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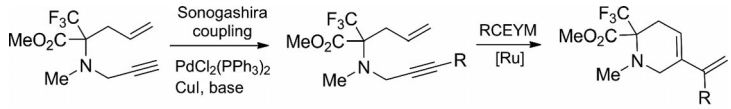

R = Ar, aroyl, acyl [Ru] = Grubbs I, II, Hoveyda–Grubbs II

An efficient method to prepare new α-CF_3 α-amino acid 1,7-enynes that contain different substituents on the triple bond has been developed that proceeds by a Sonogashira-type coupling reaction. The ring-closing enyne methathesis (RCEYM) of the obtained 1,7-enynes with commercially available Grubbs and Hoveyda catalysts provides access to a series of new cyclic α-amino acids.

Keywords: Amino acids / Enynes / Metathesis / Cyclization / Cross-coupling / Fluorine

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Access to Cyclic α-CF_3-Substituted α-Amino Acid Derivatives by Ring-Closing Metathesis of Functionalized 1,7-Enynes

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Keywords: Amino acids / Enynes / Metathesis / Cyclization / Cross-coupling / Fluorine

An efficient method for the preparation of new α-CF_3 α-amino acid 1,7-enynes that contain electron-donating and electron-withdrawing groups on the triple bond has been developed that proceeds through a Sonogashira-type coupling reaction. The ring-closing enyne methathesis (RCEYM) of the obtained 1,7-enynes with commercially available Grubbs and Hoveyda catalysts provides access to a series of new cyclic α-amino acids. The latter compounds that contain the 1,3-diene moiety are attractive building blocks for the construction of trifluoromethylated polycyclic systems.

Introduction

Cyclic α-amino acids that contain a piperidine ring are present in many biologically important compounds.[1] Pipecolic acid derivatives[2] are nonproteogenic α-amino acids that are found as metabolites in several biological systems (e.g., plants, fungi, and human physiological fluids) and often exhibit interesting pharmacological activities. The immunosuppressors rapamycin[3] and FK506[4] as well as the antitumor antibiotic sandramycin[5] are examples of compounds with a pipecolic acid fragment in their structure. Although several methods may be envisioned for the synthesis of such structures, the ring-closing metathesis (RCM) of α-amino acids that incorporates a 1,7-diene/enyne skeleton must surely rank as one of the more direct and potentially efficient methods.

Because of the unique properties of substances with fluorine substituents, such as high electronegativity and hydrophobicity, fluorinated compounds have become very important in the field of medicinal chemistry and pharmaceuticals.[6] Among them, fluorinated amino acids are interesting building blocks that can be used to design the folds of hyperstable proteins or obtain highly specific protein···protein interactions.[7] Moreover, ^{19}F NMR spectroscopy is an effective tool for conformational studies of fluorine-containing peptides. As fluorine considerably improves the profile of bioactive peptides, the synthesis of fluorinated α-amino acids is currently attracting attention.[8]

In past decades, ruthenium alkylidene-catalyzed alkene metathesis has emerged as a powerful tool of synthetic organic and biomedical chemistry for the preparation of various biologically active molecules, including natural products.[9] The ring-closing enyne metathesis (RCEYM) was revealed as one of the most versatile methods in terms of efficiency and atom-economy to afford functionalized cyclic and heterocyclic products that contain the synthetically useful 1,3-diene moiety for a cross-metathesis or Diels–Alder reaction.[10] Recent examples of biologically relevant compounds that were synthesized by sequences utilizing the RCEYM as a key step include the antitumor and antiviral agents acylfulvene and irofulven[11] as well as nucleoside analogues to the agent stavudine.[12]

The development of efficient methods for the preparation of functionally substituted 1,7-enynes and their catalytic cyclization to access new representatives of the pipecolic acid family, including their fluorinated derivatives, is of current interest. Although the RCEYM of N-tethered 1,7-enynes has successfully afforded a variety of functionalized piperidines, which include pipecolic acid derivatives,[13] this catalytic cyclization is still a capricious transformation that depends on the steric and electronic effects of the substituents of 1,7-enyne structure. Furthermore, there is a lack of straightforward methods to access functionalized enynes, and only α-H-α-amino acid 1,7-enynes that contain terminal triple bonds have been utilized for the synthesis of pipecolic acid derivatives. In this case, a high loading of the Grubbs catalyst (20 mol-%) was required to afford appropriate yields of the metathesis products.[13e–13g]

We have previously described a convenient one-step method for the synthesis of trifluoromethylated 1,7-enynes

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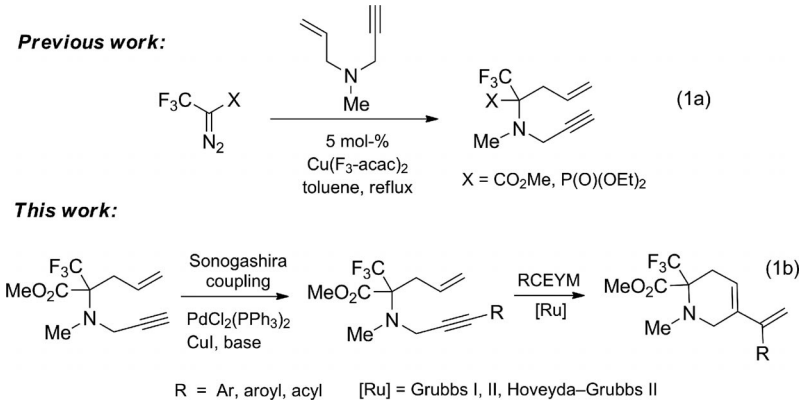


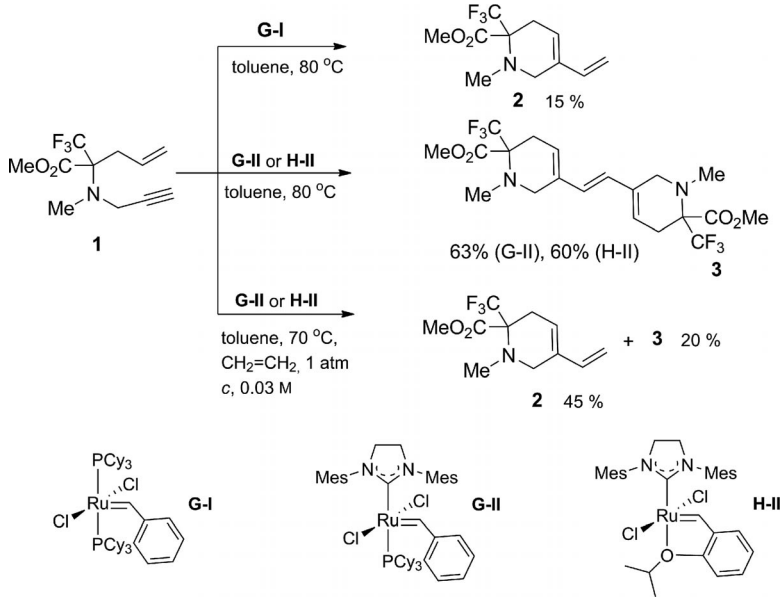
Figure 1. Synthesis and transformations of fluorinated 1,7-enynes (acac = acetylacetonate).

that incorporates α-aminocarboxylic and α-aminophosphonic acids and utilizes a highly selective Cu^{II}-catalyzed [2,3] sigmatropic rearrangement of the allyl group of an allylpropargyl-containing nitrogen CF_3-ylides[14] [see Figure 1, Equation (1a)]. Herein, we disclose the synthesis of α-CF_3-α-amino acid 1,7-enynes with electron-donating and electron-withdrawing aryl, acyl, and aroyl groups on the triple bond and their RCEYM with commercially available Grubbs II and Hoveyda II catalysts to afford new fluorinated pipecolic acid derivatives that contain the synthetically useful 1,3-diene moiety [see Figure 1, Equation (1b)].

Results and Discussion

Amine-containing compounds generally inhibit an alkene metathesis by coordinating to the metal site. The use of sterically hindered amines, acceptor-substituted amines (e.g., amides), or acidic additives [e.g., $Ti(OiPr)_4$] are the main solutions to overcome this problems.[15] Furthermore, the RCEYM of terminal alkynes often gives low yields of the cyclic product as a result of the poisoning of the active catalyst through a secondary metathesis of the diene product, which leads to a stable and unreactive Ru-carbene species.[16] The utilization of ethylene gas in a RCEYM usually prevents the latter process and provides significant improvements to the yields of cyclic 1,3-dienes,[13c,17] and the nature of the catalyst can significantly affect the outcome of the metathesis reaction.[18]

Taking into account the electronic and steric effects of the substituents of 1,7-enyne **1**, we first investigated its reaction with commercially available Ru-based metathesis catalysts (see Scheme 1). In the absence of ethylene, full conversion of the starting enyne **1** was only achieved by treatment with 5 mol-% of Grubbs I catalyst and heating at 80 °C in toluene for 8 h (monitored by TLC). This reaction, however, afforded metathesis product **2** in low yield (15%) along with a complicated mixture of byproducts (monitored by ^{19}F NMR spectroscopy). Unexpectedly, the application of Grubbs II and Hoveyda II catalysts under the same conditions for 2 h resulted in the formation of compound **3**,



Scheme 1. RCM of terminal 1,7-enyne **1** (Mes = 2,4,6-trimethylphenyl).

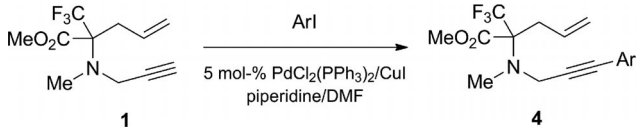
which arose from the self-metathesis of **2**. In these cases, no trace amounts of 1,3-diene **2** were detected in the reaction mixtures. The best yield of **3** (63%) was obtained by using 5 mol-% of Grubbs II in toluene at 80 °C. It is noteworthy that varying the substrate concentration to within a range of 0.03–0.2 M did not significantly affect the outcome of all above-mentioned reactions.

The yield of **2** was significantly improved by performing the reaction under an ethylene atmosphere. In this case, the reaction proceeded at 70 °C for 2 h with Grubbs II or Hoveyda II catalysts (5 mol-%) to give a mixture of **2** and **3** in a ratio of approximately 2:1, respectively. Compounds **2** and **3** were easily separated by column chromatography to afford the desired 1,3-diene **2** in 45% yield (see Scheme 1).

As the self-metathesis of 1,1-disubstituted alkenes is not a trivial task, which generally requires either forcing conditions or more active catalytic systems,[18] we decided to introduce an additional substituent on the triple bond of the starting enyne **1** to generate a 1,1-disubstituted exocyclic olefin moiety after the RCEYM step and, thus, to suppress the undesirable formation of self-metathesis products such as **3**. We performed a Sonogashira Pd-catalyzed cross-coupling reaction between **1** and different aryl iodides. The reaction of **1** with iodobenzene proceeded at room temperature in tetrahydrofuran (THF) in the presence of a 5-fold excess amount of Et_3N using a $PdCl_2(PPh_3)_2$/CuI catalytic system (5 mol-%) to afford the corresponding internal alkyne **4a** in poor yield (22%). Comparable amounts of the homocoupled derivative **5** (32%), which presumably resulted from a Cu-mediated Glaser-type coupling,[19] were also isolated as a byproduct (see Scheme 2). In the case of 4-iodoanisole, even after 24 h, the formation of a significant amount of **5** along with the incomplete conversion of **1** (68%) was detected (monitored by ^{19}F NMR spectroscopy).[20]

We were pleased that the formation of homocoupled derivative **5** could be completely suppressed by performing the reaction with 5 mol-% of $PdCl_2(PPh_3)_2$/CuI with a 20-fold excess amount of piperidine, as a base, in *N*,*N*-dimethylformamide (DMF). The reactions were completed within 4 h at ambient temperature to give cross-coupling products **4a**–**4f** in good yields (79–95%, see Table 1, Entries 1–6). The only exceptions were the reactions with NO_2-substituted iodobenzenes, in which there was rapid degradation/resinification of the starting enyne **1**, which was probably initiated by the addition of piperidine to the activated triple bond. After screening several organic bases, we found that the best yields of the corresponding enynes **4g** and **4h** (see Table 1, Entries 7 and 8) were obtained within 3 h by using NEt_3 (20-fold excess amount). This result could be explained by the enhanced reactivity of NO_2-substituted iodobenzenes.

Table 1. Synthesis of aryl-substituted 1,7-enynes **4**.



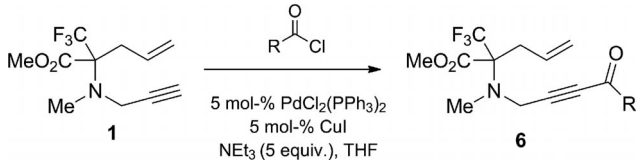
1 **4**

Entry	Ar	Product	% Yield[a]
1	Ph	**4a**	81
2	4-$MeOC_6H_4$	**4b**	79
3	4-MeC_6H_4	**4c**	87
4	4-$BocNHC_6H_4$[b]	**4d**	93
5	2-MeC_6H_4	**4e**	95
6	2-$MeOC_6H_4$	**4f**	86
7	2-$NO_2C_6H_4$	**4g**	70[c]
8	4-$NO_2C_6H_4$	**4h**	80[c]

[a] After column chromatography on silica gel (hexanes/ethyl acetate). [b] Boc = *tert*-butoxycarbonyl. [c] Reactions were performed using NEt_3 as a base.

For the preparation of 1,7-enynes that contain electron-withdrawing groups on the triple bond, the cross-coupling reaction between **1** and different acyl chlorides was successfully performed by using $PdCl_2(PPh_3)_2$/CuI as the catalyst.

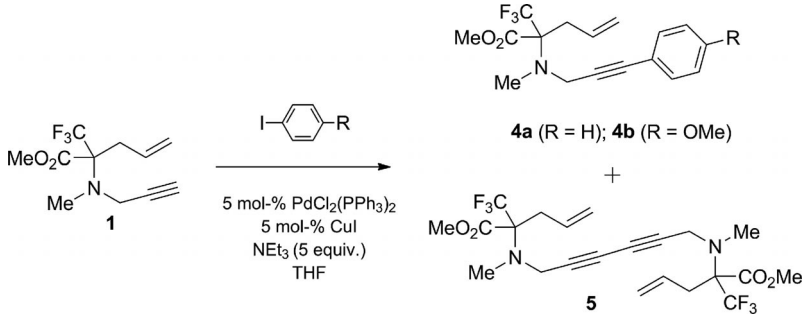
Table 2. Synthesis of acyl-substituted 1,7-enynes **6**.



1 **6**

Entry	R	Product	% Yield[a]
1	C_6H_5	**6a**	71
2	4-FC_6H_4	**6b**	64
3	2-FC_6H_4	**6c**	74
4	4-ClC_6H_4	**6d**	76
5	*t*Bu	**6e**	83

[a] After column chromatography on silica gel (hexanes/ethyl acetate).



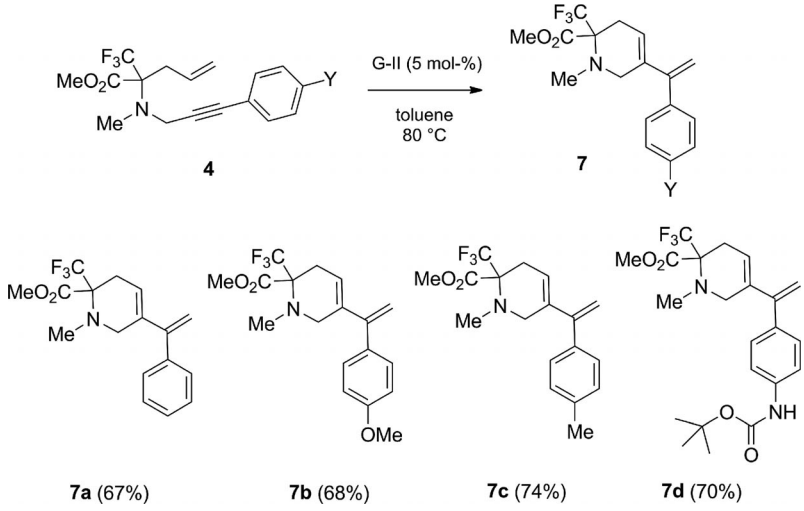
Scheme 2. Sonogashira coupling of 1,7-enyne **1** with iodobenzene and 4-iodoanisole.

The reactions readily occurred at room temperature in THF and went to completion in only 25 min to give internal α-keto alkynes **6a**–**6e** in high yields (see Table 2). The formation of byproduct **5** was not observed because of the higher activity of the acyl chlorides in comparison to the aryl iodides.

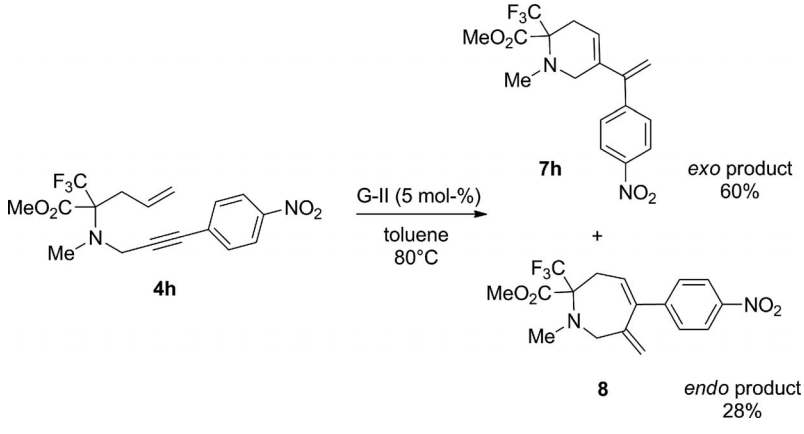
The ring-closing metathesis reactions of the new 1,7-enynes **4** and **6**, which were comprised of an internal triple bond, was then investigated with Grubbs II and Hoveyda II catalysts. The cyclization reactions of **4a**–**4d** proceeded smoothly with 5 mol-% of Grubbs II catalyst in toluene at 80 °C for 2 h to afford the desired products **7a**–**7d** in good isolated yields (see Scheme 3). Indeed, in all cases, the self-metathesis of compounds **7**, analogous to the process that formed **3** (see Scheme 1), was not observed.

Unexpectedly, 1,7-enynes **4e**–**4g** that contain an *ortho*-substituted aryl moiety on the triple bond (2-MeC_6H_4, 2-$MeOC_6H_4$, 2-$NO_2C_6H_4$) proved to be inert with respect to both Grubbs II and Hoveyda II catalysts, even with increased catalyst loading (up to 10%), elevated temperatures (boiling toluene), and an ethylene atmosphere. The starting materials were completely recovered from the reaction mixtures. An explanation for this unusual finding is the strong shielding effect of the *ortho* substituent, which prevents the coordination of a ruthenium carbene species to the triple bond during the catalytic cycle.

Until now, some aspects of the RCEYM mechanisms with regard to the competition between the yne-then-ene and ene-then-yne pathways as well as the *exo* and *endo* selectivity[21] remain unknown. There is, however, evidence that enyne metathesis reactions with substrates that have a sterically demanding alkyne moiety prefer the yne-then-ene pathway.[22] In the formation of small- to medium-sized rings, the ruthenium-catalyzed RCEYM reactions generally follow an *exo*-mode pathway, whereas tungsten- and molybdenum-catalyzed reactions with similar precursors commonly follow an *endo*-mode pathway.[23] In the case of **4h**, which contains a *para*-nitro group on the benzene ring, the reaction led to a mixture of *exo*- and *endo*-cyclic metathesis products **7h** and **8** in a ratio of 2:1, respectively (see Scheme 4). Both products were easily separated by using column chromatography and fully characterized by NMR spectroscopy, MS, and elemental analysis (see Exp. Sect.).



Scheme 3. RCM of aryl-substituted 1,7-enynes **4**.



Scheme 4. RCM of 1,7-enyne **4h**.

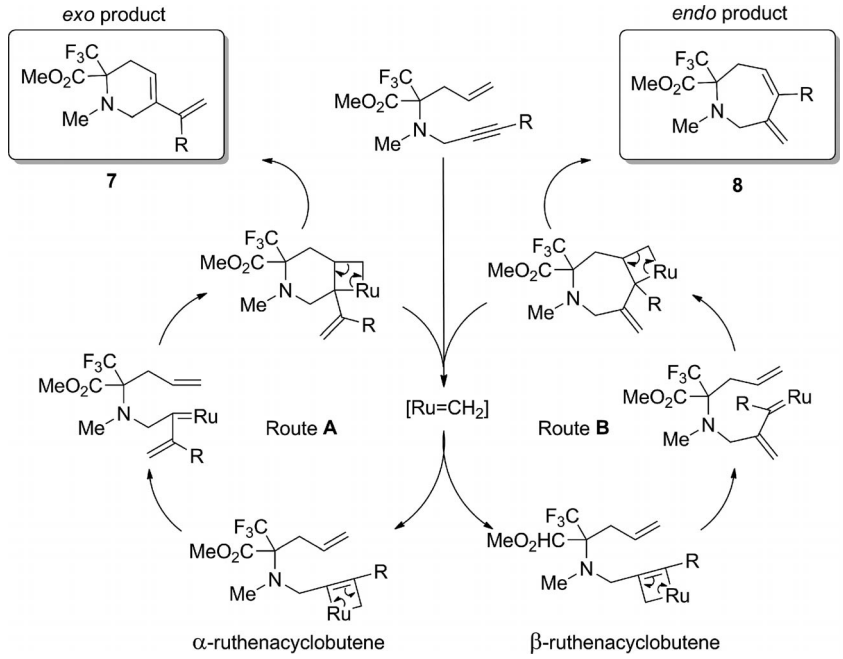
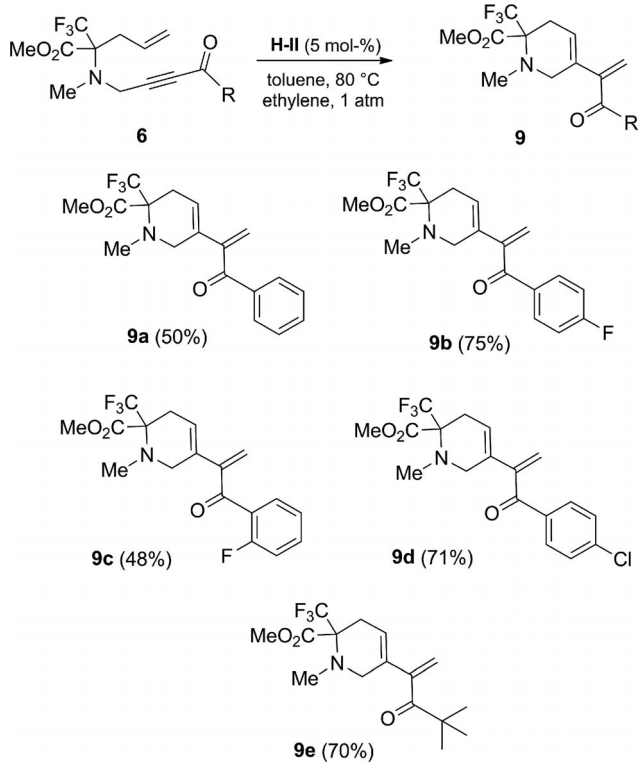


Figure 2. Proposed mechanism for the formation of *endo*- and *exo*-cyclic products.

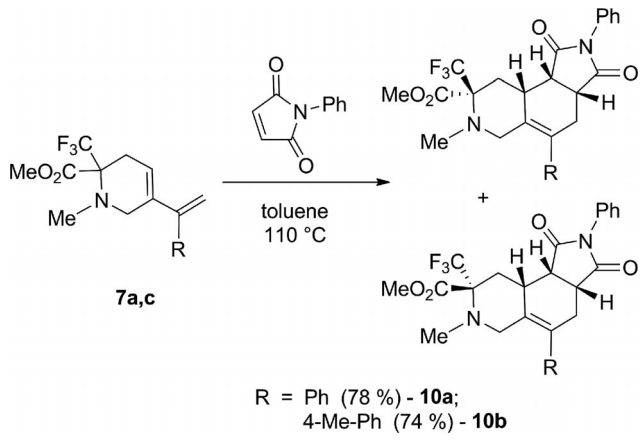
The appearance of a significant amount of *endo*-cyclic isomer **8** can be rationalized by the formation of a β-ruthenacyclobutene intermediate in the first step of the catalytic cycle (see Figure 2, Route B), whereas the formation of derivatives **7** is explained by Route A. Presumably, the electron-withdrawing impact of the NO_2 group contributes to this process.



Scheme 5. RCM of acyl-substituted 1,7-enynes **6**.

We have further investigated the RCEYM reaction of 1,7-enynes **6** that contain electron-withdrawing acyl groups on the triple bond. The first attempt to perform the reaction by applying the same conditions as those for **4** led to a complicated mixture of products. We found that **6** smoothly underwent cyclization by treatment with Hoveyda II catalyst (5 mol-%) under an ethylene atmosphere in toluene at 80 °C for 3 h to afford the desired products **9** in moderate to good yields (see Scheme 5). The formation of self-metathesis products, similar to **3**, was not observed.

To demonstrate a further synthetic application of these new cyclic α-amino acid 1,3-dienes, we studied the Diels–Alder reaction of dienes **7a** and **7c** with *N*-phenylmaleimide (see Scheme 6) to construct functionalized polycyclic compounds. The cycloaddition occurred in toluene at reflux for 24 h to afford the corresponding tricyclic derivatives **10a**



Scheme 6. Diels–Alder reaction of 1,3-dienes **7a** and **7c** with *N*-phenylmaleimide to afford **10** (relative configurations).

and **10b** in 78 and 74% isolated yield, respectively. Products **10a** and **10b** were formed as diastereomeric mixtures (ca. 3:2, determined by ^{19}F NMR analysis), which could be easily separated by column chromatography on silica gel.

Conclusions

An efficient method for the preparation of new α-CF_3-α-amino acid 1,7-enynes that contain electron-donating and electron-withdrawing groups on the triple bond has been developed that proceeds through a Sonogashira-type coupling reaction of terminal enynes. Although the RCEYM of terminal enynes is not efficient, the RCEYM of the obtained 1,7-enynes with commercially available Grubbs and Hoveyda catalysts have led to the corresponding pipecolic acid derivatives that contain the synthetically useful 1,3-diene moiety. As a result, we found that the RCEYM of 1,7-enynes that contain *para*-substituted aryl groups on the triple bond proceeded smoothly by treatment with Grubbs II catalyst. In contrast, their *ortho*-substituted counterparts proved to be absolutely inert with respect to both Grubbs II and Hoveyda II catalysts. 1,7-Enynes with electron-withdrawing acyl groups displayed low activity in the metathesis process. In these cases, acceptable yields of the corresponding cyclization products were obtained only by treatment with Hoveyda II catalyst under an ethylene atmosphere. Furthermore, the Diels–Alder cycloaddition of the synthesized 1,3-dienes with *N*-phenylmaleimide as the dienophile opened access to the hitherto unknown trifluoromethylated polycyclic amino acid derivatives. These simple and environmentally benign reactions extend the potential applications of cyclic amino acid derivatives to synthetic and medicinal chemistry.

Experimental Section

General Methods: All solvents were freshly distilled from the appropriate drying agents prior to use. All other reagents were recrystallized or distilled as necessary. The Sonogashira and metathesis reactions were performed under argon. Analytical TLC was performed with Merck silica gel 60 F254 plates. Visualization was achieved by using UV light and by spraying with a $Ce(SO_4)_2$ solution in 5% H_2SO_4 or a $KMnO_4$ solution in water. Column chromatography was carried out with Merck silica gel 60 (230–400 mesh ASTM) and a mixture of ethyl acetate/petroleum ether as the eluent. The NMR spectroscopic data were recorded at room temperature with Bruker AV-200, AV-300, and AV-600 spectrometers that operated at 300, 400, and 600 MHz, respectively (TMS reference) for ^1H NMR, at 75, 101, and 151 MHz for ^{13}C NMR, and 282 MHz for ^{19}F NMR (CF_3COOH reference). High resolution mass spectra were measured with a Bruker micro TOF II instrument using electrospray ionization. The measurements were performed either in a positive ion mode (interface capillary voltage: 4500 V) or in a negative ion mode (3200 V) with a mass range from m/z = 50 to 3000 Da, and the external or internal calibration was done with an Electrospray Calibrant Solution (Fluka). Syringe injection was used for solutions in acetonitrile, methanol, and water (flow rate: 3 μL/min). Nitrogen was applied as a dry gas, and the interface temperature was set at 180 °C. 1,7-Enyne **1** was prepared by a previously published protocol.[14]

Methyl 1-Methyl-2-(trifluoromethyl)-5-vinyl-1,2,3,6-tetrahydropyridine-2-carboxylate (2): A solution of 1,7-enyne **1** (100 mg, 0.402 mmol) in dry toluene (14 mL) was placed in a flame-dried two-necked flask that was equipped with a bubbling tube, a bubble counter, a magnetic stirring bar, and a reflux condenser. Ethylene gas was bubbled through the toluene solution for 15 min at room temperature. Then Grubbs' second-generation catalyst (17 mg, 0.02 mmol) was added, and the resulting wine-red solution was heated to 80 °C for 2 h with continuous bubbling. The resulted solution was cooled to room temp., and the solvent was removed under reduced pressure. The residual oil was chromatographed (EtOAc/petroleum ether, 1:20) to furnish compound **2** (45 mg, 45%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.01 (s, 2 H, 2 CH), 5.75 (s, 2 H, 2 CH), 3.83 (s, 6 H, 2 CO_2CH_3), 3.65 (d, J = 16.3 Hz, 2 H, 2 NCH_2), 3.53 (d, J = 17.3 Hz, 2 H, 2 NCH_2), 2.94 (dd, J = 17.9, 5.1 Hz, 2 H, 2 CH_2), 2.79–2.64 (m, 8 H, 2 NCH_3, 2 CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 168.53, 133.69, 126.01, 124.92 (q, J = 288.2 Hz), 121.68, 68.01 (q, J = 25.3 Hz), 52.74, 51.73, 40.05, 30.57 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.66 (s, 3 F, CF_3) ppm. $C_{11}H_{14}F_3NO_2$ (249.23): calcd. C 53.01, H 5.66, N 5.62; found C 53.22, H 5.32, N 5.98.

Dimethyl 5,5′-(Ethene-1,2-diyl)bis[1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate] (3): A solution of 1,7-enyne **1** (0.1 g, 0.402 mmol) in dry toluene (2 mL) was placed in a flame-dried Schlenk tube under argon, and Grubbs' second-generation catalyst (17 mg, 0.02 mmol) was added. The resulting solution was heated to 80 °C for 2 h. The mixture was cooled to room temp., and TLC showed complete disappearance of the starting material. The solvent was removed under reduced pressure, and the residual oil was chromatographed (EtOAc/petroleum ether, 1:3) to furnish compound **3** (57 mg, 60%, 3:2 mixture of isomers) as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.01 (s, 2 H, 2 CH), 5.75 (s, 2 H, 2 CH), 3.83 (s, 6 H, 2 CO_2CH_3), 3.65 (d, J = 16.3 Hz, 2 H, 2 NCH_2), 3.53 (d, J = 17.3 Hz, 2 H, 2 NCH_2), 2.94 (dd, J = 17.9, 5.1 Hz, 2 H, 2 CH_2), 2.79–2.64 (m, 8 H, 2 NCH_3, 2 CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 168.53, 133.69, 126.01, 124.92 (q, J = 288.2 Hz), 121.68, 68.01 (q, J = 25.3 Hz), 52.74, 51.73, 40.05, 30.57 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.69 (s, 3 F, CF_3), 8.58 (s, 3 F, CF_3) ppm. HRMS: calcd. for $C_{20}H_{24}F_6N_2O_4$ $[M + 1]^+$ 471.4061; found 471.4087. $C_{20}H_{24}F_6N_2O_4$ (470.41): calcd. C 51.07, H 5.14, N 5.96; found C 50.77, H 5.29, N 5.74.

General Procedure for Sonogashira Coupling of 1,7-Enyne 1 with Aryl Iodides: To a flame-dried Schlenk tube was placed a solution of the corresponding aryl iodide (3 mmol) in dry dimethylformamide (17 mL). The solution was cooled to –50 °C, and the air was replaced by argon. Then, $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), piperidine (3 mL), and a solution of 1,7-enyne **1** (0.5 g, 2 mmol) in dry dimethylformamide (3 mL) were sequentially added under an argon flow. The resulting mixture was again degassed and warmed to room temperature. CuI (19 mg, 0.1 mmol) was added under an argon flow, and the reaction mixture immediately became colorless and was stirred for 4 h. The resulting solution was poured into brine (200 mL), and the product was extracted with EtOAc (3× 70 mL). The organic fractions were combined, washed with water (2×), and dried with $MgSO_4$. The solvents were evaporated to dryness under reduced pressure. The crude product was purified by column chromatography with the appropriate mixture of EtOAc and petroleum ether.

Methyl 2-[Methyl(3-phenylprop-2-yn-1-yl)amino]-2-(trifluoromethyl)pent-4-enoate (4a): Column chromatography (EtOAc/petroleum

ether, 1:20) afforded **4a** (0.53 g, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.38 (m, 2 H, Ar), 7.32–7.25 (m, 3 H, Ar), 5.90–5.75 (m, 1 H, CH_{allyl}), 5.23–5.10 (m, 2 H, CH_{2allyl}), 3.84–3.68 (m, 5 H, CO_2CH_3, NCH_2), 2.88–2.74 (m, 2 H, CH_2), 2.67 (q, J = 1.1 Hz, 3 H, NCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 168.23, 131.70, 130.97, 128.24, 128.11, 125.98 (q, J = 294.1 Hz), 123.18, 119.62, 85.58, 84.14, 72.76 (q, J = 23.9 Hz), 52.68, 42.66 (q, J = 1.8 Hz), 36.55, 36.53 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.41 (s, 3 F, CF_3) ppm. $C_{17}H_{18}F_3NO_2$ (325.33): calcd. C 62.76, H 5.58, N 4.31; found C 63.01, H 5.75, N 4.48.

Methyl 2-{[3-(4-Methoxyphenyl)prop-2-yn-1-yl](methyl)amino}-2-(trifluoromethyl)pent-4-enoate (4b): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **4b** (0.56 g, 79%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (d, J = 8.8 Hz, 2 H, Ar), 6.88 (d, J = 8.8 Hz, 2 H, Ar), 6.01–5.80 (m, 1 H, CH_{allyl}), 5.32–5.15 (m, 2 H, CH_{2allyl}), 3.95–3.73 (m, 8 H, CO_2CH_3, OCH_3, NCH_2), 2.99–2.80 (m, 2 H, CH_2), 2.74 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.89, 159.17, 132.78, 130.73, 125.70 (q, J = 294.1 Hz), 119.20, 114.98, 113.53, 83.75, 83.67, 72.44 (q, J = 23.8 Hz), 54.85, 52.27, 42.35, 36.21, 36.20 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.38 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_3$ (355.35): calcd. C 60.84, H 5.67, N 3.94; found C 60.71, H 5.88, N 3.82.

Methyl 2-{Methyl[3-(*p*-tolyl)prop-2-yn-1-yl]amino}-2-(trifluoromethyl)pent-4-enoate (4c): Column chromatography (EtOAc/petroleum ether, 1:20) afforded **4c** (0.56 g, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.39 (d, J = 7.8 Hz, 2 H, Ar), 7.17 (d, J = 7.8 Hz, 2 H, Ar), 6.01–5.81 (m, 1 H, CH_{allyl}), 5.31–5.18 (m, 2 H, CH_{2allyl}), 3.92–3.73 (m, 5 H, CO_2CH_3, NCH_2), 2.98–2.80 (m, 2 H, CH_2), 2.75 (s, 3 H, NCH_3), 2.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.94, 137.85, 131.29, 130.74, 128.69, 125.70 (q, J = 294.1 Hz), 119.83, 119.26, 84.52, 83.95, 72.47 (q, J = 23.8 Hz), 52.34, 42.39, 36.26, 36.24, 21.12 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.36 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_2$ (339.36): calcd. C 63.71, H 5.94, N 4.13; found C 64.03, H 5.72, N 4.33.

Methyl 2-[(3-{4-[(*tert*-Butoxycarbonyl)amino]phenyl}prop-2-yn-1-yl)(methyl)amino]-2-(trifluoromethyl)pent-4-enoate (4d): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **4d** (0.52 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.41 (d, J = 8.8 Hz, 2 H, Ar), 7.36 (d, J = 8.8 Hz, 2 H, Ar), 6.58 (s, 1 H, NH), 6.03–5.77 (m, 1 H, CH_{allyl}), 5.37–5.13 (m, 2 H, CH_{2allyl}), 3.96–3.66 (m, 5 H, CO_2CH_3, NCH_2), 2.98–2.81 (m, 2 H, CH_2), 2.73 (s, 3 H, NCH_3), 1.57 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.96, 152.28, 138.15, 132.12, 130.67, 125.67 (q, J = 294.1 Hz), 119.26, 117.73, 117.02, 84.29, 83.69, 80.39, 72.42 (q, J = 23.8 Hz), 52.32, 42.36, 36.24, 36.22, 27.95 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.41 (s, 3 F, CF_3) ppm. $C_{22}H_{27}F_3N_2O_4$ (440.46): calcd. C 59.99, H 6.18, N 6.36; found C 59.81, H 6.29, N 6.55.

Methyl 2-{Methyl[3-(*o*-tolyl)prop-2-yn-1-yl]amino}-2-(trifluoromethyl)pent-4-enoate (4e): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **4e** (0.64 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49 (d, J = 7.4 Hz, 1 H, Ar), 7.39–7.14 (m, 3 H, Ar), 6.05–5.81 (m, 1 H, CH_{allyl}), 5.41–5.16 (m, 2 H, CH_{2allyl}), 4.02–3.78 (m, 5 H, CO_2CH_3, NCH_2), 3.02–2.84 (m, 2 H, CH_2), 2.78 (s, 3 H, NCH_3), 2.52 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.96, 139.88, 131.74, 130.73, 129.09, 127.82, 125.73 (q, J = 294.0 Hz), 125.19, 122.72, 119.21, 89.26, 82.71, 72.48 (q, J = 24.0 Hz), 52.30, 42.43, 36.21, 36.23, 20.39 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.15 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_2$ (339.36): calcd. C 63.71, H 5.94, N 4.13; found C 63.55, H 6.21, N 4.27.

Methyl 2-{[3-(2-Methoxyphenyl)prop-2-yn-1-yl](methyl)amino}-2-(trifluoromethyl)pent-4-enoate (4f): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **4f** (0.61 g, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (dd, J = 7.5, 1.6 Hz, 1 H, Ar), 7.26–7.10 (m, 1 H, Ar), 6.87–6.70 (m, 2 H, Ar), 5.87–5.65 (m, 1 H, CH_{allyl}), 5.18–5.01 (m, 2 H, CH_{2allyl}), 3.85–3.61 (m, 8 H, CO_2CH_3, OCH_3, NCH_2), 2.88–2.64 (m, 2 H, CH_2), 2.61 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.90, 159.77, 133.29, 130.82, 129.22, 125.65 (q, J = 293.9 Hz), 120.05, 119.16, 112.03, 110.30, 89.37, 80.25, 72.51 (q, J = 23.8 Hz), 55.36, 52.27, 42.50, 36.28, 36.12 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.24 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_3$ (355.35): calcd. C 60.84, H 5.67, N 3.94; found C 60.97, H 5.81, N 3.88.

General Procedure for Sonogashira Coupling of 1,7-Enyne 1 with 1-Iodo-4-nitrobenzene or 1-Iodo-2-nitrobenzene: The same synthetic protocol at that for **4a**–**4f** was applied, but NEt_3 was used instead of piperidine.

Methyl 2-{Methyl[3-(2-nitrophenyl)prop-2-yn-1-yl]amino}-2-(trifluoromethyl)pent-4-enoate (4g): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **4g** (0.52 g, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.99 (dd, J = 8.2, 0.9 Hz, 1 H, Ar), 7.60 (dd, J = 7.8, 1.4 Hz, 1 H, Ar), 7.53 (td, J = 7.6, 1.2 Hz, 1 H, Ar), 7.42 (td, J = 11.2, 1.5 Hz, 1 H, Ar), 5.91–5.66 (m, 1 H, CH_{allyl}), 5.30–5.03 (m, 2 H, CH_{2allyl}), 3.93–3.68 (m, 5 H, CO_2CH_3, NCH_2), 2.88–2.73 (m, 2 H, CH_2), 2.69 (s, 3 H, NCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 168.17, 149.86, 134.92, 132.73, 130.79, 128.55, 125.94 (q, J = 294.0 Hz), 124.52, 119.72, 118.54, 94.23 (q, J = 1.4 Hz), 79.26, 72.76 (q, J = 23.9 Hz), 52.73, 42.89 (q, J = 2.0 Hz), 36.63 (q, J = 1.5 Hz), 36.44 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.61 (s, 3 F, CF_3) ppm. $C_{17}H_{17}F_3N_2O_4$ (370.33): calcd. C 55.14, H 4.63, N 7.56; found C 55.22, H 4.76, N 7.49.

Methyl 2-{Methyl[3-(4-nitrophenyl)prop-2-yn-1-yl]amino}-2-(trifluoromethyl)pent-4-enoate (4h): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **4h** (0.59 g, 80%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.23 (d, J = 8.9 Hz, 2 H, Ar), 7.62 (d, J = 8.9 Hz, 2 H, Ar), 5.99–5.76 (m, 1 H, CH_{allyl}), 5.33–5.17 (m, 2 H, CH_{2allyl}), 3.87 (s, J = 4.7 Hz, 5 H, CO_2CH_3, NCH_2), 2.87 (d, J = 7.0 Hz, 2 H, CH_2), 2.75 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.65, 146.61, 132.01, 130.30, 129.70, 125.55 (q, J = 294.0 Hz), 123.08, 119.32, 91.15, 81.97, 72.31 (q, J = 24.0 Hz), 52.31, 42.28, 36.22, 36.09 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.36 (s, 3 F, CF_3) ppm. $C_{17}H_{17}F_3N_2O_4$ (370.33): calcd. C 55.14, H 4.63, N 7.56; found C 55.38, H 4.82, N 7.39.

Dimethyl 2,2′-[Hexa-2,4-diyne-1,6-diylbis(methylazanediyl)]bis[2-(trifluoromethyl)pent-4-enoate] (5): Compound **5** (yellowish oil) was isolated as a byproduct of the Sonogashira coupling of 1,7-enyne **1** with iodobenzene or 4-iodoanisole. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 5.93–5.65 (m, 2 H, 2 CH_{allyl}), 5.31–5.07 (m, 4 H, 2 CH_{2allyl}), 3.80 (s, 6 H, 2 CO_2CH_3), 3.64 (d, J = 17.5 Hz, 2 H, 2 NCH_2), 3.59 (d, J = 17.5 Hz, 2 H, 2 NCH_2), 2.89–2.69 (m, 4 H, 2 CH_2), 2.62 (s, 6 H, 2 NCH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 168.01, 130.67, 125.82 (q, J = 293.8 Hz), 119.67, 74.67, 72.56 (q, J = 24.0 Hz), 68.45, 52.67, 42.57, 36.41, 36.42 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 11.00 (s, 6 F, 2 CF_3) ppm. $C_{22}H_{26}F_6N_2O_4$ (496.45): calcd. C 53.23, H 5.28, N 5.64; found C 53.49, H 5.56, N 5.77.

General Procedure for Sonogashira Coupling of 1,7-Enyne 1 with Acyl Chlorides: In a flame-dried Schlenk tube, a solution of 1,7-

enyne **1** (0.3 g, 1.2 mmol) with the corresponding acyl chloride (1.8 mmol) in dry tetrahydrofuran (5 mL) was mixed together. The reaction mixture was cooled to –78 °C, and the air was replaced by argon. Then, $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol) and CuI (11 mg, 0.06 mmol) were sequentially added under an argon flow. The resulting suspension was warmed to room temperature, and NEt_3 (0.21 mL, 1.8 mmol) was injected through a rubber septum. After stirring for 5 min, much of the white precipitate appeared, and the reaction mixture was stirred for an additional 20 min. TLC analysis showed full conversion of the starting 1,7-enyne. The resulting mixture was filtered to remove the NEt_3·HCl, and the solvents were evaporated to dryness under reduced pressure. The crude product was purified by column chromatography with the appropriate mixture of EtOAc and petroleum ether as the eluent.

Methyl 2-[Methyl(4-oxo-4-phenylbut-2-yn-1-yl)amino]-2-(trifluoromethyl)pent-4-enoate (6a): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **6a** (0.3 g, 71%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.21 (d, J = 7.5 Hz, 2 H, Ar), 7.68 (t, J = 7.4 Hz, 1 H, Ar), 7.55 (t, J = 7.5 Hz, 2 H, Ar), 5.94–5.75 (m, 1 H, CH_{allyl}), 5.35–5.16 (m, 2 H, CH_{2allyl}), 3.94 (s, 2 H, NCH_2), 3.87 (s, 3 H, CO_2CH_3), 2.87 (d, J = 6.9 Hz, 2 H, CH_2), 2.78 (s, 3 H, NCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 177.74, 167.97, 136.78, 134.15, 130.58, 129.62, 128.63, 125.93 (q, J = 293.5 Hz), 119.82, 91.23, 82.23, 72.65 (q, J = 24.2 Hz), 52.76, 42.46 (q, J = 1.9 Hz), 36.96, 36.45 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 10.77 (s, 3 F, CF_3) ppm. $C_{18}H_{18}F_3NO_3$ (353.34): calcd. C 61.19, H 5.13, N 3.96; found C 61.03, H 5.31, N 4.15.

Methyl 2-{[4-(4-Fluorophenyl)-4-oxobut-2-yn-1-yl](methyl)amino}-2-(trifluoromethyl)pent-4-enoate (6b): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **6b** (0.28 g, 64%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.34–8.07 (m, 2 H, Ar), 7.29–7.10 (m, 2 H, Ar), 5.97–5.68 (m, 1 H, CH_{allyl}), 5.39–5.09 (m, 2 H, CH_{2allyl}), 3.90 (s, 2 H, NCH_2), 3.84 (s, J = 5.6 Hz, 3 H, CO_2CH_3), 2.84 (d, J = 6.9 Hz, 2 H, CH_2), 2.74 (s, 3 H, NCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 176.08, 167.92, 166.51 (d, J = 256.6 Hz), 133.30 (d, J = 2.7 Hz), 132.28 (d, J = 9.6 Hz), 130.52, 125.92 (q, J = 293.5 Hz), 119.83, 115.84 (d, J = 22.2 Hz), 91.55, 81.91, 72.62 (q, J = 24.3 Hz), 52.77, 42.45 (q, J = 1.9 Hz), 36.93, 36.42 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 10.75 (s, 3 F, CF_3), –25.53 (s, 1 F, CF_{Ar}) ppm. $C_{18}H_{17}F_4NO_3$ (371.33): calcd. C 58.22, H 4.61, N 3.77; found C 58.39, H 4.49, N 3.93.

Methyl 2-{[4-(2-Fluorophenyl)-4-oxobut-2-yn-1-yl](methyl)amino}-2-(trifluoromethyl)pent-4-enoate (6c): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **6c** (0.32 g, 74%) as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.09 (td, J = 7.7, 1.8 Hz, 1 H, Ar), 7.77–7.48 (m, 1 H, Ar), 7.36–7.26 (m, 1 H, Ar), 7.20 (ddd, J = 11.0, 8.3, 0.8 Hz, 1 H, Ar), 6.02–5.66 (m, 1 H, CH_{allyl}), 5.42–5.07 (m, 2 H, CH_{2allyl}), 3.90 (s, 2 H, NCH_2), 3.85 (s, 3 H, CO_2CH_3), 2.85 (d, J = 6.9 Hz, 2 H, CH_2), 2.74 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.66, 167.55, 161.66 (d, J = 262.0 Hz), 135.20 (d, J = 9.1 Hz), 131.64, 130.12, 125.46 (q, J = 293.6 Hz), 125.01 (d, J = 7.6 Hz), 123.77 (d, J = 4.0 Hz), 119.32 (d, J = 10.8 Hz), 116.66 (d, J = 21.8 Hz), 90.76, 83.08, 72.18 (q, J = 24.1 Hz), 52.33, 42.04, 36.42, 35.98 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 10.76 (s, 3 F, CF_3), –33.87 (s, 1 F, CF_{Ar}) ppm. $C_{18}H_{17}F_4NO_3$ (371.33): calcd. C 58.22, H 4.61, N 3.77; found C 58.05, H 4.82, N 4.01.

Methyl 2-{[4-(4-Chlorophenyl)-4-oxobut-2-yn-1-yl](methyl)-amino}-2-(trifluoromethyl)pent-4-enoate (6d): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **6d** (0.35 g, 76%) as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.13 (d, J = 8.6 Hz, 2 H, Ar), 7.51 (d, J = 8.7 Hz, 2 H, Ar), 5.97–5.73 (m, 1 H, CH_{allyl}), 5.33–5.18 (m, 2 H, CH_{2allyl}), 3.93 (s, 2 H, NCH_2), 3.86 (s, 3 H, CO_2CH_3), 2.86 (d, J = 6.9 Hz, 2 H, CH_2), 2.76 (s, 3 H, NCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 175.97, 167.51, 140.36, 134.71, 130.49, 130.04, 128.58, 125.49 (q, J = 293.5 Hz), 119.48, 91.42, 81.44, 72.17 (q, J = 24.3 Hz), 52.40, 42.05, 36.52, 35.99 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 10.78 (s, 3 F, CF_3) ppm. $C_{18}H_{17}ClF_3NO_3$ (387.78): calcd. C 55.75, H 4.42, N 3.61; found C 55.59, H 4.63, N 3.72.

Methyl 2-[(5,5-Dimethyl-4-oxohex-2-yn-1-yl)(methyl)amino]-2-(trifluoromethyl)pent-4-enoate (6e): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **6e** (0.33 g, 83%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.91–5.70 (m, 1 H, CH_{allyl}), 5.37–5.08 (m, 2 H, CH_{2allyl}), 3.82 (s, 3 H, CO_2CH_3), 3.80 (s, 2 H, NCH_2), 2.80 (d, J = 6.9 Hz, 2 H, CH_2), 2.67 (s, 3 H, NCH_3), 1.23 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 193.83, 167.89, 130.47, 125.83 (q, J = 293.8 Hz), 119.72, 90.12, 81.42, 72.48 (q, J = 24.2 Hz), 52.69, 44.64, 42.10, 36.63, 36.30, 25.85 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 10.66 (s, 3 F, CF_3) ppm. $C_{16}H_{22}F_3NO_3$ (333.35): calcd. C 57.65, H 6.65, N 4.20; found C 57.92, H 6.77, N 4.48.

General Procedure for Ruthenium-Catalyzed RCEYM of Aryl-Substituted 1,7-Enynes 4a–4d and 4h: A solution of corresponding aryl-substituted 1,7-enyne **4** (1.5 mmol) in dry toluene (15 mL) was placed in a flame-dried Schlenk tube under argon, and Grubbs' second-generation catalyst (64 mg, 0.075 mmol) was added. The resulting solution was heated to 80 °C for 2 h. Then, the reaction mixture was cooled to room temp., and ^{19}F NMR analysis indicated full conversion of the starting material. The solvent was removed under reduced pressure, and the residual oil was chromatographed with the appropriate mixture of EtOAc and petroleum ether to furnish the desired product.

Methyl 1-Methyl-5-(1-phenylvinyl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (7a): Column chromatography (EtOAc/petroleum ether, 1:30) afforded **7a** (0.33 g, 67%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.39–7.30 (m, 3 H, Ar), 7.29–7.25 (m, 2 H, Ar), 5.61 (br. s, 1 H, CH), 5.19 (s, 1 H, CH_2), 5.12 (s, 1 H, CH_2), 3.84 (s, 3 H, CO_2CH_3), 3.70 (d, J = 17.5 Hz, 1 H, NCH_2), 3.58 (d, J = 17.5 Hz, 1 H, NCH_2), 2.88 (d, J = 17.9 Hz, 1 H, CH_2), 2.71 (q, J = 1.3 Hz, 3 H, NCH_3), 2.67 (d, J = 17.9 Hz, 1 H, CH_2) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 168.61, 147.85, 140.67, 135.58, 128.50, 128.07, 127.51, 125.03 (q, J = 288.7 Hz), 121.25, 112.60, 67.53 (q, J = 25.1 Hz), 53.10, 52.68, 39.95, 30.38 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.83 (s, 3 F, CF_3) ppm. $C_{17}H_{18}F_3NO_2$ (325.33): calcd. C 62.76, H 5.58, N 4.31; found C 62.57, H 5.43, N 4.59.

Methyl 5-[1-(4-Methoxyphenyl)vinyl]-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (7b): Column chromatography (EtOAc/petroleum ether, 1:15) afforded **7b** (0.29 g, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.24 (d, J = 8.6 Hz, 2 H, Ar), 6.91 (d, J = 8.6 Hz, 2 H, Ar), 5.68 (br. s, 1 H, CH), 5.16 (s, 1 H, CH_2), 5.12 (s, 1 H, CH_2), 3.87 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, OCH_3), 3.73 (d, J = 16.4 Hz, 1 H, NCH_2), 3.59 (d, J = 16.4 Hz, 1 H, NCH_2), 2.93 (d, J = 18.1 Hz, 1 H, CH_2), 2.74 (s, 3 H, NCH_3), 2.64 (d, J = 18.1 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 168.58, 159.18, 147.42, 136.00, 132.99, 129.50, 125.07 (q, J = 288.6 Hz), 120.90, 113.47, 111.69, 67.54 (q, J = 25.2 Hz), 55.15, 53.29, 52.57, 39.86, 30.37 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.79 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_3$ (355.35): calcd. C 60.84, H 5.67, N 3.94; found C 61.15, H 5.95, N 3.76.

Methyl 1-Methyl-5-[1-(*p*-tolyl)vinyl]-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (7c): Column chromatography (EtOAc/petroleum ether, 1:30) afforded **7c** (0.3 g, 74%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.20 (s, 4 H, Ar), 5.67 (br. s, 1 H, CH), 5.19 (s, 1 H, CH_2), 5.14 (s, 1 H, CH_2), 3.88 (s, 3 H, CO_2CH_3), 3.73 (d, J = 16.8 Hz, 1 H, NCH_2), 3.60 (d, J = 16.8 Hz, 1 H, NCH_2), 2.91 (d, J = 17.9 Hz, 1 H, CH_2), 2.80–2.64 (m, 4 H, NCH_3, CH_2), 2.42 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.33, 147.45, 137.44, 137.01, 135.44, 128.69, 128.09, 124.73 (q, J = 288.8 Hz), 120.75, 111.92, 67.28 (q, J = 25.2 Hz), 52.94, 52.45, 39.68, 30.08, 20.89 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.79 (s, 3 F, CF_3) ppm. $C_{18}H_{20}F_3NO_2$ (339.36): calcd. C 63.71, H 5.94, N 4.13; found C 63.92, H 5.81, N 4.29.

Methyl 5-(1-{4-[(*tert*-Butoxycarbonyl)amino]phenyl}vinyl)-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (7d): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **7d** (0.37 g, 70%) as a white powder; m.p. 43–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, J = 8.0 Hz, 2 H, Ar), 7.17 (d, J = 8.3 Hz, 2 H, Ar), 6.61 (s, J = 29.1 Hz, 1 H, NH), 5.60 (br. s, 1 H, CH), 5.10 (s, 1 H, CH_2), 5.06 (s, 1 H, CH_2), 3.81 (s, 3 H, CO_2CH_3), 3.64 (d, J = 16.6 Hz, 1 H, NCH_2), 3.52 (d, J = 16.6 Hz, 1 H, NCH_2), 2.84 (d, J = 15.1 Hz, 1 H, CH_2), 2.73–2.58 (m, 4 H, NCH_3, CH_2), 1.52 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 168.59, 152.79, 147.28, 137.79, 135.70, 135.29, 129.03, 124.98 (q, J = 288.5 Hz), 121.06, 118.16, 112.07, 80.60, 67.49 (q, J = 25.1 Hz), 53.20, 52.71, 39.92, 30.32, 28.32 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.83 (s, 3 F, CF_3) ppm. $C_{22}H_{27}F_3N_2O_4$ (440.46): calcd. C 59.99, H 6.18, N 6.36; found C 60.19, H 5.94, N 6.71.

Methyl 1-Methyl-5-[1-(4-nitrophenyl)vinyl]-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (7h): Column chromatography (EtOAc/petroleum ether, 1:12) afforded **7h** (0.26 g, 60%) as a yellowish solid; m.p. 94–95 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.87 (d, J = 8.8 Hz, 2 H, Ar), 6.94 (d, J = 8.8 Hz, 1 H, Ar), 5.29 (br. s, J = 2.1 Hz, 1 H, CH), 5.03 (s, 1 H, CH_2), 4.88 (s, 1 H, CH_2), 3.67 (d, J = 16.5 Hz, 1 H, NCH_2), 3.40 (d, J = 16.5 Hz, 1 H, NCH_2), 3.33 (s, 3 H, CO_2CH_3), 2.85 (dd, J = 17.7, 5.4 Hz, 1 H, CH_2), 2.70 (q, J = 1.4 Hz, 3 H, NCH_3), 2.62 (dq, J = 17.7, 3.0 Hz, 1 H, CH_2) ppm. ^{13}C NMR (151 MHz, C_6D_6, 25 °C): δ = 168.04, 147.30, 146.75, 146.18, 135.13, 128.99, 125.44 (q, J = 288.2 Hz), 123.18, 122.22, 114.27, 67.48 (q, J = 25.8 Hz), 52.91, 51.86, 39.56, 30.84 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.82 (s, 3 F, CF_3) ppm. MS (EI): m/z (%) = 370 (15) $[M]^+$, 311 (100) $[M - CO_2Me]^+$, 163 (20) $[M - CO_2Me - CH_2{=}CH\text{-}C_6H_4\text{-}NO_2]^{2+}$. HRMS: calcd. for $C_{17}H_{17}F_3N_2O_4$ $[M + 1]^+$ 371.3232; found 371.3210. $C_{17}H_{17}F_3N_2O_4$ (370.33): calcd. C 55.14, H 4.63, N 7.56; found C 55.30, H 4.29, N 7.81.

Methyl 1-Methyl-6-methylene-5-(4-nitrophenyl)-2-(trifluoromethyl)-2,3,6,7-tetrahydro-1*H*-azepine-2-carboxylate (8): Column chromatography (EtOAc/petroleum ether, 1:12) afforded **8** (0.12 g, 28%) as a yellowish oil. ^{1}H NMR (600 MHz, C_6D_6, 25 °C): δ = 7.94 (d, J = 8.8 Hz, 2 H, Ar), 7.02 (d, J = 8.8 Hz, 2 H, Ar), 5.33–5.29 (m, 1 H, CH), 4.82 (s, 1 H, CH_2), 4.56 (s, 1 H, CH_2), 3.92 (d, J = 16.3 Hz, 1 H, NCH_2), 3.44 (d, J = 16.3 Hz, 1 H, NCH_2), 3.40 (s, 3 H, CO_2CH_3), 2.87 (dd, J = 16.1, 5.7 Hz, 1 H, CH_2), 2.75 (dd, J = 16.1, 8.2 Hz, 1 H, CH_2), 2.65 (s, 3 H, NCH_3) ppm. ^{13}C NMR (151 MHz, C_6D_6, 25 °C): δ = 168.10, 148.48, 147.13, 145.06, 143.29, 129.51, 126.09 (q, J = 290.0 Hz), 125.00, 123.14, 116.52, 73.37 (q, J = 24.8 Hz), 57.40, 51.73, 39.26, 30.78 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 6.40 (s, 3 F, CF_3) ppm. MS (EI): m/z (%) = 370 (15) $[M]^+$, 311 (100) $[M - CO_2Me]^+$. HRMS: calcd. for $C_{17}H_{17}F_3N_2O_4$ $[M + 1]^+$ 371.3232; found 371.3214. $C_{17}H_{17}F_3N_2O_4$ (370.33): calcd. C 55.14, H 4.63, N 7.56; found C 55.51, H 4.37, N 7.88.

General Procedure for Ruthenium-Catalyzed RCEYM of Acyl-Substituted 1,7-Enynes 6a–6e: A solution of the corresponding acyl-substituted 1,7-enyne **6** (0.8 mmol) in dry toluene (40 mL) was placed in flame-dried Schlenk tube under argon. The Hoveyda–Grubbs' second-generation catalyst (25 mg, 0.04 mmol) was added, and the argon atmosphere was replaced by ethylene gas. The resulting solution was heated to 80 °C for 3 h. Then, the reaction mixture was cooled to room temp., and ^{19}F NMR analysis showed full conversion of the starting material. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography with the appropriate mixture of EtOAc and petroleum ether as the mobile phase.

Methyl 1-Methyl-5-(3-oxo-3-phenylprop-1-en-2-yl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9a): Column chromatography (EtOAc/petroleum ether, 1:8) afforded **9a** (0.14 g; 50%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.92 (d, J = 7.3 Hz, 2 H, Ar), 7.61 (t, J = 7.3 Hz, 1 H, Ar), 7.49 (t, J = 7.3 Hz, 2 H, Ar), 5.75 (br. s, 1 H, CH), 5.54 (s, 1 H, CH_2), 5.30 (s, 1 H, CH_2), 3.86–3.73 (m, 4 H, CO_2CH_3, NCH_2), 3.66 (d, J = 16.2 Hz, 1 H, NCH_2), 2.86 (dd, J = 18.0, 4.8 Hz, 1 H, CH_2), 2.76 (s, 3 H, NCH_3), 2.64 (dd, J = 18.0, 2.8 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 197.05, 167.85, 145.98, 136.21, 133.20, 131.57, 129.54, 128.19, 124.49 (q, J = 288.2 Hz), 122.27, 115.23, 67.02 (q, J = 25.3 Hz), 52.44, 51.46, 39.61 (q, J = 2.0 Hz), 30.05 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 9.19 (s, 3 F, CF_3) ppm. $C_{18}H_{18}F_3NO_3$ (353.34): calcd. C 61.19, H 5.13, N 3.96; found C 60.95, H 5.29, N 4.15.

Methyl 5-[3-(4-Fluorophenyl)-3-oxoprop-1-en-2-yl]-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9b): Column chromatography (EtOAc/petroleum ether, 1:8) afforded **9b** (0.22 g, 75%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.90 (dd, J = 8.9, 5.4 Hz, 2 H, Ar), 7.10 (t, J = 8.6 Hz, 2 H, Ar), 5.68 (br. s, 1 H, CH), 5.48 (s, 1 H, CH_2), 5.24 (s, 1 H, CH_2), 3.77 (s, 3 H, CO_2CH_3), 3.72 (d, J = 16.5 Hz, 1 H, NCH_2), 3.60 (d, J = 16.5 Hz, 1 H, NCH_2), 2.81 (dd, J = 18.1, 5.2 Hz, 1 H, CH_2), 2.70 (q, J = 1.1 Hz, 3 H, NCH_3), 2.59 (dd, J = 18.2, 2.9 Hz, 1 H, CH_2) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 195.73, 168.10, 165.98 (d, J = 255.7 Hz), 146.05, 132.87 (d, J = 2.1 Hz), 132.52 (d, J = 9.4 Hz), 131.76, 124.78 (q, J = 288.5 Hz), 122.69, 115.66 (d, J = 22.0 Hz), 115.32, 67.27 (q, J = 25.4 Hz), 52.73, 51.65, 39.88, 29.68 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.85 (s, 3 F, CF_3), –26.12 (s, 1 F, CF_{Ar}) ppm. $C_{18}H_{17}F_4NO_3$ (371.33): calcd. C 58.22, H 4.61, N 3.77; found C 58.45, H 4.52, N 3.95.

Methyl 5-[3-(2-Fluorophenyl)-3-oxoprop-1-en-2-yl]-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9c): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **9c** (0.14 g, 48%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.71 (t, J = 7.4 Hz, 1 H, Ar), 7.63–7.46 (m, 1 H, Ar), 7.25 (t, J = 7.5 Hz, 1 H, Ar), 7.17–7.06 (m, 1 H, Ar), 5.81 (br. s, 1 H, CH), 5.60 (s, 1 H, CH_2), 5.46 (s, 1 H, CH_2), 3.82 (s, 3 H, CO_2CH_3), 3.72 (d, J = 16.8 Hz, 1 H, NCH_2), 3.60 (d, J = 16.8 Hz, 1 H, NCH_2), 2.87 (dd, J = 18.0, 4.8 Hz, 1 H, CH_2), 2.72 (s, 3 H, NCH_3), 2.62 (dd, J = 18.0, 2.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 193.66, 168.02, 160.81 (d, J = 255.9 Hz), 147.71, 134.01 (d, J = 8.7 Hz), 131.36, 130.75, 126.22 (d, J = 12.0 Hz), 124.55 (q, J = 288.1 Hz), 124.03 (d, J = 3.6 Hz), 121.61, 118.85, 116.24 (d, J = 22.1 Hz), 67.16 (q, J = 25.5 Hz), 52.40, 52.17, 39.56, 29.87 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.46 (s, 3 F, CF_3), –34.52

(s, 1 F, CF_{Ar}) ppm. $C_{18}H_{17}F_4NO_3$ (371.33): calcd. C 58.22, H 4.61, N 3.77; found C 58.50, H 4.73, N 3.59.

Methyl 5-[3-(4-Chlorophenyl)-3-oxoprop-1-en-2-yl]-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9d): Column chromatography (EtOAc/petroleum ether, 1:10) afforded **9d** (0.22 g, 71%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.83 (d, J = 8.5 Hz, 2 H, Ar), 7.44 (d, J = 8.5 Hz, 2 H, Ar), 5.70 (br. s, 1 H, CH), 5.53 (s, 1 H, CH_2), 5.28 (s, 1 H, CH_2), 3.86–3.70 (m, 4 H, CO_2CH_3, NCH_2), 3.62 (d, J = 16.3 Hz, 1 H, NCH_2), 2.84 (dd, J = 18.1, 4.9 Hz, 1 H, CH_2), 2.73 (q, J = 1.2 Hz, 3 H, NCH_3), 2.68–2.56 (m, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 195.53, 167.69, 145.57, 139.55, 134.50, 131.39, 130.77, 128.42, 127.36 (q, J = 288.2 Hz), 122.36, 115.36, 66.90 (q, J = 25.4 Hz), 52.27, 51.32, 39.49, 29.96 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.65 (s, 3 F, CF_3) ppm. $C_{18}H_{17}ClF_3NO_3$ (387.78): calcd. C 55.75, H 4.42, N 3.61; found C 55.61, H 4.65, N 3.83.

Methyl 5-(4,4-Dimethyl-3-oxopent-1-en-2-yl)-1-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9e): Column chromatography (EtOAc/petroleum ether, 1:8) afforded **9e** (0.18 g; 70%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 5.45 (br. s, 1 H, CH), 5.10 (s, 1 H, CH_2), 4.88 (s, 1 H, CH_2), 3.72 (s, 3 H, CO_2CH_3), 3.56 (d, J = 16.5 Hz, 1 H, NCH_2), 3.47 (d, J = 16.5 Hz, 1 H, NH_2), 2.82 (dd, J = 18.0, 5.4 Hz, 1 H, CH_2), 2.64 (d, J = 1.3 Hz, 3 H, NCH_3), 2.60–2.54 (m, 1 H, CH_2), 1.12 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 213.53, 168.09, 147.45, 131.50, 124.69 (q, J = 288.3 Hz), 121.44, 109.95, 67.31 (q, J = 25.4 Hz), 52.64, 51.39, 44.40, 39.79, 30.21, 27.01 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 8.61 (s, 3 F, CF_3) ppm. $C_{16}H_{22}F_3NO_3$ (333.35): calcd. C 55.65, H 6.65, N 4.20; found C 55.41, H 6.39, N 4.11.

General Procedure for Diels–Alder Reaction of Compounds 7a and 7c with *N*-Phenylmaleimide: A mixture of the corresponding 1,3-diene (2.4 mmol) and *N*-phenylmaleimide (0.44 g, 2.52 mmol) in dry toluene (10 mL) was placed in a flame-dried Schlenk tube under argon. The resulting mixture was heated at 110 °C for 24 h. TLC analysis showed full conversion of the starting material. The solvent was evaporated to dryness under reduced pressure, and the crude mixture was purified by column chromatography with the appropriate mixture of EtOAc/petroleum ether to give the desired product as a mixture of diastereomers.

Methyl 7-Methyl-1,3-dioxo-2,5-diphenyl-8-(trifluoromethyl)-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-pyrrolo[3,4-*f*]isoquinoline-8-carboxylate (10a): Column chromatography (gradient of EtOAc/petroleum ether, from 1:8 to 1:5 and 1:1) afforded **10a** (0.93 g, 78%) as a mixture of diasteromers (A/B, 2:1). Data for diastereomer A: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.46 (t, J = 7.6 Hz, 2 H, Ar), 7.40 (t, J = 7.4 Hz, 1 H, Ar), 7.35 (t, J = 7.5 Hz, 2 H, Ar), 7.29 (t, J = 7.4 Hz, 1 H, Ar), 7.14 (d, J = 7.4 Hz, 1 H, Ar), 7.10 (d, J = 7.1 Hz, 2 H, Ar), 3.85 (s, 3 H, CO_2CH_3), 3.75 (dt, J = 14.1, 2.5 Hz, 1 H, NCH_2), 3.51–3.40 (m, 2 H, NCH_2, CH_2), 3.35–3.28 (m, 2 H, CH_2), 3.15 (d, J = 13.8 Hz, 1 H, CH_2), 2.96–2.89 (m, 1 H, CH), 2.85–2.77 (m, 1 H, CH), 2.48 (dd, J = 15.3, 4.8 Hz, 1 H, CH), 2.38 (s, 3 H, NCH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 178.18, 176.86, 168.90, 139.38, 134.21, 131.71, 131.45, 129.25, 128.78, 128.35, 128.05, 127.39, 126.46, 125.94 (q, J = 286.4 Hz), 68.99 (q, J = 25.8 Hz), 52.25, 50.66, 42.41, 40.43, 40.17, 31.72, 30.96, 28.33 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 5.38 (s, 3 F, CF_3) ppm. $C_{27}H_{25}F_3N_2O_4$ (498.50): calcd. C 65.05, H 5.05, N 5.62; found C 64.81, H 5.21, N 5.77. Data for diastereomer B: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.45 (t, J = 7.6 Hz, 2 H, Ar), 7.39 (t, J = 7.4 Hz, 1 H, Ar), 7.34 (t, J = 7.5 Hz, 2 H, Ar), 7.28 (t, J = 6.8 Hz, 1 H, Ar), 7.13 (d, J = 7.2 Hz, 2 H, Ar), 7.08 (d, J = 7.0 Hz, 2 H, Ar), 3.87 (s, 3 H, CO_2CH_3), 3.83 (d, J = 14.7 Hz, 1 H, NCH_2), 3.47–3.41 (m, 1 H, NCH_2), 3.34–3.28 (m, 2 H, CH_2), 3.17–3.07 (m, 2 H, CH_2), 2.86–2.73 (m, 2 H, 2 CH), 2.57 (dd, J = 14.8, 4.1 Hz, 1 H, CH), 2.52 (q, J = 1.7 Hz, 3 H, NCH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 178.20, 176.81, 169.79, 139.48, 134.26, 131.65, 130.86, 129.23, 128.77, 128.29, 127.99, 127.39, 126.40, 126.07 (q, J = 294.6 Hz), 69.07 (q, J = 24.6 Hz), 53.14, 50.09, 42.19, 40.02, 39.27, 31.80, 30.56, 29.09 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 7.69 (s, 3 F, CF_3) ppm. $C_{27}H_{25}F_3N_2O_4$ (498.50): calcd. C 65.05, H 5.05, N 5.62; found C 65.31, H 5.33, N 5.43.

Methyl 7-Methyl-1,3-dioxo-2-phenyl-5-(*p*-tolyl)-8-(trifluoromethyl)-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-pyrrolo[3,4-*f*]isoquinoline-8-carboxylate (10b): Column chromatography (gradient of EtOAc/petroleum ether, from 1:8 to 1:5 and 1:1) afforded **10b** (0.91 g, 74%) as a diasteromeric mixture (A/B, 2:1). Data for diastereomer A: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.46 (t, J = 7.6 Hz, 2 H, Ar), 7.40 (t, J = 7.4 Hz, 1 H, Ar), 7.16 (d, J = 7.8 Hz, 2 H, Ar), 7.13 (d, J = 7.2 Hz, 2 H, Ar), 7.00 (d, J = 8.0 Hz, 2 H, Ar), 3.85 (s, 3 H, CO_2CH_3), 3.75 (dt, J = 14.1, 2.6 Hz, 1 H, NCH_2), 3.47 (t, J = 14.1 Hz, 1 H, NCH_2), 3.44–3.39 (m, 1 H, CH_2), 3.34 (d, J = 14.0 Hz, 1 H, CH_2), 3.29 (dd, J = 8.9, 5.8 Hz, 1 H, CH_2), 3.13 (dd, J = 14.5, 1.1 Hz, 1 H, CH_2), 2.95–2.87 (m, 1 H, CH), 2.82–2.75 (m, 1 H, CH), 2.47 (dd, J = 15.3, 4.8 Hz, 1 H, CH), 2.38 (s, 3 H, NCH_3), 2.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 178.23, 176.94, 168.94, 137.13, 136.49, 133.62, 131.73, 131.34, 129.24, 129.02, 128.76, 127.96, 126.49, 125.97 (q, J = 286.6 Hz), 69.00 (q, J = 25.4 Hz), 52.25, 50.73, 42.43, 40.44, 40.18, 31.71, 31.04, 28.33, 21.20 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 5.11 (s, 3 F, CF_3) ppm. $C_{28}H_{27}F_3N_2O_4$ (512.53): calcd. C 65.62, H 5.31, N 5.47; found C 65.43, H 5.53, N 5.34. Data for diastereomer B: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.44 (t, J = 7.6 Hz, 2 H, Ar), 7.38 (t, J = 7.4 Hz, 1 H, Ar), 7.14 (d, J = 7.8 Hz, 2 H, Ar), 7.12 (d, J = 7.2 Hz, 2 H, Ar), 6.96 (d, J = 8.0 Hz, 2 H, Ar), 3.87 (s, 3 H, CO_2CH_3), 3.82 (d, J = 14.6 Hz, 1 H, NCH_2), 3.42 (t, J = 8.3 Hz, 1 H, NCH_2), 3.33–3.26 (m, 2 H, CH_2), 3.15–3.07 (m, 2 H, CH_2), 2.83–2.72 (m, 2 H, 2 CH), 2.56 (dd, J = 14.8, 4.1 Hz, 1 H, CH), 2.51 (q, J = 1.4 Hz, 3 H, NCH_3), 2.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 178.24, 176.87, 169.86, 137.11, 136.60, 133.67, 131.67, 130.72, 129.20, 128.96, 128.74, 127.89, 126.42, 126.10 (q, J = 294.9 Hz), 69.08 (q, J = 24.4 Hz), 53.12, 50.13, 42.21, 40.04, 39.27, 31.79, 30.63, 29.13, 21.19 ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = 7.70 (s, 3 F, CF_3) ppm. $C_{28}H_{27}F_3N_2O_4$ (512.53): calcd. C 65.62, H 5.31, N 5.47; found C 65.82, H 5.45, N 5.79.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectroscopic data for representative compounds.

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