methodology.

After successfully testing different electron-deficient alkenes, we explored the scope of different donors (Scheme 3). When N,N-dimethylformamide was used as a donor, product 6a was procured with 72% isolated yield. Similarly, N,N-dimethylpropionamide and N,N-dimethylbutanamide gave products 6b and 6c in excellent yields of 93% and 97%, respectively. Interestingly, 2-chloro-N,N-dimethylacetamide delivered product 6d in 75% yield without affecting the C–Cl bond, underscoring the high chemoselectivity of our methodology. Although we obtained a lower yield for 6e–6h with the standard reaction conditions, improved results were obtained with 20 mol % 2,6-lutidine as the additive after 40 h. Product 6i was obtained in 38% yield with 20 mol % of 2,6-lutidine in 40 h reaction time, when N,N-dimethylbenzenesulfonamide

Table 1. Optimization of Reaction Conditions^a

Acridinium salts Eosin-Y, PC-IV Pyrylium salts ($\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbpy})\text{PF}_6$), PC-VIII
 R₁=H, R₂=Me, X=ClO₄, PC-I R=Me, PC-V R=Me, PC-VI R=OMe, PC-VII
 R₁=H, R₂=Ph, X=BF₄, PC-II R=Cl, PC-VI R=Cl, PC-VII
 R₁=^tBu, R₂=Ph, X=BF₄, PC-III

entry	photocatalyst	solvent	yield 4a (%) ^b	yield 5a (%) ^b
1	PC-I	DCM	30	33
2	PC-II	DCM	42	46
3	PC-III	DCM	29	48
4	PC-IV	DCM	0	9
5	PC-V	DCM	12	52
6	PC-VI	DCM	0	0
7	PC-VII	DCM	15	42
8	PC-VIII	DCM	0	12
9	PC-II	DCE	28	36
10	PC-II	chlorobenzene	30	44
11	PC-II	benzene	44	16
12	PC-II	EtOAc	14	46
13	PC-II	acetone	19	56
14	PC-II	CH ₃ CN	56	39
15 ^c	PC-II	CH ₃ CN	68	24
16 ^d	PC-II	CH ₃ CN	79	6
17 ^{d,e}	PC-II	CH ₃ CN	91	8
18 ^{d,e,f}	PC-II	CH ₃ CN	97	0

^aReaction conditions: 1a (1.0 mmol, 5 equiv), 2a (0.2 mmol, 1 equiv), 3 (0.3 mmol, 1.5 equiv), photocatalyst (5 mol %), solvent (2.0 mL), irradiation using a 40 W 456 nm blue LED under N₂, 25 °C, 24 h. ^b¹H NMR yield using tetrachloroethane as the internal standard. ^c1.0 mL of CH₃CN was used. ^d0.5 mL of CH₃CN was used. ^eReaction at 40 °C. ^f2.5 equiv (0.5 mmol) of 3 was used.

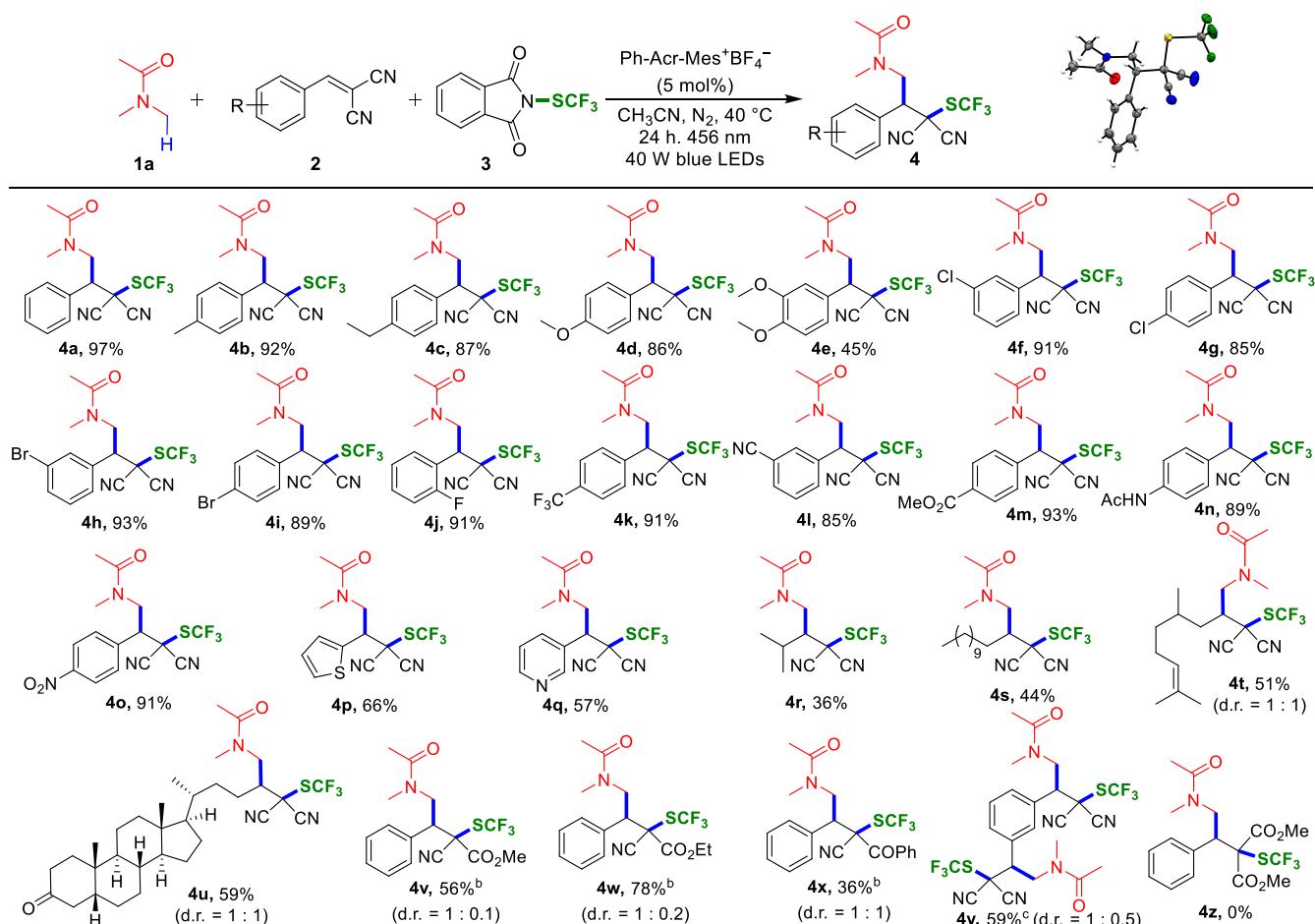
was used as a donor. *N,N*-dimethylaniline was also able to produce product 6j but in a lower yield of 29%. Tetrahydrofuran and dioxane gave products 6k and 6l in 61% and 34%, respectively, with 20 mol % of 2,6-lutidine in 40 h reaction time.

The reaction was carried out in the gram scale (10 mmol) to demonstrate the scalability of this methodology, and the expected product 4a was obtained in 87% (2.97 g) yield as a colorless solid (see the Supporting Information). Product 4a has successfully functionalized to products 7 and 8, as depicted in Scheme 4.

Mechanistic insights into the reaction were garnered by performing different control experiments, as shown in Scheme 5. When we performed the reaction without light and the photocatalyst, no trace of the product was observed, highlighting the essential role of the photocatalyst and light. The radical quencher 2,2,6,6-tetramethylpiperidine-1-oxyl

(TEMPO) completely stopped the reaction, indicating that the reaction proceeds through the radical mechanism. When the reaction was performed in the open air or in the presence of O₂, reduced yields were obtained, suggesting the necessity of an inert atmosphere and that the reaction proceeds through the triplet state of the photocatalyst. Most importantly, when the reaction was carried out between 5a and 3 using 1 equiv of 2,6-lutidine, the desired product was obtained in 91% yield, indicating that trifluoromethylthiolation occurs through anion formation (see the Supporting Information).

Based on our studies and the previous literature, a plausible mechanism is depicted in Scheme 6. Upon irradiation of organophotocatalyst Ph-Mes-Acr⁺ using a blue LED, excited-state species Ph-Mes-Acr^{*+} is produced, which takes an electron from 1a via a single-electron transfer (SET) process to generate the radical cation intermediate A along with the regeneration of Ph-Mes-Acr⁺. Intermediate A then loses a

Scheme 2. Substrate Scope of Different Electron-Deficient Alkenes^a

^aReaction conditions: **1a** (1.0 mmol, 5 equiv), **2** (0.2 mmol, 1 equiv), **3** (0.5 mmol, 2.5 equiv), Ph-Acr-Mes⁺BF₄⁻ (5 mol %), CH₃CN (0.5 mL), 40 W 456 nm blue LED, 40 °C, 24 h, ^b20 mol % 2,6-lutidine was used with 40 h reaction time, ^cequiv of **3** (0.6 mmol) used.

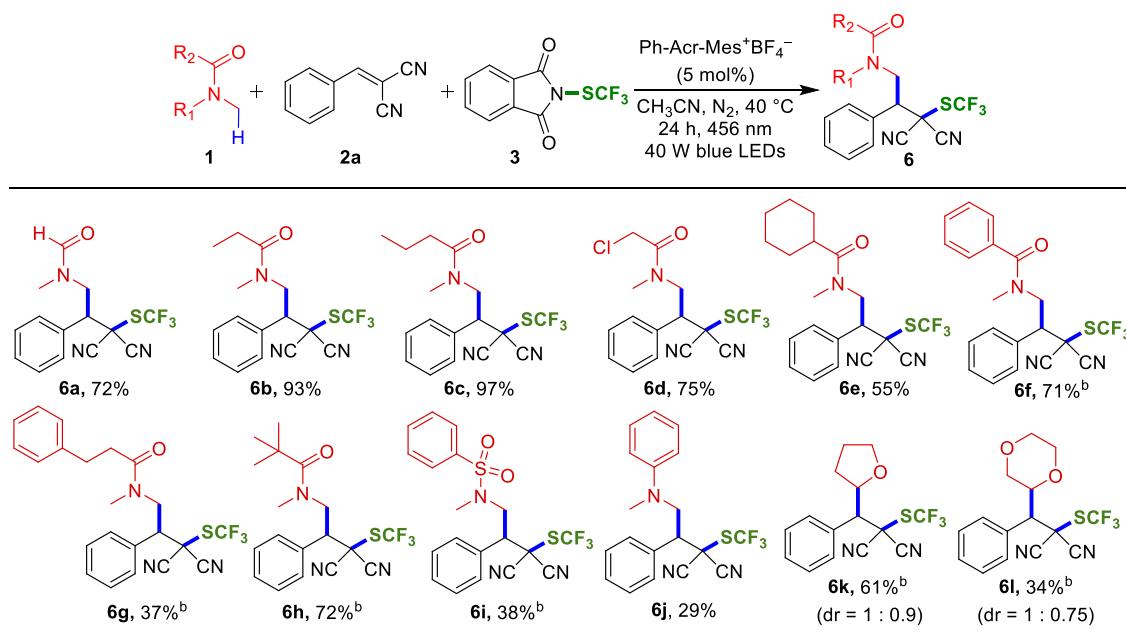
proton to produce radical intermediate **B** that reacts with alkene **2a** to deliver intermediate **C**. Intermediate **C** regenerates photocatalyst Ph-Mes-Acr⁺ by abstracting one electron from Ph-Mes-Acr[•]. Next, intermediate **C** is converted to the anionic intermediate **D**, followed by the trifluoromethylthiolation by **3** that offers the final product **4a**.

In summary, we have developed a metal-free organophotocatalyzed methodology for carbotrifluoromethylthiolation via difunctionalization of activated alkenes using a multicomponent strategy under mild conditions. The commercially available and easily accessible organophotocatalyst (Ph-Acr-Mes⁺BF₄⁻) and electrophilic trifluoromethylthiolating reagents were used. Our methodology shows high functional group tolerance and chemoselectivity and provides excellent yields. The scalability of the carbotrifluoromethylthiolation reaction and functionalization of the product were successfully achieved for future applications.

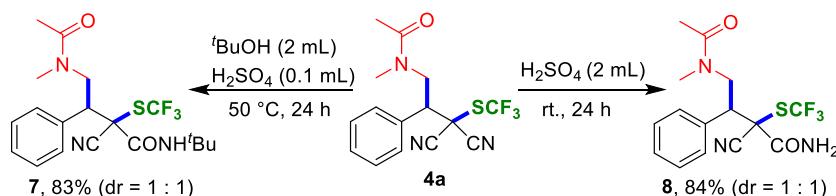
EXPERIMENTAL SECTION

General Information. All solvents were dried, and commercial reagents were purified following L. L Chai and Armarego Purification of Laboratory Chemicals guidelines. Acr-mes⁺ClO₄⁻ was purchased from Tokyo Chemical Industries Chemicals (TCI); eosin Y and all-metal and other photocatalysts were either prepared as per literature procedures or purchased (Sigma-Aldrich) and used without

purification unless otherwise specified. Other reagents were obtained from commercial suppliers (Alfa Aesar and Spectrochem). All reactions were conducted in dried glassware with magnetic stirring under a nitrogen atmosphere unless otherwise stated. Thin-layer chromatography was performed using silica gel 60 F254, and visualization was performed under ultraviolet light or using iodine stain. Flash column chromatography was performed using silica gel (230–400 μm, Merck) using the eluent system described for each experiment. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Kessil blue LEDs, 456 nm (40 W), were used as the visible-light source. Details of the photoreaction setup are described. All crystallization processes were carried out in an acetonitrile solvent under slow evaporation of the solvent at room temperature. All NMR spectra were recorded on 400 MHz Jeol or 500 MHz Bruker spectrometers. ¹H, ¹³C{¹H}, and ¹⁹F NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm), and coupling constants (J) are measured in hertz (Hz). The following abbreviations are used to describe multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, br = broad, and m = multiplet. NMR spectra were processed in MestReNova, keeping the CDCl₃ residual peak at 7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C{¹H} NMR. High-resolution mass spectra (HRMS, *m/z*) were recorded on a Micro-TOF spectrometer (Bruker). IR spectra were recorded on a PerkinElmer Frontier FT-IR spectrometer. All fluorescence spectra and UV-vis spectra were recorded on a HORIBA FluoroMax Plus spectrofluorometer and a Hitachi UV-vis spectrophotometer. X-ray diffraction data were collected at 100 K

Scheme 3. Substrate Scope of Different Donors^a

^aReaction conditions: 1 (1.0 mmol, 5 equiv), 2a (0.2 mmol, 1 equiv), 3 (0.5 mmol, 2.5 equiv), Ph-Acr-Mes⁺BF₄⁻ (5 mol %), CH₃CN (0.5 mL), 40 W 456 nm blue LED, 40 °C, 24 h. ^b20 mol % of 2,6-lutidine was used with 40 h reaction time.

Scheme 4. Further Functionalization

on a SuperNova Eos diffractometer using monochromatic Cu K α radiation ($\lambda = 1.54184 \text{ \AA}$). The diastereomeric ratio and rotameric ratio are abbreviated as dr and rr, respectively.

General Procedure for the Preparation of 1.^{12a} All the amides and other donors were either obtained from commercially available sources or prepared through the previously reported literature methods.

General Procedure for the Preparation of 2.^{12b} To a 100 mL round-bottom flask equipped with a magnetic stir bar were added the corresponding aldehyde (10 mmol, 1 equiv) and malononitrile (10.0 mmol, 1.0 equiv) in 25 mL of ethanol. Then, two–three drops of piperidine were added and stirred for 2 h. The solid precipitate was then filtered off and washed with cold ethanol. In the case of liquid products, the solvent was removed under reduced pressure, and purification was performed via column chromatography. Except for products 2s and 2u, all the Michael acceptors have previously been reported.

2-Dodecylidenemalononitrile (2s). R_f = 0.4 (ethyl acetate/n-hexane, 1:9); colorless oil; yield 62% (1.4 g); ¹H NMR (500 MHz, CDCl₃): δ 7.33 (t, *J* = 8.0 Hz, 1H), 2.59 (dd, *J* = 15.1, 7.6 Hz, 2H), 1.63–1.50 (m, 2H), 1.42–1.20 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 169.9, 112.3, 110.7, 90.0, 33.0, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.7, 22.8, 14.2; HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₇H₃₈N₂ONa, 429.2882; found, 429.2862.

2-((4*R*)-4-((8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentylidene)-malononitrile (2u). R_f = 0.3 (ethyl acetate/n-hexane, 2:8); colorless solid; yield 32% (1.3 g); ¹H NMR (400 MHz, CDCl₃-D): δ 7.33 (t, *J* = 8.0 Hz, 1H), 2.76–2.44 (m, 3H), 2.33 (td, *J* = 14.5, 5.3 Hz, 1H), 2.21–2.13 (m, 1H), 2.08–1.97 (m, 3H), 1.92–1.76 (m, 3H), 1.63

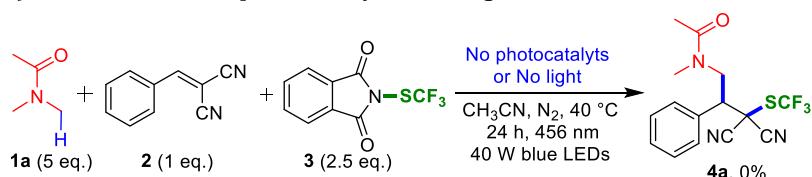
(dd, *J* = 9.8, 3.3 Hz, 2H), 1.51–1.40 (m, 5H), 1.35–1.20 (m, 6H), 1.20–1.05 (m, 4H), 1.02 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.70 (s, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 213.5, 170.4, 110.7, 89.9, 56.5, 55.91, 44.4, 43.1, 42.5, 40.9, 40.2, 37.4, 37.1, 35.7, 35.0, 33.9, 30.0, 28.4, 26.7, 25.9, 24.3, 22.8, 21.3, 18.5, 12.2; HRMS (ESI) *m/z* [M + Na]⁺ calcd for C₂₇H₃₈N₂ONa, 429.2882; found, 429.2862.

Synthesis of the Photocatalyst.¹³ Photocatalyst Acr-Mes⁺ClO₄⁻ (PC-I) was purchased from TCI and eosin Y (PC-IV) and (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (PC-VIII) were obtained from SigmaAldrich, which were used without further purification. Other acridinium (PC-II and PC-III)-based and pyrylium (PC-V, PC-VI, and PC-VII)-based organophotocatalysts were synthesized from commercially available chemical sources in our lab following the reported synthetic procedure with slight necessary modification. The elaborate synthetic procedure for photocatalyst PC-II is discussed below.

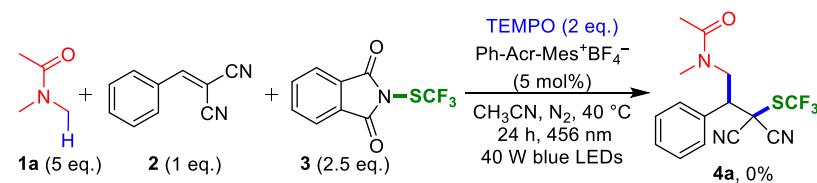
Preparation of 9-Mesityl-10-phenylacridin-10-ium Tetrafluoroborate (Ph-Acr-Mes⁺BF₄⁻), PC-II. According to the reported procedure, to a flame-dried 250 mL round-bottom flask with a magnetic stir bar, N-phenyl anthranilic acid (15 g, 70.4 mmol, 1 equiv) was dissolved in 60 mL of concentrated sulfuric acid, and the reaction mixture was heated at 100 °C with continuous stirring. After 3 h of the reaction, the hot dark green-colored mixture was cooled to room temperature and poured on crushed ice, and yellow-colored precipitation was observed immediately. Then, the excess acid was neutralized by ammonium hydroxide solution. The resulting yellow precipitate was isolated by using a Büchner funnel setup. The residue was thoroughly washed with distilled water and air-dried for 24 h. The yellow solid was further purified via recrystallization from acetic acid,

Scheme 5. Control Experiments

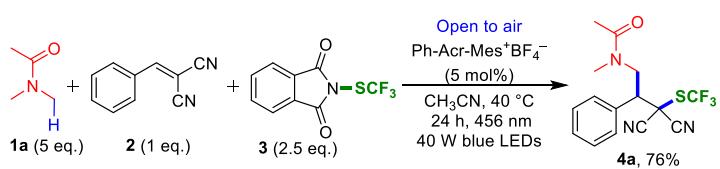
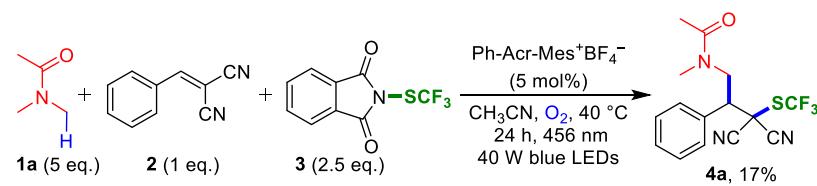
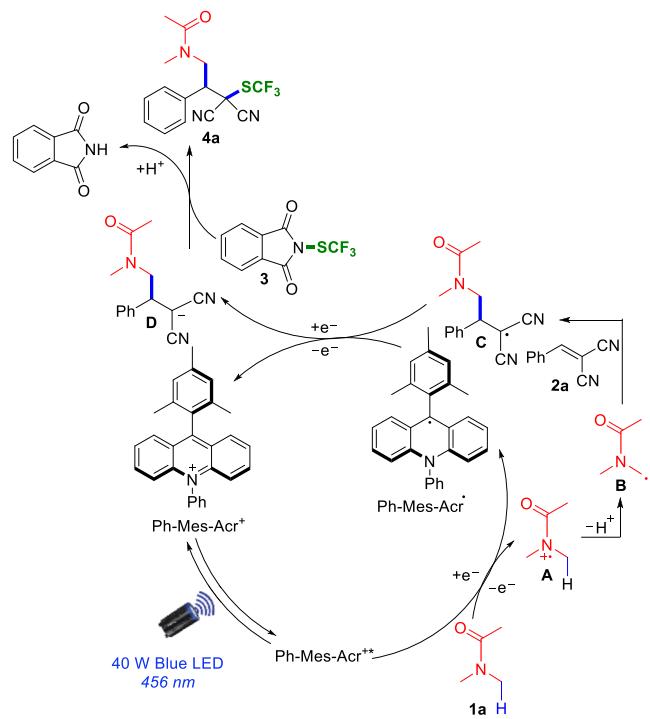
a) Reaction without photocatalysts and light



b) Reaction with TEMPO



c) Reaction in the presence of air

d) Reaction in the presence of O₂**Scheme 6. Plausible Reaction Mechanism**

N-Phenylation of acridin-9(10H)-one was obtained by modifying the previously reported process.^{13a} According to our modified procedure, acridin-9(10H)-one (4 g, 20.5 mmol, 1.0 equiv), CuI (780 mg, 4.1 mmol, 0.2 equiv), and K₂CO₃ (5.6 g, 41.0 mmol, 2.0 equiv) were added in a 500 mL sealed tube under a nitrogen atmosphere inside a glovebox. Then, 100 mL of freshly dried DMF was added. Iodobenzene (2.8 mL, 24.6 mmol, 1.2 equiv) and 2,2,6,6-tetramethylheptane-3,5-dione (1.7 mL, 8.2 mmol, 0.4 equiv) were added. After closing the cap, the sealed tube was taken out from the glovebox, and the reaction mixture was heated at 140 °C using an oil bath with continuous stirring. After 48 h, the reaction mixture was cooled to room temperature and quenched with 3 M HCl (aq.) until the bubbles of carbon dioxide stopped. Then, the aqueous solution was extracted with DCM (3 × 100 mL). The combined organic layer was washed with saturated sodium bicarbonate (150 mL), followed by (150 mL) saturated ammonium chloride and brine, and collected on anhydrous sodium sulfate. After the evaporation of the solvent, the crude was purified via column chromatography (5:1 hexane/ethyl acetate), and 4.7 g of 10-phenylacridin-9(10H)-one was obtained with 85% yield.

To an oven-dried 500 mL, double-neck round-bottom flask equipped with a magnetic stir bar, 10-phenylacridin-9(10H)-one (3.0 g, 11.1 mmol, 1.0 equiv) was added in 250 mL of dry tetrahydrofuran under an argon atmosphere. Then, freshly prepared mesityl magnesium bromide (7.4 g, 33.3 mmol, 3.0 equiv) was added dropwise and the mixture was stirred at room temperature for 24 h, and then, the solution was heated at 50 °C using an oil bath. After 72 h, the red-colored solution was cooled to room temperature and quenched with saturated sodium bicarbonate solution (200 mL). The aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layer was washed with brine, collected through anhydrous sodium sulfate, and concentrated using a rotary evaporator. Then, the crude mixture was dried for 4 h under high vacuum. To the red crude

and 10.5 g of acridin-9(10H)-one was collected in 76% yield after drying under vacuum.

oil, 75 mL of diethyl ether was added, and the solution was stirred for 30 min. The purple-colored solution was decanted to another round-bottom flask equipped with a magnetic stir bar, and the tetrafluoroboric acid diethyl ether complex (0.5 mL diluted in 25 mL of diethyl ether) was added dropwise with continuous stirring until the yellow-colored precipitation disappeared. Again, the purple-colored diethyl ether solution was extracted, and the procedure was repeated two times. Then, the combined yellow precipitate was collected via filtration, and the residue was thoroughly washed with ether and dried under vacuum for 6 h, which afforded 3.6 g of 9-mesityl-10-phenylacridin-10-iun tetrafluoroborate with 70% yield.

Synthesis of 2-((Trifluoromethyl)thio)isoindoline-1,3-dione (3). Initially, reagent AgSCF₃ was prepared following a previously reported procedure.¹⁴ Briefly, AgF (15 g, 118 mmol) was added under an argon atmosphere, followed by CS₂ (15 mL, 248 mmol, 2.1 equiv), and 75 mL of dry acetonitrile, and the reaction mixture were refluxed at 80 °C using an oil bath. After 14 h, the reaction mixture was cooled to room temperature, and excess CS₂ and solvent were evaporated under reduced pressure in the dark. Then, the residue was dissolved in EtOAc and filtered through Celite, and the filtrate was concentrated under reduced pressure in the dark. After that, the yellow residue was dissolved in a minimum amount of dry acetonitrile. The yellow solution was layered with 60 mL of diethyl ether and kept at -20 °C for crystallization for 24 h with covered aluminum foil. Then, a white crystalline solid was collected via filtration, dried in a vacuum, and stored in a refrigerator (7.3 g, 89% yield).

In an oven-dried 100 mL round-bottom flask, N-chloro phthalimide (6.7 gm, 37 mmol, 1.0 equiv) was dissolved in 60 mL of dry acetonitrile under an argon atmosphere. Then, AgSCF₃ (9.2 g, 48 mmol, 1.3 equiv) was added, and the solution was stirred at room temperature overnight. After that, the solvent of the reaction mixture was concentrated using a rotary evaporator. The residue was dissolved in 60 mL of DCM and filtered through a pad of Celite and washed with DCM (3 × 20 mL), the filtrate was concentrated, and the crude was purified via column chromatography (7: 3 DCM/hexane), which afforded 8.3 g of 2-((trifluoromethyl)thio)isoindoline-1,3-dione with 92% yield.

Experimental Procedure for the Synthesis of 4 and 6. To an oven-dried 20 mL reaction tube equipped with a magnetic stir bar, 2 (0.2 mmol, 1 equiv), Ph-Acr-Mes⁺BF₄⁻ (0.01 mmol, 0.05 equiv), 3 (0.5 mmol, 2.5 equiv), and 1 (1.0 mmol, 1.0 equiv) were added. Then, the reaction tube was kept under vacuum for 5 min and then backfilled with nitrogen, and this cycle was repeated another four times, and a rubber septum was put on the top of the reaction tube tightly, with continuous nitrogen flow. A photoreaction setup was prepared, a water-filled crystal clean 250 mL glass beaker was placed on a heating stirrer, 40 °C was maintained, and a Kessil 40 W, 456 nm blue LED lamp was fitted at a 1 cm distance from the glass wall of the beaker. After adding 0.5 mL of the freshly dried acetonitrile solvent, the reaction tube was dipped into a water-filled beaker so that the distance of the reaction tube from the light source could be maintained at 3 cm overall. After 24 h of irradiation under a blue LED, the reaction tube was removed from the setup, and the reaction mixture was diluted with 5 mL of DCM, followed by 10 mL of brine solution, and extracted with DCM (3 × 20 mL). The combined organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product was then purified via flash column chromatography on 230-400 mesh silica gel using ethyl acetate and hexane as the eluent to afford products 4 and 6. In the case of liquid 1, it was added to the reaction mixture after the addition of the solvent. To obtain products 4r, 4(w-y), 6(f-h), 6l, and 6m, 20 mol % 2,6-lutidine was added after the solvent addition with a prolonged reaction time of 40 h.

Gram-Scale Synthesis of 4a. To an oven-dried 50 mL two-neck round-bottom flask equipped with a magnetic stir bar, 2a (1.54 g, 10 mmol, 1 equiv), 3a (6.15 g, 25 mmol, 2.5 equiv), and Ph-Acr-Mes⁺BF₄⁻ (230 mg, 0.5 mmol, 0.05 equiv) were added. After fitting a septum on one neck and an adapter with a stopcock on the other, the reaction flask was subjected to vacuum for 10 min and backfilled with nitrogen, which was repeated for four more cycles, and a balloon filled

with nitrogen was connected to the adapter. Then, 15 mL of freshly dried acetonitrile was added, followed by 1a (4.35 g, 50 mmol, 5 equiv), using a syringe. Then, the round-bottom flask was placed to our photoreaction setup using two Kessil 40 W 456 nm blue LEDs at 40 °C in such a way that the distance of the reaction tube from the light source could be maintained at a 3 cm distance overall from both lights. After 24 h of irradiation, the reaction mixture was diluted with 25 mL of DCM, and 30 mL of brine solution was added, added, and extracted with DCM (3 × 50 mL). The combined organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product was then purified via flash column chromatography on silica gel mesh 230-400 using ethyl acetate and hexane as the eluent to afford 2.97 g of product 4a in 87% yield.

Characterization Data of 4 and 6. *N*-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)propyl)-*N*-methylacetamide (**4a**). rr = 1:0.07; R_f = 0.3 (ethyl acetate/n-hexane, 3:7); colorless solid; yield 97% (66.1 mg); ¹H NMR (400 MHz, CDCl₃): δ 7.50–7.41 (m, SH), 4.28 (dd, J = 13.6, 5.9 Hz, 1H), 3.98 (dd, J = 8.5, 6.0 Hz, 1H), 3.76 (dd, J = 13.7, 8.5 Hz, 1H), 2.82 (s, 3H), 2.01 (s, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 171.8, 132.4, 130.4, 129.8, 129.5, 128.9, 127.6 (q, J = 313.4 Hz), 111.6, 51.0, 49.3, 38.2, 38.01 (q, J = 1.7 Hz), 21.8; ¹⁹F NMR (376 MHz, CDCl₃): δ -37.41, -37.67; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₅H₁₅F₃N₃OS 342.0888, found 342.0883.

N-(3,3-Dicyano-2-(*p*-tolyl)-3-((trifluoromethyl)thio)-propyl)-*N*-methylacetamide (**4b**). rr = 1:0.08; R_f = 0.4 (ethyl acetate/n-hexane, 3:7); colorless solid; yield 92% (65.2 mg); ¹H NMR (400 MHz, CDCl₃): δ 7.32 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.26 (dd, J = 13.6, 6.0 Hz, 1H), 3.94 (dd, J = 8.5, 6.0 Hz, 1H), 3.75 (dd, J = 13.6, 8.5 Hz, 1H), 2.84 (s, 3H), 2.38 (s, 3H), 2.02 (s, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.0, 140.8, 130.4, 129.5, 129.0, 127.8 (q, J = 313.3 Hz), 111.9, 111.8, 51.4, 49.3, 38.6, 38.3, 22.0, 21.4; ¹⁹F NMR (376 MHz, CDCl₃): δ -37.45, -37.69; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₇F₃N₃OS, 356.1044; found, 356.1043.

N-(3,3-Dicyano-2-(4-ethylphenyl)-3-((trifluoromethyl)-thio)-propyl)-*N*-methylacetamide (**4c**). rr = 1:0.08; R_f = 0.4 (ethyl acetate/n-hexane, 3:7); colorless solid; yield 87% (64.3 mg); ¹H NMR (400 MHz, CDCl₃): δ 7.32 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 4.23 (dd, J = 13.6, 6.1 Hz, 1H), 3.93 (dd, J = 8.3, 6.1 Hz, 1H), 3.73 (dd, J = 13.6, 8.4 Hz, 1H), 2.81 (s, 3H), 2.65 (q, J = 7.6 Hz, 2H), 2.00 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.0, 146.9, 129.7, 129.1, 129.0, 127.8 (q, J = 313.4 Hz), 111.9, 111.8, 51.5, 49.3, 38.6, 38.3 (q, J = 1.6 Hz), 28.6, 22.0, 15.2; ¹⁹F NMR (376 MHz, CDCl₃): δ -37.46, -37.70; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₇H₁₈F₃N₃OSNa, 392.1020; found, 392.1027.

N-(3,3-Dicyano-2-(4-methoxyphenyl)-3-((trifluoromethyl)thio)-propyl)-*N*-methylacetamide (**4d**). rr = 1:0.07; R_f = 0.5 (ethyl acetate/n-hexane, 4:6); colorless semisolid; yield 86% (63.7 mg); ¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.23 (dd, J = 13.6, 6.0 Hz, 1H), 3.94 (dd, J = 8.5, 5.9 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, J = 13.6, 8.5 Hz, 1H), 2.85 (s, 3H), 2.02 (s, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.0, 161.2, 130.4, 127.8 (q, J = 313.6 Hz), 124.2, 115.0, 111.9, 111.8, 55.5, 51.4, 49.0, 38.5, 38.51, 22.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -37.48, -37.71; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₆H₁₆F₃N₃O₂SnA, 394.0813; found, 394.0808.

N-(3,3-Dicyano-2-(3,4-dimethoxyphenyl)-3-((trifluoromethyl)thio)propyl)-*N*-methylacetamide (**4e**). rr = 1:0.07; R_f = 0.3 (ethyl acetate/n-hexane, 4:6); yellow oil; yield 45% (36.0 mg); ¹H NMR (400 MHz, CDCl₃): δ 6.98–6.95 (m, 2H), 6.88 (d, J = 8.2 Hz, 1H), 4.20 (dd, J = 13.4, 5.8 Hz, 1H), 3.95–3.81 (m, 8H), 2.88 (s, 3H), 2.03 (s, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 172.0, 127.8 (q, J = 313.4 Hz), 124.4, 122.0, 121.9, 112.0, 111.8, 111.5, 56.2, 56.1, 51.2, 49.4, 38.5, 22.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -37.46, -37.68; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₇H₁₈F₃N₃O₃SnA, 424.0919; found, 424.0906.

N-(2-(3-chlorophenyl)-3,3-Dicyano-3-((trifluoromethyl)thio)-propyl)-*N*-methylacetamide (**4f**). rr = 1:0.05; R_f = 0.4 (ethyl acetate/n-hexane, 4:6; colorless solid; yield 91% (68.3 mg); ¹H NMR (400 MHz, CDCl₃): δ 7.62–7.57 (m, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 4.20 (dd, J = 13.8, 6.2 Hz, 1H), 3.99 (dd, J = 8.0,

6.4 Hz, 1H), 3.77 (dd, $J = 13.7, 8.1$ Hz, 1H), 2.88 (s, 3H), 2.04 (d, $J = 8.6$ Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.2, 135.6, 134.6, 131.0, 130.8, 129.3, 127.6 (q, $J = 313.5$ Hz), 127.0, 111.5, 111.4, 51.5, 49.0, 38.7, 37.9 (d, $J = 1.8$ Hz), 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.19, -37.50; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{ClF}_3\text{N}_3\text{OSNa}$, 398.0318; found, 398.0323.

N-(2-(4-Chlorophenyl)-3,3-Dicyano-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4g). $\text{rr} = 1:0.05$; $R_f = 0.5$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 85% (63.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.44–7.38 (m, 4H), 4.20 (dd, $J = 13.7, 6.0$ Hz, 1H), 4.00 (dd, $J = 8.4, 6.0$ Hz, 1H), 3.78 (dd, $J = 13.7, 8.5$ Hz, 1H), 2.86 (s, 3H), 2.02 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.1, 136.8, 131.1, 130.4, 130.0, 127.6 (q, $J = 313.4$ Hz), 111.6, 111.5, 51.3, 48.9, 38.6, 38.0, 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.23, -37.52; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{ClF}_3\text{N}_3\text{OSNa}$, 398.0318; found, 398.0306.

N-(2-(3-Bromophenyl)-3,3-dicyano-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4h). $\text{rr} = 1:0.04$; $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 93% (77.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.62–7.57 (m, 2H), 7.43 (d, $J = 7.9$ Hz, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 4.20 (dd, $J = 13.8, 6.2$ Hz, 1H), 3.98 (dd, $J = 8.1, 6.3$ Hz, 1H), 3.77 (dd, $J = 13.7, 8.2$ Hz, 1H), 2.88 (s, 3H), 2.04 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.2, 134.9, 133.8, 132.2, 131.2, 127.6 (q, $J = 313.5$ Hz), 127.4, 123.6, 111.5, 111.4, 51.5, 48.9, 38.7, 37.9 (q, $J = 1.8$ Hz), 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.16, -37.47; HRMS (ESI) m/z : [M + H]⁺ calcd for $\text{C}_{15}\text{H}_{14}\text{BrF}_3\text{N}_3\text{OS}$, 419.9993; found, 419.9994.

N-(2-(4-Bromophenyl)-3,3-Dicyano-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4i). $\text{rr} = 1:0.04$; $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 89% (74.6 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.58 (d, $J = 8.5$ Hz, 2H), 7.32 (d, $J = 8.5$ Hz, 2H), 4.20 (dd, $J = 13.7, 5.9$ Hz, 1H), 3.98 (dd, $J = 8.4, 5.9$ Hz, 1H), 3.78 (dd, $J = 13.7, 8.5$ Hz, 1H), 2.85 (s, 3H), 2.00 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.1, 133.0, 131.6, 130.6, 127.7 (q, $J = 313.8$ Hz), 125.0, 111.6, 111.5, 51.3, 49.0, 38.7, 37.9, 22.0; ^{19}F NMR (471 MHz, CDCl_3): δ -37.31, -37.60; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{BrF}_3\text{N}_3\text{OSNa}$, 441.9812; found, 441.9817.

N-(3,3-Dicyano-2-(2-fluorophenyl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4j). $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); colorless semisolid; yield 91% (65.4 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.80–7.59 (m, 1H), 7.48–7.43 (m, 1H), 7.29–7.25 (m, 1H), 7.20–7.15 (m, 1H), 4.49–4.32 (m, 1H), 4.25 (dd, $J = 13.7, 5.8$ Hz, 1H), 3.89 (dd, $J = 13.7, 8.6$ Hz, 1H), 2.88 (s, 3H), 2.02 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 171.9, 161.3 (d, $J = 249.4$ Hz), 132.2 (d, $J = 7.1$ Hz), 131.5, 129.0, 127.7 (q, $J = 313.5$ Hz), 126.5, 125.5 (d, $J = 3.6$ Hz), 124.0, 120.1 (d, $J = 14.0$ Hz), 116.5 (d, $J = 22.8$ Hz), 111.6, 111.3, 50.2, 40.3, 37.9 (d, $J = 3.7$ Hz), 34.1, 21.9; ^{19}F NMR (376 MHz, CDCl_3): δ -37.19, -37.51, -115.57 (bs); HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{F}_4\text{N}_3\text{OSNa}$, 382.0613; found, 382.0617.

N-(3,3-Dicyano-2-(4-(trifluoromethyl)phenyl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4k). $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 91% (74.5 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 2H), 4.22 (dd, $J = 13.6, 6.1$ Hz, 1H), 4.11 (dd, $J = 8.0, 6.2$ Hz, 1H), 3.84 (dd, $J = 13.6, 8.2$ Hz, 1H), 2.87 (s, 3H), 2.03 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.2, 136.7, 132.8 (q, $J = 32.7$ Hz), 127.6 (q, $J = 313.6$ Hz), 129.65, 126.7 (q, $J = 3.5$ Hz), 123.6 (q, $J = 272.7$ Hz), 51.4, 49.13, 38.7, 37.8, 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.12, -37.44, -62.90; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{16}\text{H}_{13}\text{F}_6\text{N}_3\text{OSNa}$, 432.0581; found, 432.0589.

N-(3,3-Dicyano-2-(3-cyanophenyl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4l). $\text{rr} = 1:0.04$; $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 85% (62.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.79–7.71 (m, 3H), 7.61 (t, $J = 7.8$ Hz, 1H), 4.17–4.07 (m, 2H), 3.88 (dd, $J = 13.1, 7.5$ Hz, 1H), 2.91 (s, 3H), 2.04 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.3, 134.5, 134.1, 133.2, 132.7, 127.5 (q, $J = 313.9$ Hz), 117.7, 114.1, 111.3, 51.3, 49.0, 38.7, 37.8 (q, $J = 1.6$ Hz), 22.0; ^{19}F NMR (471 MHz, CDCl_3): δ

-37.06, -37.41; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_4\text{OSNa}$, 389.0660; found, 389.0656.

Methyl-4-(1,1-dicyano-3-(N-methylacetamido)-1-((trifluoromethylthio)propan-2-yl)benzoate (4m). $\text{rr} = 1:0.04$; $R_f = 0.2$ (ethyl acetate/n-hexane, 3:7); colorless solid; yield 93% (74.2 mg); ^1H NMR (400 MHz, CDCl_3): δ 8.09 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 2H), 4.25 (dd, $J = 13.7, 5.9$ Hz, 1H), 4.06 (dd, $J = 8.4, 5.9$ Hz, 1H), 3.92 (s, 3H), 3.79 (dd, $J = 13.7, 8.5$ Hz, 1H), 2.82 (s, 3H), 2.00 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.0, 166.1, 137.4, 132.3, 130.7, 129.2, 127.6 (q, $J = 313.6$ Hz), 111.4, 52.5, 51.3, 49.2, 38.6, 37.8 (q, $J = 1.6$ Hz), 21.9; ^{19}F NMR (376 MHz, CDCl_3): δ -37.25, -37.54; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_3\text{SNa}$, 422.0762; found, 422.0764.

N-(2-(4-Acetamidophenyl)-3,3-dicyano-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4n). $\text{rr} = 1:0.07$; $R_f = 0.2$ (ethyl acetate/n-hexane, 5:5); light yellow solid; yield 89% (70.7 mg); ^1H NMR (400 MHz, CDCl_3): δ 8.00 (bs, 1H), 7.62 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H), 4.19 (dd, $J = 12.6, 4.9$ Hz, 1H), 3.95–3.85 (m, 2H), 2.87 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.1, 169.0, 140.4, 129.8, 127.7 (q, $J = 313.4$ Hz), 127.3, 120.3, 111.7, 50.9, 49.2, 38.3, 24.7, 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.39, -37.61; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_2\text{SNa}$, 421.0922; found, 421.0932.

N-(3,3-Dicyano-2-(4-nitrophenyl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4o). $R_f = 0.4$ (ethyl acetate/n-hexane, 4:6); colorless solid; yield 91% (70.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 8.32 (d, $J = 8.8$ Hz, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 4.21–4.15 (m, 2H), 3.91 (dd, $J = 15.5, 9.9$ Hz, 1H), 2.91 (s, 3H), 2.04 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.3, 149.2, 139.6, 130.3, 127.5 (q, $J = 313.8$ Hz), 124.7, 111.3, 111.3, 51.4, 49.0, 38.7, 37.7 (q, $J = 1.9$ Hz), 21.99; ^{19}F NMR (376 MHz, CDCl_3): δ -37.28, -37.29; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_3\text{SNa}$, 409.0558; found, 409.0562.

N-(3,3-Dicyano-2-(thiophen-2-yl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4p). $\text{rr} = 1:0.06$; $R_f = 0.5$ (ethyl acetate/n-hexane, 4:6); yellow oil; yield 66% (45.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.43 (d, $J = 5.1$ Hz, 1H), 7.26–7.24 (m, 1H), 7.08 (dd, $J = 5.0, 3.7$ Hz, 1H), 4.39 (dd, $J = 8.2, 6.0$ Hz, 1H), 4.30 (dd, $J = 13.5, 6.0$ Hz, 1H), 3.66 (dd, $J = 13.5, 8.3$ Hz, 1H), 2.89 (s, 3H), 2.05 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.2, 134.1, 129.7, 128.1, 127.8, 127.7 (q, $J = 313.4$ Hz), 111.5, 111.3, 53.1, 45.3, 38.7, 38.7, 22.0; ^{19}F NMR (376 MHz, CDCl_3): δ -37.29, -37.58; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{N}_3\text{OS}_2\text{Na}$, 370.0272; found, 370.0262.

N-(3,3-Dicyano-2-(pyridin-2-yl)-3-((trifluoromethyl)thio)propyl)-N-methylacetamide (4q). $R_f = 0.2$ (ethyl acetate/n-hexane, 4:6); yellow oil; yield 57% (39.0 mg); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (dd, $J = 4.8, 1.5$ Hz, 1H), 8.62 (d, $J = 2.2$ Hz, 1H), 7.93–7.89 (m, 1H), 7.41 (dd, $J = 8.0, 4.8$ Hz, 1H), 4.18 (dd, $J = 13.5, 5.9$ Hz, 1H), 4.05 (dd, $J = 8.4, 6.0$ Hz, 1H), 3.90 (dd, $J = 13.5, 8.4$ Hz, 1H), 2.88 (s, 3H), 2.01 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.1, 151.8, 150.5, 136.0, 128.7, 127.5 (q, $J = 313.7$ Hz), 124.3, 111.3, 50.9, 47.2, 38.4, 37.91 (q, $J = 1.6$ Hz), 21.88; ^{19}F NMR (376 MHz, CDCl_3): δ -37.35; HRMS (ESI) m/z : [M + H]⁺ calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{N}_4\text{OS}$, 343.0840; found, 343.0843.

N-(2-(Dicyano((trifluoromethyl)thio)methyl)-3-methylbutyl)-N-methylacetamide (4r). $R_f = 0.3$ (ethyl acetate/n-hexane, 3:7); yellow oil; yield 36% (22.2 mg); ^1H NMR (400 MHz, CDCl_3): δ 4.00 (dd, $J = 14.6, 4.2$ Hz, 1H), 3.40 (dd, $J = 14.6, 9.0$ Hz, 1H), 3.14 (s, 3H), 2.93–2.89 (m, 1H), 2.46–2.36 (m, 1H), 2.09 (s, 3H), 1.21 (d, $J = 7.1$ Hz, 3H), 1.11 (d, $J = 7.1$ Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.8, 127.8 (q, $J = 313.5$ Hz), 112.5, 111.9, 48.2, 47.1, 39.0, 38.2 (q, $J = 1.9$ Hz), 29.9, 22.5, 22.0, 16.4; ^{19}F NMR (376 MHz, CDCl_3): δ -37.67; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{N}_3\text{OSNa}$, 330.0864; found, 330.0863.

N-(2-(Dicyano((trifluoromethyl)thio)methyl)tridecyl)-N-methylacetamide (4s). $R_f = 0.4$ (ethyl acetate/n-hexane, 3:7); light yellow oil; yield 44% (36.7 mg); ^1H NMR (400 MHz, CDCl_3): δ 3.80 (dd, $J = 14.4, 5.5$ Hz, 1H), 3.43 (dd, $J = 14.5, 7.9$ Hz, 1H), 3.11 (s, 3H), 2.89–2.78 (m, 1H), 2.09 (s, 3H), 1.83–1.74 (m, 1H), 1.57–1.46 (m, 2H),

1.38–1.16 (m, 18H), 0.87 (t, J = 6.8 Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.6, 127.8 (q, J = 313.0 Hz), 112.0, 111.6, 50.4, 44.0, 38.9 (d, J = 1.8 Hz), 38.8, 32.0, 30.4, 29.7, 29.6, 29.5, 29.4, 29.3, 27.1, 22.8, 22.2, 14.2; ^{19}F NMR (376 MHz, CDCl_3): δ –37.41; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{20}\text{H}_{32}\text{F}_3\text{N}_3\text{OSNa}$, 442.2116; found, 442.2137.

N-(2-(Dicyano((trifluoromethyl)thio)methyl)-4,8-dimethylnon-7-en-1-yl)-N-methylacetamide (4t). dr = 1:1; Inseparable diastereomer; R_f = 0.4 (ethyl acetate/n-hexane, 3:7); yellow oil; yield 51% (39.7 mg); ^1H NMR (400 MHz, CDCl_3): δ 5.11–5.04 (m, 2H), 3.84–3.74 (m, 2H), 3.42 (dd, J = 14.4, 8.1 Hz, 1H), 3.32 (dd, J = 14.6, 8.6 Hz, 1H), 3.12 (d, J = 2.5 Hz, 6H), 3.04–2.98 (m, 1H), 2.95–2.87 (m, 1H), 2.09 (s, 6H), 2.06–1.93 (m, 4H), 1.75–1.61 (m, 1SH), 1.52–1.41 (m, 3H), 1.37–1.28 (m, 3H), 1.23–1.17 (m, 1H), 1.01 (d, J = 6.3 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.8, 172.6, 132.1, 127.9 (q, J = 313.1 Hz), 124.1, 112.1, 112.0, 111.7, 111.6, 51.4, 51.2, 42.2, 42.0, 39.4 (d, J = 2.0 Hz), 39.3 (d, J = 1.9 Hz), 39.2, 38.9, 38.2, 37.9, 37.7, 36.0, 31.3, 30.7, 25.8, 25.5, 25.2, 22.3, 22.3, 20.1, 19.0, 17.9; ^{19}F NMR (376 MHz, CDCl_3): δ –37.31, –37.31; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{18}\text{H}_{26}\text{F}_3\text{N}_3\text{OSNa}$ 412.1646, found 412.1657.

N-((5R)-2-(Dicyano((trifluoromethyl)thio)methyl)-5-((5R,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)hexyl)-N-methylacetamide (4u). dr = 1:0.1; Inseparable diastereomer; R_f = 0.5 (ethyl acetate/n-hexane, 4:6); colorless solid; yield 59% (71.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 3.84–3.76 (m, 2H), 3.46–3.36 (m, 2H), 3.11 (s, 6H), 2.78 (dd, J = 15.4, 7.4 Hz, 2H), 2.67 (dd, J = 21.2, 7.1 Hz, 2H), 2.36–2.28 (m, 2H), 2.19–2.12 (m, 3H), 2.09 (s, 6H), 2.05–1.99 (m, 7H), 1.92–1.78 (m, 8H), 1.72–1.55 (m, 4H), 1.50–1.31 (m, 18H), 1.29–1.10 (m, 16H), 1.00 (s, 6H), 0.94 (d, J = 6.5 Hz, 6H), 0.67 (d, J = 5.3 Hz, 6H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 213.4, 172.6, 172.5, 112.0, 111.63, 56.5, 56.4, 55.91, 55.7, 50.6, 50.3, 44.7, 44.4, 44.3, 42.9, 42.9, 42.5, 40.8, 40.1, 40.1, 39.0–38.8 (m), 38.8, 37.3, 37.1, 36.1, 35.8, 35.6, 35.0, 33.5, 33.3, 28.4, 27.2, 26.71, 25.9, 25.8, 24.3, 22.7, 22.2, 21.3, 18.7, 18.5, 12.2; ^{19}F NMR (376 MHz, CDCl_3): δ –37.36, –37.36; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{32}\text{H}_{46}\text{F}_3\text{N}_3\text{O}_2\text{SNa}$, 616.3161; found, 616.3154.

Methyl 2-Cyano-4-(N-methylacetamido)-3-phenyl-2-((trifluoromethyl)thio)butanoate (4v). dr = 1:0.1; Inseparable diastereomer; R_f = 0.3 (ethyl acetate/n-hexane, 5:5); yellow oil; yield 56% (42.0 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.38–7.34 (m, 5H), 4.40 (dd, J = 13.5, 4.2 Hz, 1H), 3.74 (dd, J = 10.1, 4.1 Hz, 1H), 3.56 (dd, J = 13.5, 10.1 Hz, 1H), 3.47 (s, 3H), 2.61 (s, 3H), 1.98 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 171.4, 170.8, 164.4, 134.7, 134.4, 133.6, 132.3, 130.1, 129.9, 129.5, 129.4, 129.1, 124.8, 114.9, 114.5, 54.7, 54.4, 53.1, 52.6 (d, J = 1.2 Hz), 51.7, 50.2, 48.4, 38.6, 34.2, 32.1, 21.9, 21.3; ^{19}F NMR (376 MHz, CDCl_3): δ –38.02, –38.66; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{SNa}$, 397.0810; found, 397.0826.

Ethyl 2-Cyano-4-(N-methylacetamido)-3-phenyl-2-((trifluoromethyl)thio)butanoate (4w). dr = 1:0.2, rr = 1:0.15; Inseparable diastereomer; R_f = 0.4 (ethyl acetate/n-hexane, 4:6); yellow oil; yield 78% (60.6 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.47–7.32 (m, 6.75H), 4.44–4.37 (m, 1.45H), 4.07–3.87 (m, 2.9H), 3.72–3.66 (m, 1.2H), 3.54 (dd, J = 13.4, 10.0 Hz, 1H), 3.34 (dd, J = 9.3, 4.6 Hz, 0.14H), 2.73 (s, 0.45H), 2.64 (s, 0.6H), 2.59 (s, 3H), 1.97 (s, 3H), 1.93 (s, 0.6H), 1.90 (s, 0.45H), 1.42–1.39 (m, 1.05H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 171.4, 171.3, 170.8, 164.7, 163.8, 163.6, 134.8, 133.8, 133.7, 129.9, 129.8, 129.3, 129.2, 129.04, 128.6 (q, J = 311.3 Hz), 115.2, 115.0, 114.6, 65.1, 64.6, 64.2, 53.3, 52.5, 51.9, 51.2, 50.1, 48.3, 38.5, 38.3, 34.2, 32.0, 29.8, 29.4, 21.9, 21.8, 21.3, 14.2, 13.8, 13.4; ^{19}F NMR (376 MHz, CDCl_3): δ –37.85, –38.49; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{SNa}$, 411.0966; found, 411.0952.

N-(3-Cyano-4-oxo-2,4-diphenyl-3-((trifluoromethyl)thio)butyl)-N-methylacetamide (4x). dr = 1:1, rr = 1:0.15; Inseparable diastereomer; R_f = 0.4 (ethyl acetate/n-hexane, 3:7); yellow oil; yield 36% (30.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 8.25 (dd, J =

14.5, 4.2 Hz, 2H), 7.76–7.71 (m, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.56–7.48 (m, 5H), 7.48–7.39 (m, 3H), 7.32 (dd, J = 14.1, 6.1 Hz, 3H), 7.23–7.17 (m, 1H), 7.12 (t, J = 7.4 Hz, 2H), 7.07 (bs, 1H), 4.61–4.51 (m, 2H), 4.04 (dd, J = 10.0, 4.1 Hz, 1H), 3.83–3.69 (m, 2H), 3.54 (dd, J = 13.4, 10.1 Hz, 1H), 2.64 (s, 3H), 2.55 (s, 3H), 2.00 (s, 3H), 1.67 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 188.4, 188.3, 171.8, 171.6, 135.0, 134.6, 134.5, 134.3, 133.9, 133.7, 133.0, 130.2, 129.9, 129.4, 129.3, 129.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4 (q, J = 311.9 Hz), 128.3 (q, J = 312.1 Hz), 127.9, 127.9, 116.2, 116.0, 58.5, 57.5, 53.1, 51.9, 48.6, 48.3, 38.8, 38.6, 29.8, 29.5, 22.8, 22.0, 21.7; ^{19}F NMR (376 MHz, CDCl_3): δ –36.34, –36.59, –36.85, –36.94; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2\text{SNa}$, 443.1017; found, 443.1027.

N,N'-(1,3-Phenylenebis(3,3-dicyano-3-((trifluoromethyl)thio)propane-2,1-diyl))bis(N-methylacetamide) (4y). dr = 1:0.5; Inseparable diastereomer; R_f = 0.4 (ethyl acetate/n-hexane, 4:6); light yellow solid; yield 59% (71.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.71–7.54 (m, 5H), 7.51 (s, 1H), 4.34 (dd, J = 13.6, 4.6 Hz, 1H), 4.29 (dd, J = 13.5, 4.7 Hz, 2H), 4.01–3.90 (m, 3H), 3.82–3.71 (m, 3H), 2.78 (s, 6H), 2.76 (s, 3H), 2.00 (s, 6H), 1.98 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.1, 172.0, 134.9, 131.1, 131.0, 127.6 (q, J = 313.4 Hz), 111.5, 111.4, 111.3, 50.9, 50.8, 49.4, 49.1, 38.6, 38.4, 38.3 (q, J = 1.9 Hz), 38.2 (q, J = 1.7 Hz), 21.8; ^{19}F NMR (376 MHz, CDCl_3): δ –37.51; HRMS (ESI) m/z : [M + H]⁺ calcd for $\text{C}_{24}\text{H}_{23}\text{F}_6\text{N}_2\text{O}_2\text{S}_2$, 605.1228; found, 605.1227.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylformamide (6a). rr = 1:0.4; R_f = 0.3 (ethyl acetate/n-hexane, 3:7); yellow oil; yield 72% (47.1 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.95 (s, 1H), 7.84 (s, 0.4H), 7.51–7.38 (m, 7H), 4.26–4.19 (m, 1H), 4.11–4.05 (m, 0.8H), 3.93–3.86 (m, 2H), 3.58 (dd, J = 9.1, 5.3 Hz, 0.4H), 2.82 (s, 1.2H), 2.72 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 163.4, 162.5, 131.8, 131.3, 130.8, 130.2, 129.7, 129.2, 127.7 (q, J = 313.2 Hz), 127.5 (q, J = 313.9 Hz), 111.7, 111.5, 111.4, 111.2, 51.4, 51.0, 49.2, 47.2, 38.3, 37.9, 36.1, 30.3; ^{19}F NMR (376 MHz, CDCl_3): δ –37.33, –37.50; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{N}_3\text{OSNa}$, 350.0551; found, 350.0546.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylpropionamide (6b). R_f = 0.4 (ethyl acetate/n-hexane, 4:6); colorless solid; yield 93% (66.1 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.49–7.39 (m, 5H), 4.30 (dd, J = 13.6, 5.9 Hz, 1H), 3.99 (dd, J = 8.6, 5.8 Hz, 1H), 3.75 (dd, J = 13.5, 8.6 Hz, 1H), 2.79 (s, 3H), 2.32–2.16 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 175.1, 132.7, 130.5, 129.7, 129.1, 127.8 (q, J = 313.3 Hz), 111.8, 111.7, 51.8, 49.5, 38.1 (d, J = 1.7 Hz), 37.8, 26.9, 8.9; ^{19}F NMR (376 MHz, CDCl_3): δ –37.69; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{N}_3\text{OSNa}$, 378.0864; found, 378.0865.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylbutyramide (6c). R_f = 0.3 (ethyl acetate/n-hexane, 4:6); colorless solid; yield 97% (71.4 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.50–7.37 (m, 5H), 4.30 (dd, J = 13.5, 5.6 Hz, 1H), 3.98 (dd, J = 8.7, 5.6 Hz, 1H), 3.77 (dd, J = 13.6, 8.8 Hz, 1H), 2.79 (s, 3H), 2.27–2.13 (m, 2H), 1.60 (h, J = 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 174.3, 132.7, 130.5, 129.7, 129.1, 127.8 (q, J = 313.3 Hz), 111.7, 51.7, 49.5, 38.2 (q, J = 1.7 Hz), 37.9, 35.6, 18.1, 13.9; ^{19}F NMR (376 MHz, CDCl_3): δ –37.68; HRMS (ESI) m/z [M + H]⁺ calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_3\text{OS}$, 370.1201; found, 370.1208.

2-Chloro-N-(3,3-dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylacetamide (6d). R_f = 0.2 (ethyl acetate/n-hexane, 2:5); yellow oil; yield 75% (56.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.51–7.41 (m, 5H), 4.35 (dd, J = 13.5, 5.2 Hz, 1H), 4.03–3.93 (m, 3H), 3.79 (dd, J = 13.5, 9.2 Hz, 1H), 2.85 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 167.6, 132.2, 130.8, 129.8, 129.1, 127.7 (q, J = 313.4 Hz), 111.6, 111.6, 52.0, 49.2, 41.2, 38.1; ^{19}F NMR (376 MHz, CDCl_3): δ –37.57; HRMS (ESI) m/z [M + H]⁺ calcd for $\text{C}_{15}\text{H}_{14}\text{ClF}_3\text{N}_3\text{OS}$, 376.0498; found, 376.0495.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylcyclohexanecarboxamide (6e). R_f = 0.3 (ethyl acetate/n-hexane, 4:6); colorless solid; yield 55% (44.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.51–7.34 (m, 5H), 4.33 (dd, J = 13.4, 5.0 Hz, 1H), 3.94 (dd, J = 9.4, 5.0 Hz, 1H), 3.68 (dd, J = 13.4, 9.4 Hz, 1H), 2.75 (s,

3H), 2.32 (tt, $J = 11.5, 3.3$ Hz, 1H), 1.75–1.35 (m, 7H), 1.26–1.13 (m, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 177.2, 132.7, 130.4, 129.56, 129.1, 111.6, 51.6, 49.3, 40.9, 38.12 (q, $J = 1.7$ Hz), 37.6, 29.1, 28.7, 25.8, 25.7; ^{19}F NMR (376 MHz, CDCl_3): δ –37.74; HRMS (ESI) m/z [M + H]⁺ calcd for $\text{C}_{20}\text{H}_{23}\text{F}_3\text{N}_3\text{OS}$, 410.1514; found, 410.1510.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylbenzamide (6f). $R_f = 0.3$ (ethyl acetate/n-hexane, 4:6); yellow oil; yield 71% (57.1 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.52–7.32 (m, 8H), 7.17 (d, $J = 6.9$ Hz, 2H), 4.44–4.41 (m, 1H), 4.13–3.96 (m, 2H), 2.77 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 172.3, 135.3, 130.7, 130.2, 129.7, 129.1, 128.6, 127.7 (d, $J = 313.5$ Hz), 126.95, 111.7, 111.6, 50.8, 49.5, 39.9, 38.2; ^{19}F NMR (376 MHz, CDCl_3): δ –37.55; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{OSNa}$, 426.0864; found, 426.0861.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methyl-3-phenylpropanamide (6g). $R_f = 0.3$ (ethyl acetate/n-hexane, 3:7); yellow oil; yield 37% (31.9 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.49–7.40 (m, 5H), 7.31–7.27 (m, 2H), 7.23–7.17 (m, 3H), 4.33 (dd, $J = 13.6, 5.8$ Hz, 1H), 3.97 (dd, $J = 8.7, 5.8$ Hz, 1H), 3.76 (dd, $J = 13.6, 8.7$ Hz, 1H), 2.99–2.91 (m, 2H), 2.75 (s, 3H), 2.60–2.47 (m, 2H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 173.5, 141.1, 132.7, 131.5, 130.5, 129.7, 129.1, 128.7, 128.5, 127.8 (d, $J = 313.5$ Hz), 126.4, 111.7, 51.9, 49.5, 38.13 (q, $J = 1.7$ Hz), 37.8, 35.5, 30.9; ^{19}F NMR (376 MHz, CDCl_3): δ –37.73; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{22}\text{H}_{20}\text{F}_3\text{N}_3\text{OSNa}$, 454.1177; found, 454.1151.

N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylpivalamide (6h). $R_f = 0.3$ (ethyl acetate/n-hexane, 2:8); yellow oil; yield 72% (67.2 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.47–7.40 (m, 5H), 4.38 (dd, $J = 13.3, 4.8$ Hz, 1H), 3.97 (dd, $J = 9.7, 4.8$ Hz, 1H), 3.58 (dd, $J = 13.3, 9.7$ Hz, 1H), 2.82 (s, 3H), 1.16 (s, 9H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 178.5, 133.0, 130.4, 129.5, 129.1, 127.8 (q, $J = 313.3$ Hz), 111.7, 53.7, 49.1, 39.5, 38.9, 38.2 (q, $J = 1.8$ Hz), 27.79; ^{19}F NMR (376 MHz, CDCl_3): δ –37.75; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{18}\text{H}_{20}\text{F}_3\text{N}_3\text{OSNa}$, 406.1177; found, 406.1188.

(S)-N-(3,3-Dicyano-2-phenyl-3-((trifluoromethyl)thio)-propyl)-N-methylenesulfonamide (6i). $R_f = 0.3$ (ethyl acetate/n-hexane, 3:7); yellow oil; yield 38% (33.36 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.79–7.76 (m, 2H), 7.66–7.62 (m, 1H), 7.55 (dd, $J = 10.4, 4.6$ Hz, 2H), 7.52–7.44 (m, 5H), 3.95–3.86 (m, 2H), 3.57 (dd, $J = 14.0, 9.1$ Hz, 1H), 2.60 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 136.3, 133.4, 131.8, 130.7, 129.7, 129.5, 129.2, 127.7 (q, $J = 313.5$ Hz), 127.6, 111.7, 111.3, 52.4, 52.3, 38.1 (d, $J = 1.7$ Hz), 37.7; ^{19}F NMR (376 MHz, CDCl_3): δ –37.66; HRMS (ESI) m/z : [M + Na]⁺ calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2\text{S}_2\text{Na}$, 462.0534; found, 462.0507.

2-(Methyl(phenyl)amino)-1-phenylethyl-2-((trifluoromethyl)thio)malononitrile (6j). $R_f = 0.3$ (ethyl acetate/n-hexane, 1:9); yellow oil; yield 29% (21.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.50–7.40 (m, 5H), 7.30 (dd, $J = 8.5, 7.4$ Hz, 2H), 6.85 (t, $J = 7.3$ Hz, 1H), 6.74 (d, $J = 8.1$ Hz, 2H), 4.27 (dd, $J = 15.1, 7.2$ Hz, 1H), 3.95 (dd, $J = 15.1, 6.9$ Hz, 1H), 3.76 (t, $J = 7.0$ Hz, 1H), 2.83 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 147.7, 133.0, 130.5, 129.74, 129.1, 127.9 (q, $J = 315.9$ Hz), 118.8, 113.7, 112.3, 111.8, 55.8, 50.4, 41.3, 38.56 (d, $J = 1.7$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ –38.06; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{SNa}$, 398.0909; found, 398.0913.

2-(Phenyl(tetrahydrofuran-2-yl)methyl)-2-((trifluoromethyl)thio)malononitrile (6k). $dr = 1:0.9$; Inseparable diastereomer; $R_f = 0.4$ (ethyl acetate/n-hexane, 2:8); colorless oil; yield 61% (39.8 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.57–7.55 (m, 2H), 7.49–7.38 (m, 7.5H), 4.75–4.65 (m, 1.9H), 4.13–4.08 (m, 0.9H), 3.96 (dd, $J = 15.3, 7.0$ Hz, 0.9H), 3.87–3.84 (m, 2H), 3.34 (d, $J = 2.9$ Hz, 1H), 3.30 (d, $J = 10.2$ Hz, 0.9H), 2.12–2.04 (m, 1H), 2.01–1.78 (m, 3.6H), 1.63–1.42 (m, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 132.5, 131.0, 131.0, 130.5, 130.2, 129.7, 128.0 (d, $J = 313.4$ Hz), 127.9 (d, $J = 313.4$ Hz), 112.8, 112.4, 112.2, 112.1, 79.8, 78.0, 69.6, 69.1, 58.4, 56.3, 39.2 (d, $J = 1.7$ Hz), 38.6 (d, $J = 1.6$ Hz), 31.4, 30.4, 25.6, 25.3; ^{19}F NMR (376 MHz, CDCl_3): δ –37.65, –38.08; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{OSNa}$, 349.0598; found, 349.0599.

2-((1,4-Dioxan-2-yl) (phenyl)methyl)-2-((trifluoromethyl)thio)malononitrile (6l). $dr = 1:0.75$; Inseparable diastereomer; $R_f = 0.3$ (ethyl acetate/n-hexane, 2:8); colorless oil; yield 34% (23.3 mg); ^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, $J = 7.0$ Hz, 1.5H), 7.48–7.37 (m, 7.25H), 4.48–4.44 (m, 0.75H), 4.36–4.30 (m, 1H), 4.04–3.99 (m, 1.75H), 3.90–3.83 (m, 1.75H), 3.78–3.70 (m, 1.75H), 3.67–3.61 (m, 1H), 3.56–3.49 (m, 1.5H), 3.45 (d, $J = 10.6$ Hz, 1H), 3.34–3.22 (m, 2.75H), 3.06 (dd, $J = 11.5, 9.9$ Hz, 0.75H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 131.0, 130.9, 130.6, 130.4, 129.9, 129.3, 127.8 (q, $J = 313.6$ Hz), 112.6, 112.0, 111.8, 111.7, 76.1, 74.9, 69.1, 68.6, 67.6, 66.9, 66.3, 66.3, 54.8, 53.6, 38.7 (d, $J = 1.7$ Hz), 37.9 (d, $J = 1.6$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ –37.34, –37.94; HRMS (ESI) m/z [M + K]⁺ calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{SK}$, 381.0287; found, 381.0271.

Procedure for Further Functionalization of Product 4a. ¹⁵ **N-(tert-Butyl)-2-cyano-4-(N-methylacetamido)-3-phenyl-2-((trifluoromethyl)thio)-butanamide (7).** To an oven-dried 20 mL reaction tube equipped with a magnetic stir bar were added 0.2 mmol 4a (1 equiv), 0.1 mL of concentrated H_2SO_4 , and 2 mL of tBuOH. After sealing with a septum, the reaction tube was heated at 50 °C for 24 h. Then, the reaction mixture was neutralized with saturated NaHCO_3 solution (added dropwise) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 , and the solvent was evaporated under reduced pressure. The crude product was then purified via flash column chromatography on silica gel mesh 230–400 using ethyl acetate and hexane as the eluent to afford 68.6 mg of product 7 in 83% yield. Both the diastereomers are separated via gradual elution of ethyl acetate and hexane; yield 83% (68.6 mg); $dr = 1:1$; Isomer (\pm)-7': (rr = 1:0.2); $R_f = 0.4$ (ethyl acetate/n-hexane, 5:5); colorless solid; ^1H NMR (500 MHz, CDCl_3): δ 7.48–7.27 (m, 6H), 5.89 (s, 1H), 5.79 (s, 0.2H), 4.29 (dd, $J = 13.2, 4.0$ Hz, 1H), 4.04 (dd, $J = 14.8, 4.3$ Hz, 0.2H), 3.96 (dd, $J = 14.8, 9.9$ Hz, 0.2H), 3.74–3.59 (m, 2H), 3.43 (dd, $J = 9.9, 4.3$ Hz, 0.2H), 2.69 (s, 0.6H), 2.62 (s, 3H), 1.96 (s, 0.6H), 1.94 (s, 3H), 0.99 (s, 10.2H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 171.3, 160.0, 134.7, 129.6, 129.2, 129.1, 128.9, 128.71 (q, $J = 311.3$ Hz), 116.7, 54.0, 52.8, 51.1, 48.8, 37.9, 27.8, 27.7, 21.9; ^{19}F NMR (471 MHz, CDCl_3): δ –37.63, –38.04; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{19}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_2\text{SNa}$ 438.1439, found 438.1442; Isomer (\pm)-7'': (rr = 1:0.4); $R_f = 0.3$ (ethyl acetate/n-hexane, 5:5); colorless solid; ^1H NMR (500 MHz, CDCl_3): δ 7.51–7.29 (m, 7H), 6.43 (s, 0.4H), 6.36 (s, 1H), 4.07 (dd, $J = 12.4, 9.9$ Hz, 1H), 3.90 (dd, $J = 14.2, 10.5$ Hz, 0.4H), 3.83–3.70 (m, 2.4H), 3.62 (dd, $J = 14.3, 3.3$ Hz, 0.4H), 2.63 (s, 4.2H), 1.86 (s, 3H), 1.84 (s, 1.2H), 1.43 (s, 3.6H), 1.42 (s, 9H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ 171.1, 161.0, 160.6, 133.6, 133.2, 129.8, 129.7, 129.6, 129.1, 128.6 (d, $J = 311.7$ Hz), 117.4, 116.5, 54.3, 54.0, 53.6, 52.9, 52.6, 50.0, 49.0, 48.8, 37.2, 34.3, 28.1, 21.9, 21.1; ^{19}F NMR (471 MHz, CDCl_3): δ –37.82, –38.00; HRMS (ESI) m/z [M + Na]⁺ calcd for $\text{C}_{19}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_2\text{SNa}$, 438.1439; found, 438.1451.

2-Cyano-4-(N-methylacetamido)-3-phenyl-2-((trifluoromethyl)thio)butanamide (8). To an oven-dried 20 mL reaction tube equipped with a magnetic stir bar were added 0.2 mmol 4a (1 equiv) and 2 mL of concentrated H_2SO_4 . After sealing with a septum, the reaction tube was stirred at room temperature for 24 h. Then, the reaction mixture was neutralized with saturated NaHCO_3 solution (added dropwise) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 , and the solvent was evaporated under reduced pressure. The crude product was then purified via flash column chromatography on silica gel mesh 230–400 using ethyl acetate and hexane as the eluent to afford 60.4 mg of product 8 in 84% yield. Both the diastereomers are separated via gradual elution of ethyl acetate and hexane; yield 84% (60.4 mg); $dr = 1:1$; Isomer (\pm)-8': (rr = 1:0.3); $R_f = 0.3$ (ethyl acetate); colorless solid; ^1H NMR (500 MHz, DMSO- d_6): δ 8.11 (bs, 0.3H), 8.09 (bs, 1H), 7.90 (bs, 0.3H), 7.80 (bs, 1H), 7.47–7.25 (m, 6.5H), 4.07 (dd, $J = 12.9, 3.6$ Hz, 1H), 4.01 (dd, $J = 14.5, 3.6$ Hz, 0.3H), 3.88 (dd, $J = 14.3, 9.9$ Hz, 0.3H), 3.82 (dd, $J = 10.3, 3.6$ Hz, 1.3H), 3.75 (dd, $J = 12.7, 10.4$ Hz, 1H), 2.57 (s, 0.9H), 2.55 (s, 3H), 1.85 (s, 3H), 1.80 (s, 0.9H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, DMSO- d_6): δ 170.2, 169.6, 163.7, 163.7, 134.9, 134.7, 129.2, 128.8, 128.6 (q, $J = 310.8$ Hz), 128.6,

128.5, 128.4 (q, $J = 310.9$ Hz), 128.3, 115.7, 54.5, 53.8, 52.9, 50.1, 47.3, 46.7, 36.7, 33.4, 21.5, 21.0; ^{19}F NMR (471 MHz, DMSO- d_6): δ -37.55, -37.85; HRMS (ESI) m/z [M + Na]⁺ calcd for C₁₅H₁₆F₃N₃O₂SnA 382.0813, found 382.0818; Isomer (\pm)-8": (rr = 1.04); R_f = 0.2 (ethyl acetate); colorless solid; ^1H NMR (500 MHz, DMSO- d_6): δ 8.50 (bs, 0.4H), 8.41 (bs, 0.4H), 8.40 (bs, 1H), 8.26 (bs, 1H), 7.63–7.32 (m, 7H), 4.13 (dd, $J = 13.2, 10.3$ Hz, 1H), 4.02 (dd, $J = 10.3, 4.8$ Hz, 1H), 3.97–3.85 (m, 0.8H), 3.69 (dd, $J = 13.7, 2.7$ Hz, 0.4H), 3.51 (dd, $J = 13.3, 4.9$ Hz, 1H), 2.66 (s, 3H), 2.51 (s, 1.2H), 1.81 (s, 1.2H), 1.77 (s, 3H); $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, DMSO): δ 170.6, 170.1, 165.2, 134.4, 134.31, 130.0, 129.7, 129.5, 129.1, 128.9 (q, $J = 311.4$ Hz), 128.8 (d, $J = 311.6$ Hz), 116.2, 116.2, 55.4, 54.9, 52.0, 48.6, 48.0, 47.4, 36.9, 33.9, 22.0, 21.3; ^{19}F NMR (471 MHz, DMSO- d_6): δ -37.86, -37.91; HRMS (ESI) m/z : [M + Na]⁺ calcd for C₁₅H₁₆F₃N₃O₂SnA, 382.0813; found, 382.0799.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c00783>.

X-ray data for 4a and 8", experimental procedure, characterization data, and copies of ^1H , $^{13}\text{C}\{\text{H}\}$, and ^{19}F NMR spectra of all new compounds ([PDF](#))

Accession Codes

CCDC 2121174 and 2151136 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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