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A Straightforward Approach towards Isoxazoline Amino Acid Esters by Domino Michael Additions/Nitrile Oxide Cycloadditions

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The syntheses of new heterocyclic isoxazoline amino acids are described based on a domino Michael addition/nitrile oxide formation/[3+2] cycloaddition approach. Chelated amino acid ester enolates can be added to nitroalkenes, and the generated nitronates are directly converted into nitrile oxides. These can be trapped intramolecularly by an alkene as a dipolarophile. The alkene can be introduced either via the nitroalkene or via the chelated enolate. Therefore, different types of heterocyclic amino acids can be obtained in a simple one-pot protocol.

Introduction

Isoxazolines are an interesting class of N,O-heterocycles not only found as a core structure in a wide range of biologically active compounds, but also as synthetic intermediates.[1] Several 1,3-bifunctional compounds such as β-hydroxy ketones, α,β-unsaturated ketones or γ-amino acids can be generated from these heterocycles.[2] According to Huisgen et al., isoxazolines are easily available by 1,3-dipolar cycloadditions of nitrile oxides to alkenes.[3] The nitrile oxides required are accessible either from oximes by oxidation[4] or from nitro compounds by dehydration.[5] They are highly reactive species, undergoing rapid additions to alkenes, alkynes or carbonyl groups,[6] but the high reactivity also results in the formation of a wide range of side products.[7] Therefore, generation of nitrile oxides directly in the presence of dipolarophiles is recommended, and the dipolarophiles should also be used in excess. Not surprisingly, sufficiently good results are obtained in intramolecular nitrile oxide cycloadditions (INOC), which makes this approach interesting for natural-product and drug synthesis.[8]

Nitroalkenes are especially interesting nitrile oxide precursors. The electron-poor double bond of nitroalkenes is an excellent Michael acceptor, allowing the introduction of a dipolarophile by Michael addition. The nitronate formed in situ can be treated with dehydrating agents such as phenyl isocyanate[9] or chloroformates[10] to generate the reactive nitrile oxide, which undergoes an INOC.[11] Frequently used nucleophiles are allyl alcohols,[12] allyl thiols,[13] allylamine derivatives[14] as well as α-allylated malonates.[15]

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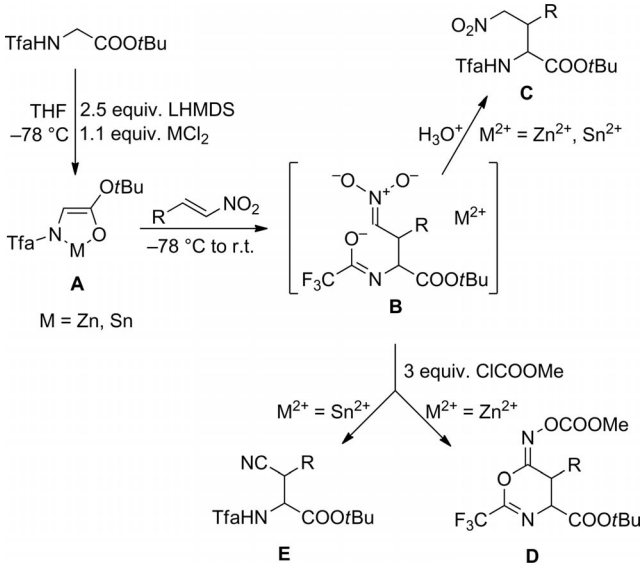
Our group is involved in amino acid synthesis, investigating reactions of chelated amino acid ester enolates **A**.[16] These enolates are easily obtained by double deprotonation of amino acid esters in the presence of a metal salt such as $ZnCl_2$ or $SnCl_2$ (Scheme 1).



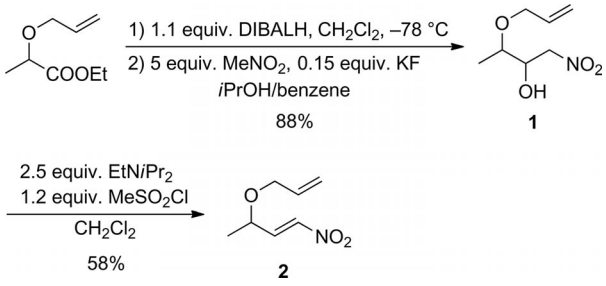
Scheme 1. Michael additions of chelated enolates to nitroalkenes.

They can undergo Claisen rearrangements when allylic esters are used,[17] and they are suitable nucleophiles in allylic alkylations[18] and Michael additions,[19] including Michael-induced ring closing reactions (MIRC).[20] Nitroalkenes are excellent acceptors for these chelated enolates **A**, and give access to a wide range of products, depending on the reaction and workup conditions (Scheme 1). If the nitronates **B** formed in situ are hydrolyzed, the expected Michael addition products **C** are formed in good yields and reasonably good diastereoselectivities (depending on the metal salt used for chelation).[21] On the other hand, if ni-

tronates **B**, obtained in the reaction of the zinc enolates, are trapped with an excess of acyl halides or chloroformates, the deprotonated amides undergo cyclization with the iminooxazines **D**.[22] In contrast, if $SnCl_2$ is used as a chelating metal salt, the formation of nitriles **E** is observed.[23] Shimizu reported, that nitronates can be converted into nitrile oxides by using chloroformates.[10] In our case, the nitrile oxide formed in situ is either reduced by Sn^{2+} or is intramolecularly attacked by the deprotonated TFA amide.

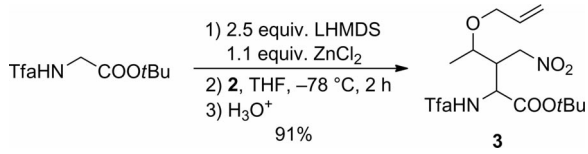
Results and Discussion

These observations inspired the idea to combine a chelated enolate Michael addition with an in situ nitrile oxide formation/[3+2] cycloaddition to obtain access to isoxazoline amino acids. To be able to generate different types of amino acids, we decided to incorporate the dipolarophile in both the nitroalkene and the chelated enolate. Therefore, we synthesized nitroalkene **2** from *O*-allylated ethyl lactate[24] by DIBALH reduction, Henry reaction and subsequent elimination with $MeSO_2Cl$/Hünig base (Scheme 2).[25]



Scheme 2. Synthesis of nitroalkene **2**.

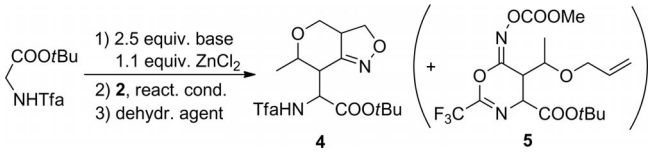
With this Michael acceptor in hand we first investigated the Michael addition to optimize the initial step of the reaction. Under standard reaction conditions, with LHMDS as a base, the addition product **3** was obtained after 2 h at –78 °C in excellent yield (Scheme 3). Other amide bases such as LDA (89%) and lithium 2,2,4,4-tetramethylpiperidide (LTMP, 94%) gave comparable results. Out of the four possible stereoisomers, two were formed preferentially (85%) as a 1:1 diastereomeric mixture. Based on our previous observations,[21] we assumed that the 85:15 ratio corresponded to the simple diastereoselectivity (*syn*/*anti*), and that the induced diastereoselectivity could be neglected.



Scheme 3. Michael addition to nitroalkene **2**.

With these good results in hand, we directly investigated the Michael addition/cycloaddition tandem process by adding dehydrating agents (Table 1). As a first reagent we used methyl chloroformate, which gave good results in the Michael addition/iminooxazine formation.[22] In principle, 1 equiv. of chloroformate should be sufficient to generate the nitrile oxide, but with 1.2 equiv. only 13% of the expected [3+2]-cycloaddition product **4** was formed (Entry 1). The major product was the iminooxazine **5**. With a larger excess of chloroformate, **5** was formed exclusively, albeit in moderate yield (Entry 2). This clearly indicates that an acylation of the nitrile oxide is faster than the [3+2] cycloaddition, and a subsequent intramolecular nucleophilic attack of the deprotonated amide results in the formation of heterocycle **5** according to Scheme 1.

Table 1. Domino Michael addition/cycloaddition of nitroalkene **2**.

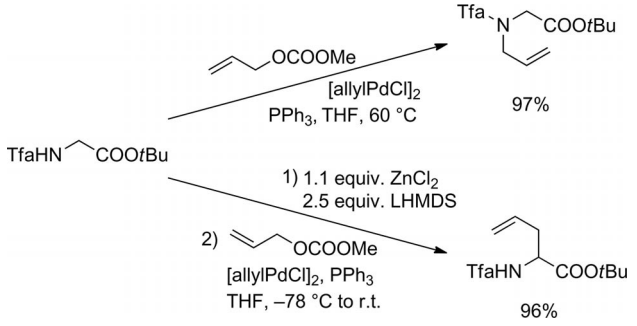


Entry	Base	Dehydration agent	Reaction conditions[a]	Yield [%]
1	LHMDS	1.2 equiv. ClCOOMe	MA: –78 °C, 2 h CA: –78 °C to r.t., 16 h	13 (**4**), 25 (**5**)
2	LHMDS	3.0 equiv. ClCOOMe	MA: –78 °C, 2 h CA: –78 °C to r.t., 16 h	40 (**5**)
3	LHMDS	2.2 equiv. PhNCO	MA: –78 °C, 2 h CA: –78 °C to r.t., 16 h	traces
4	LHMDS	3.0 equiv. TCT	MA: –78 °C, 2 h CA: –78 °C to r.t., 16 h	72 (**4**)
5	LHMDS	3.0 equiv. TCT	MA: –78 °C, 2 h CA: –78 °C, 3 h	69 (**4**)
6	LDA	3.0 equiv. TCT	MA: –78 °C, 2 h CA: –78 °C, 3 h	91 (**4**)
7	LTMP	3.0 equiv. TCT	MA: –78 °C, 2 h CA: –78 °C, 3 h	94 (**4**)

[a] MA: Michael addition; CA: cycloaddition.

The application of phenyl isocyanate, a reagent introduced by Mukaiyama for nitrile oxide formation (Entry 3) was also not satisfying.[26] So far the best results were obtained by using cyanuric chloride (2,4,6-trichloro-1,3,5-triazone, TCT). When the Michael addition was quenched with 3 equiv. of TCT at –78 °C and the mixture was warmed up to room temperature overnight, the expected cycloadduct was obtained in good yield (Entry 4). At least 3 equiv. of the dehydrating reagent are required; with less than 3 equiv. the yield dropped dramatically. The nitrile oxide formation and cycloaddition occur at very low temperature. A comparable yield was obtained after 3 h at –78 °C (Entry 5). Under these conditions, the reaction proceeds without significant formation of side products, which were observed at temperatures above 0 °C. One of the side products results from a reaction of the cyanuric chloride with the base LHMDS. To suppress this side reaction, and based on the good results obtained in the Michael addition with other bases, we also investigated LDA and LTMP in the one-pot protocol (Entries 6 and 7). With these bases, the yields could be increased to above 90%.

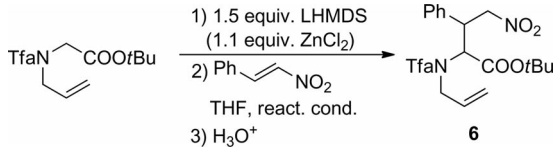
Next, we investigated reactions where the dipolarophile was introduced by the nucleophile, using allylated glycinates. Two different options were considered: the *N*- and *C*-allylglycinates. Both can easily be obtained from *N*-trifluoroacetylated glycinate by Pd-catalyzed allylic alkylation (Scheme 4). When *N*-protected *tert*-butyl glycinate was treated with allyl carbonate in the presence of allylpalladium chloride/PPh_3, the *N*-allylated product was obtained in almost quantitative yield. During the π-allyl complex formation methylate is liberated, which deprotonates the rather acidic trifluoroamide, generating the actual nucleophile that undergoes allylation.[27] On the other hand, if the TFA glycinate was first converted into the chelated enolate **A**, the corresponding *C*-allylation product was formed exclusively in comparable yield. Here, chelation results in a protection of the TFA amide, and allylation occurs only at the enolate.[28]



Scheme 4. Preparation of *N*- and *C*-allylated glycinates.

With these glycine esters in hand, we first investigated the Michael addition using the *N*-allyl derivative (Table 2). With this pronucleophile no chelate complex formation should be possible, and therefore we first checked the reaction of the corresponding lithium enolate. The Michael addition product **6** was obtained in moderate yield (Entry 1). The yield could slightly be increased by keeping the reaction temperature at –78 °C (Entry 2). Here also, the usage of the corresponding zinc enolate proved to be superior (Entries 3 and 4). It should be mentioned that in the presence of other metal salts [$SnCl_2$, $Ti(OiPr)_4$] the yield dropped dramatically (< 20%), and LDA and LTMP also led to less satisfying results (31–37% yield).

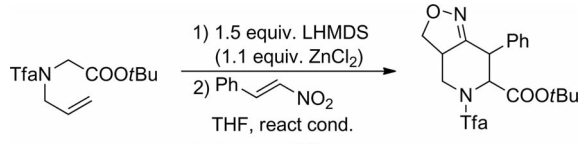
Table 2. Michael addition of *N*-allylated glycinate to nitrostyrene.



Entry	($ZnCl_2$)	Reaction conditions	Yield [%]
1	–	–78 °C to r.t., 16 h	43
2	–	–78 °C, 2 h	50
3	$ZnCl_2$	–78 °C to r.t., 16 h	68
4	$ZnCl_2$	–78 °C, 2 h	65

Therefore, we focused our investigations of the domino process on the lithium and zinc enolates, generated with LHMDS as base (Table 3). Also, the use of chloroformate here provided only traces of the cycloaddition product. However, with TCT, both the lithium and the zinc enolates gave rise to the required bicyclic amino acid derivative **7** in acceptable yield. No significant influence of the reaction temperature was observed, thus the yields obtained after 2 h at –78 °C were comparable to reactions, where the temperature was allowed to rise to room temperature overnight.

Table 3. Domino Michael addition/cycloaddition of *N*-allylated glycinate.

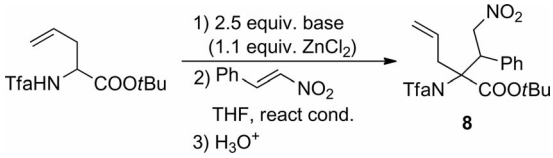


Entry	($ZnCl_2$)	Reaction conditions	Yield [%]
1	–	MA: –78 °C to r.t., 16 h CA: –78 °C to r.t., 16 h	46
2	$ZnCl_2$	MA: –78 °C to r.t., 16 h CA: –78 °C to r.t., 16 h	41
3	–	MA: –78 °C, 2 h CA: –78 °C, 2 h	48
4	$ZnCl_2$	MA: –78 °C, 2 h CA: –78 °C, 2 h	44

Next we examined the *C*-allylated glycine derivative (Table 4). Deprotonation of amino acid esters other than glycine esters can be a serious problem, especially with LHMDS.[29] Therefore, we prolonged the enolate formation time from 10 min to 2 h to obtain reasonable yields of the Michael addition product **8**. The Li enolate (Entry 1) gave a slightly better yield compared to the zinc enolate (Entry 2). Interestingly, no addition product was obtained with the corresponding tin enolate. By using stronger bases such as

LDA or LTMP, the enolate formation time could be reduced to 10 min, and the yields, especially with the zinc enolate, increased significantly (Entries 3, 4 and 5).

Table 4. Michael addition of *C*-allylated glycinate to nitrostyrene.

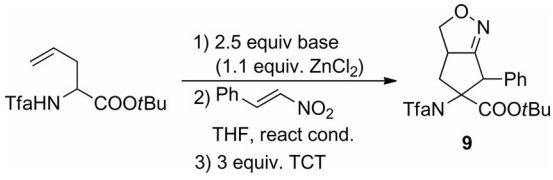


Entry	Base	($ZnCl_2$)	Reaction conditions	Yield [%]
1	LHMDS[a]	–	–78 °C to r.t., 16 h	65
2	LHMDS[a]	$ZnCl_2$	–78 °C to r.t., 16 h	56
3	LDA	–	–78 °C, 2 h	58
4	LDA	$ZnCl_2$	–78 °C, 2 h	79
5	LTMP	$ZnCl_2$	–78 °C, 2 h	95

[a] Enolate formation time: 2 h.

Under these optimized conditions, we investigated the one-pot process using TCT as the dehydrating agent (Table 5). With LHMDS, the yields obtained were in the range of 40%, independent of whether the Li or Zn enolate was used (Entries 1 and 2). With the use of stronger bases the yield could be increased (Entries 3 and 4). In this case, LDA gave the best results.

Table 5. Domino Michael addition/cycloaddition of *C*-allylated glycinate.



Entry	Base	($ZnCl_2$)	Reaction conditions	Yield [%]
1	LHMDS[a]	–	MA: –78 °C, 2 h CA: –78 °C, 3 h	40
2	LHMDS[a]	$ZnCl_2$	MA: –78 °C, 2 h CA: –78 °C, 3 h	38
3	LDA	$ZnCl_2$	MA: –78 °C, 2 h CA: –78 °C, 3 h	76
4	LTMP	$ZnCl_2$	MA: –78 °C, 2 h CA: –78 °C, 3 h	54

[a] Enolate formation time: 2 h.

Conclusions

We have shown that the domino process Michael addition/nitrile oxide formation/intramolecular [3+2] cycloaddition is a straightforward approach towards unusual cyclic and bicyclic amino acids. The dipolarophile required for the last step of the sequence can be introduced either via the Michael acceptor or via the nucleophile, giving rise to different classes of heterocyclic amino acids, which might be interesting scaffolds for drug-like molecules.

Experimental Section

General Remarks: Reactions with dry solvents were carried out in oven-dried glassware (100 °C) under nitrogen. Solvents were dried as follows: THF was distilled from $LiAlH_4$ and CH_2Cl_2 from CaH_2. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of ethyl acetate (EtOAc) and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Macherey-Nagel, Dueren). Visualization was accomplished with UV light or $KMnO_4$ solution. ^1H and ^{13}C NMR spectra were obtained at room temperature with a Bruker AV 400 spectrometer. Chemical shifts are expressed in ppm relative to internal solvent. The diastereomeric ratios were determined by ^1H NMR spectra of the diastereomeric mixture. Selected signals for the minor isomers were extracted from the spectra of the isomeric mixture. Melting points were determined with a MEL-TEMP II apparatus. High-resolution mass spectra were recorded with a Finnigan MAT 95Q by using the CI technique. Elemental analyses were performed with a Leco CHN900.

3-Allyloxy-1-nitrobutan-2-ol (1): A solution of DIBALH in hexane (1 M, 7.50 mL, 7.50 mmol) was added dropwise at –78 °C to a solution of *O*-allylated ethyl lactate (1.08 g, 6.81 mmol) in dry dichloromethane (14 mL). After stirring the reaction mixture at –78 °C for 2 h, it was poured into a mixture of 10% aqueous tartaric acid (33 mL) and dichloromethane (14 mL). After vigorous stirring for 30 min and separation of the layers, the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was dissolved in dry isopropyl alcohol (15 mL) and benzene (2 mL). Nitromethane (1.80 mL, 34.0 mmol) and potassium fluoride (67.0 mg, 34.0 mmol) were added, and the reaction mixture was stirred overnight. After filtration through Celite, the solvent was removed in vacuo, and the crude product was purified by flash chromatography (hexane/EtOAc, 9:1) to yield **1** (1.05 g, 5.99 mmol, 88%) as a yellow oil. R_f = 0.17 (hexane/EtOAc, 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, $^3J_{4,3}$ = 6.3 Hz, 3 H, 4-H), 2.74 (br. s, 1 H, OH), 3.57 (m, 1 H, 3-H), 3.92 (m, 1 H, 5-H), 4.12 (m, 1 H, 5′-H), 4.23 (m, 1 H, 2-H), 4.50 (dd, $^2J_{1,1'}$ = 19.7, $^3J_{1,2}$ = 9.6 Hz, 1 H, 1-H), 4.60 (dd, $^2J_{1',1}$ = 13.2, $^3J_{1',2}$ = 2.8 Hz, 1 H, 1′-H), 5.21 (ddt, $^3J_{7E,6}$ = 10.3, $^2J_{7E,7Z}$ = $^4J_{7E,5}$ = 1.3 Hz, 1 H, 7-H$_E$), 5.27 (ddt, $^3J_{7Z,6}$ = 17.3, $^2J_{7Z,7E}$ = $^4J_{7Z,5}$ = 1.3 Hz, 1 H, 7-H$_Z$), 5.87 (m, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (q, C-4), 69.9 (t, C-5), 71.6 (d, C-2), 75.2 (d, C-3), 77.6 (t, C-1), 117.5 (t, C-7), 134.2 (d, C-6) ppm. $C_7H_{13}NO_4$ (175.18): calcd. C 47.99, H 7.48, N 8.00; found C 47.98, H 7.41, N 7.60. HRMS (CI): calcd. for $C_7H_{13}NO_4$ $[M]^+$ 175.0845; found 175.0857.

3-Allyloxy-1-nitrobut-1-ene (2): Methanesulfonyl chloride (1.67 g, 14.6 mmol) was added at –78 °C to a solution of **1** (2.14 g, 12.2 mmol) in dry dichloromethane (120 mL). After stirring the reaction mixture at –78 °C for 10 min, Hünig base (5.18 mL, 30.5 mmol) was added dropwise, and the mixture was warmed to room temperature overnight. The reaction mixture was washed with water, 2 N hydrochloric acid and saturated aqueous ammonium chloride, dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 9:1) to yield **2** (1.08 g, 6.86 mmol, 58%) as a yellow oil. R_f = 0.50 (hexane/EtOAc, 8:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, $^3J_{4,3}$ = 6.6 Hz, 3 H, 4-H), 4.01 (d, $^3J_{5,6}$ = 5.6 Hz, 2 H, 5-H), 4.23 (m, 1 H, 3-H), 5.21 (ddt, $^3J_{7E,6}$ = 10.4, $^2J_{7E,7Z}$ = $^4J_{7E,5}$ = 1.5 Hz, 1 H, 7-H$_E$), 5.29 (ddt, $^3J_{7Z,6}$ = 17.3, $^2J_{7Z,7E}$ = $^4J_{7Z,5}$ = 1.5 Hz, 1 H, 7-H$_Z$), 5.88 (m, 1 H, 6-H), 7.15 (m, 2 H, 1-H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (q, C-4), 70.1 (t, C-5), 71.0 (d, C-3), 117.5 (t, C-

7), 134.0 (d, C-6), 139.4 (d, C-1), 143.0 (d, C-2) ppm. $C_7H_{11}NO_3$ (157.17): calcd. C 53.49, H 7.05, N 8.91; found C 53.19, H 6.78, N 8.64. HRMS (CI): calcd. for $C_7H_{11}NO_3$ $[M]^+$ 157.0739; found 157.0748.

General Procedure for the Michael Additions: In a Schlenk tube, HMDS/TMP or DIPA (0.94 mmol, 3.13 equiv.) was dissolved in dry THF (1 mL). After the solution had been cooled to –78 °C, *n*-butyllithium in hexane (1.6 M, 0.75 mmol, 2.50 equiv.) was added slowly. The cooling bath was removed, and the solution was stirred for 10 min. In a second Schlenk flask, $ZnCl_2$ (0.33 mmol, 1.10 equiv.) was dried with a heat gun under vacuum before it was dissolved in dry THF (1 mL). After the solution had been cooled to room temperature, Tfa-Gly-O*t*Bu (0.33 mmol, 1.10 equiv.) was added. The freshly prepared LHMDS solution was cooled again to –78 °C before the Tfa-Gly-O*t*Bu/$ZnCl_2$ solution was added dropwise. This solution was stirred at –78 °C for 30 min. At the same time, a solution of the nitro olefin (0.30 mmol, 1 equiv.) was prepared in THF (0.30 mL). The nitro olefin solution was added to the enolate at –78 °C. The reaction mixture was stirred at –78 °C for 2 h before it was diluted with ethyl acetate and hydrolyzed with 1 M aqueous potassium bisulfate. The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc).

***tert*-Butyl-4-(allyloxy)-3-(nitromethyl)-2-(2,2,2-trifluoroacetamido)pentanoate (3):** According to the general Michael addition procedure, Tfa-Gly-O*t*Bu (75.0 mg, 0.33 mmol, 1.10 equiv.) and nitro olefin **2** (47.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.) to give a pale yellow oil (108 mg, 0.28 mmol, 94%); R_f = 0.13 (hexane/EtOAc, 9:1). Major diastereomers (85%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, $^3J_{10,9}$ = 6.3 Hz, 3 H, 10-H), 1.48 (s, 9 H, 6-H), 2.91 and 3.05 (m, 1 H, 9-H), 3.70 (m, 1 H, 8-H), 3.83 (ddt, $^2J_{11,11'}$ = 12.5, $^3J_{11,12}$ = 6.4, $^4J_{11,13}$ = 1.2 Hz, 1 H, 11-H), 4.01 and 4.10 (ddt, $^2J_{11',11}$ = 12.5, $^3J_{11',12}$ = 6.4, $^4J_{11',13}$ = 1.2 Hz, 1 H, 11′-H), 4.63 (m, 3 H, 8′-H, 3-H, 7-H), 5.21 (m, 1 H, 13-H), 5.83 (m, 1 H, 12-H), 7.32 and 7.69 (br. s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 and 17.0 (q, C-10), 27.9 and 28.0 (q, C-6), 44.4 and 44.7 (d, C-3/C-7), 53.4 and 54.6 (d, C-3/C-7), 69.7 and 70.1 (t, C-8), 72.4 (d, C-9/t, C-11), 72.5 (d, C-9/t, C-11), 84.1 and 84.7 (s, C-5), C-1 not visible, 118.0 and 119.1 (t, C-13), 133.3 and 133.8 (d, C-12), 157.2 (s, C-2), 167.5 and 167.9 (s, C-4) ppm. Minor diastereomers (15%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (m, 1 H, 9-H), 7.87 (br. s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8 (q, C-10), 27.8 (q, C-6), 42.8 (d, C-3/C-7), 52.9 (d, C-3/C-7), 69.6 (t, C-8), 83.8 (s, C-5), 117.9 (t, C-13), 132.9 (d, C-12), 167.4 (s, C-4) ppm. $C_{15}H_{23}F_3N_2O_6$ (384.35): calcd. C 46.87, H 6.03, N 7.29; found C 46.96, H 6.05, N 7.47. HRMS (CI): calcd. for $C_{15}H_{24}F_3N_2O_6$ $[M + H]^+$ 385.1586; found 385.1563.

***tert*-Butyl-2-(*N*-allyl-2,2,2-trifluoroacetamido)-4-nitro-3-phenylbutanoate (6):** According to the general Michael addition procedure, *N*-Allyl-Tfa-Gly-O*t*Bu (88.0 mg, 0.33 mmol, 1.10 equiv.) and (*E*)-β-nitrostyrene (45.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.) to give a pale yellow oil (83 mg, 0.20 mmol, 65%); R_f = 0.15 (hexane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 9-H), 3.09 (dd, $^3J_{3,3'}$ = 16.0, $^3J_{3,4}$ = 8.2 Hz, 1 H, 3-H), 3.88 (dd, $^3J_{3,3'}$ = 16.0, $^3J_{3,4}$ = 8.2 Hz, 1 H, 3′-H), 4.01 (d, $^3J_{6,10}$ = 10.4 Hz, 1 H, 6-H), 4.51 (dt, $^3J_{10,6}$ = 10.4, $^3J_{10,15}$ = 4.3 Hz, 1 H, 10-H), 4.92 (dd, $^3J_{15,15'}$ = 13.2, $^3J_{15,10}$ = 9.9 Hz, 1 H, 15-H), 5.28 (m, 3 H, 15′-H, 5-H), 5.61 (m, 1 H, 4-H), 7.26 (m, 5 H, 12-H, 13-H, 14-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 (q, C-9), 42.7 (d, C-10), 52.7 (t, C-3), 61.7 (d, C-6), 77.8 (t, C-15), 83.7 (s, C-8), 114.4 (s, C-1), 120.7 (t, C-5), 128.1 (d, C-12/C-13/C-14), 128.6 (d, C-12/C-13/C-14), 129.0 (d, C-12/C-13/C-14), 131.7 (d, C-4), 135.8 (s, C-11), C-2 signal not visible, 166.9 (s, C-7) ppm. $C_{19}H_{23}F_3N_2O_5$ (416.39): calcd. C 54.80, H 5.57, N 6.73; found C 55.13, H 5.58, N 7.11. HRMS (CI): calcd. for $C_{15}H_{16}F_3N_2O_5$ [M – *t*Bu + H]$^+$ 361.1011; found 361.1025.

***tert*-Butyl-2-(2-nitro-1-phenylethyl)-2-(2,2,2-trifluoroacetamido)-pent-4-enoate (8):** According to the general Michael addition procedure, *C*-Allyl-Tfa-Gly-O*t*Bu (88.0 mg, 0.33 mmol, 1.10 equiv.) and (*E*)-β-nitrostyrene (45.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.) to give a pale yellow oil (101 mg, 0.29 mmol, 95%); R_f = 0.10 (hexane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 6-H), 2.75 (dd, $^2J_{7,7'}$ = 13.7, $^3J_{7,8}$ = 6.8 Hz, 1 H, 7-H), 3.42 (dd, $^2J_{7,7'}$ = 13.7, $^3J_{7',8}$ = 6.8 Hz, 1 H, 7′-H), 4.68 (dd, $^3J_{10,11'}$ = 9.8, $^3J_{10,11}$ = 5.4 Hz, 1 H, 10-H), 5.14 (m, 4 H, 9-H, 11-H), 5.48 (m, 1 H, 8-H), 7.01 (br. s, 1 H, NH), 7.23 (m, 5 H, 13-H, 14-H, 15-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (q, C-6), 37.8 (t, C-7), 47.0 (d, C-10), 66.4 (s, C-3), 76.6 (t, C-11), 86.2 (s, C-5), C-1 signal not visible, 121.8 (t, C-9), 128.9 (d, C-13/C-14/C-15), 128.9 (d, C-13/C-14/C-15), 129.0 (d, C-13/C-14/C-15), 129.5 (d, C-8), 134.4 (s, C-12), 156.1 (s, C-2), 168.7 (s, C-4) ppm. $C_{19}H_{23}F_3N_2O_5$ (416.39): calcd. C 54.80, H 5.57, N 6.73; found C 55.04, H 5.46, N 6.73. HRMS (CI): calcd. for $C_{19}H_{24}F_3N_2O_5$ $[M + H]^+$ 417.1638; found 417.1606.

General Procedure for the Domino Michael Additions/Cycloadditions: The Michael addition product was generated as shown in the general procedure for the Michael additions. After the Michael addition was complete (–78 °C, 2 h), cyanuric chloride (0.90 mmol, 3.00 equiv.) in dry THF (0.50 mL) was slowly added over 15 min. The reaction mixture was stirred at –78 °C for 3 h before it was diluted with ethyl acetate and hydrolyzed with 1 M aqueous potassium bisulfate. The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc).

***tert*-Butyl 2-(6-Methyl-3a,4,6,7-tetrahydro-3-*H*-pyrano[4,3-*c*]-isoxazol-7-yl)-2-(2,2,2-trifluoroacetamido)acetate (4):** According to the general Michael addition procedure, Tfa-Gly-O*t*Bu (75.0 mg, 0.33 mmol, 1.10 equiv.) and nitro olefin **2** (47.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.). After the Michael addition, cyanuric chloride (166 mg, 0.90 mmol, 3.00 equiv.) was added to yield a colorless solid (103 mg, 0.28 mmol, 94%); m.p. 94–98 °C; R_f = 0.43 (hexane/EtOAc, 8:2). Major diastereomers (77%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (m, 12 H, 6-H, 9-H), 3.10 (dd, $^2J_{7,8}$ = 10.0, $^3J_{7,3}$ = 2.9 Hz, 1 H, 7-H), 3.64 (m, 5 H, 10-H, 11-H, 12-H), 4.40 (m, 1 H, 8-H), 4.69 and 4.93 (dd, $^3J_{3,NH}$ = 9.7, $^3J_{3,7}$ = 2.9 Hz, 1 H, 3-H), 7.29 and 7.64 (d, $^3J_{NH,3}$ = 9.7 Hz, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 and 19.4 (q, C-9), 27.7 and 27.8 (q, C-6), 46.0 (d, C-7), 48.2 (d, C-11), 50.5 (d, C-3), 69.7 (d, C-8), 71.5 (t, C-12), 76.2 (t, C10), 83.8 and 84.0 (s, C-5), C-1 signal not visible, 152.9 (s, C-13), 157.3 (s, C-2), 167.1 and 168.0 (s, C-4) ppm. Minor diastereomers (23%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94 (dd, $^2J_{7,8}$ = 10.0, $^3J_{7,3}$ = 2.9 Hz, 1 H, 7-H), 4.87 (dd, $^3J_{3,NH}$ = 9.7, $^3J_{3,7}$ = 2.9 Hz, 1 H, 3-H), 7.01 (d, $^3J_{NH,3}$ = 9.7 Hz, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4 (q, C-9), 27.9 (q, C-6), 84.5 (s, C-5), 167.3 (s, C-4) ppm. $C_{15}H_{21}F_3N_2O_5$

(366.14): calcd. C 49.18, H 5.78, N 7.65; found C 49.16, H 5.78, N 7.80. HRMS (CI): calcd. for $C_{15}H_{22}F_3N_2O_5$ $[M + H]^+$ 367.1481; found 367.1510.

***tert*-Butyl 7-Phenyl-5-(2,2,2-trifluoroacetyl)-3,3a,4,5,6,7-hexahydroisoxazolo[4,3-*c*]pyridine-6-carboxylate (7):** According to the general Michael addition procedure, *N*-Allyl-Tfa-Gly-O*t*Bu (88.0 mg, 0.33 mmol, 1.10 equiv.) and (*E*)-β-nitrostyrene (45.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.). After the Michael addition, cyanuric chloride (166 mg, 0.90 mmol, 3.00 equiv.) was added to yield a colorless solid (55 mg, 0.14 mmol, 48%); m.p. 108–109 °C; R_f = 0.47 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 9 H, 6-H), 3.46 (m, 1 H, 14-H), 4.30 (m, 5 H, 7-H, 13-H, 15-H), 5.51 (d, $^3J_{3,7}$ = 6.4 Hz, 1 H, 3-H), 7.43 (m, 5 H, 9-H, 10-H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (q, C-6), 40.8 (t, C-15), 43.6 (d, C-7), 47.8 (q, C-14), 57.1 (d, C-3), 71.0 (t, C-13), 84.4 (s, C-5), 117.6 (s, C-1), 126.5 (d, C-9/C-10/C-11), 127.9 (d, C-9/C-10/C-11), 129.3 (d, C-9/C-10/C-11), 135.4 (s, C-8), 155.7 (s, C-2), 157.3 (s, C-12), 166.5 (s, C-4) ppm. $C_{19}H_{21}F_3N_2O_4$ (398.15): calcd. C 57.28, H 5.31, N 7.03; found C 57.49, H 5.59, N 6.69. HRMS (CI): calcd. for $C_{19}H_{22}F_3N_2O_4$ $[M + H]^+$ 399.1532; found 399.1504.

***tert*-Butyl 6-Phenyl-5-(2,2,2-trifluoroacetamido)-3a,4,5,6-tetrahydro-3*H*-cylopenta[c]isoxazole-5-carboxylate (9):** According to the general Michael addition procedure, *C*-Allyl-Tfa-Gly-O*t*Bu (88.0 mg, 0.33 mmol, 1.10 equiv.) and (*E*)-β-nitrostyrene (45.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.). After the Michael addition, cyanuric chloride (166 mg, 0.90 mmol, 3.00 equiv.) was added to yield a colorless solid (91 mg, 0.23 mmol, 76%); m.p. 97–101 °C; R_f = 0.45 (hexane/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9 H, 6-H), 2.20 (dd, $^3J_{7,7'}$ = 14.0, $^3J_{7,8}$ = 7.3 Hz, 1 H, 7-H), 2.77 (dd, $^3J_{7',7}$ = 14.0, $^3J_{7',8}$ = 11.1 Hz, 1 H, 7′-H), 3.94 (dd, $^3J_{9,8}$ = 13.0, $^3J_{9,9'}$ = 7.8 Hz, 1 H, 9-H), 4.49 (m, 1 H, 8-H), 4.71 (dd, $^3J_{9',8}$ = 10.1, $^3J_{9',9}$ = 7.8 Hz, 1 H, 9′-H), 5.06 (s, 1 H, 11-H), 7.35 (m, 5 H, 13-H, 14-H, 15-H), 7.92 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (q, C-6), 36.0 (t, C-7), 45.9 (d, C-11), 51.3 (d, C-8), 72.3 (s, C-3), 75.3 (t, C-9), 85.7 (s, C-5), C-1 not visible, 128.4 (d, C-13/C-14/C-15), 128.5 (d, C-13/C-14/C-15), 129.1 (d, C-13/C-14/C-15), 131.8 (s, C-12), 155.7 (s, C-1), 166.5 (s, C-10), 169.7 (s, C-4) ppm. $C_{19}H_{21}F_3N_2O_4$ (398.15): calcd. C 57.28, H 5.31, N 7.03; found C 57.22, H 5.52, N 7.05. HRMS (CI): calcd. for $C_{15}H_{13}F_3N_2O_4$ $[M - t\text{BuH}]^+$ 342.0827; found 342.0797.

***tert*-Butyl 5-[1-(Allyloxy)ethyl]-6-{[(methoxycarbonyl)oxy]imino}-2-(trifluoromethyl)-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate (5):** According to the general Michael addition procedure, Tfa-Gly-O*t*Bu (75.0 mg, 0.33 mmol, 1.10 equiv.) and nitro olefin **2** (47.0 mg, 0.30 mmol, 1.00 equiv.) were allowed to react in the presence of $ZnCl_2$ (45.0 mg, 0.33 mmol, 1.10 equiv.). After the Michael addition, methyl chloroformate (85.0 mg, 0.90 mmol, 3.00 equiv.) was added, and the mixture was allow to warm to room temperature (16 h) to yield a colorless oil (49 mg, 0.12 mmol, 40%); R_f = 0.25 (hexane/EtOAc, 8:2). Major diastereomers (89%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 and 1.30 (d, $^3J_{9,8}$ = 6.2 Hz, 3 H, 9-H), 1.45 and 1.49 (s, 9 H, 6-H), 3.03 and 3.05 (dd, $^3J_{7,8}$ = 6.7, $^3J_{7,3}$ = 1.2 Hz, 1 H, 7-H), 3.84 (m, 2 H, 8-H, 10-H), 3.93 (s, 3 H, 15-H), 4.05 (m, 1 H, 10′-H), 4.57 and 4.84 (s, 1 H, 3-H), 5.22 (m, 2 H, 11-H), 5.82 (m, 1 H, 12-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 and 17.5 (q, C-9), 27.7 (q, C-6), 40.1 and 41.4 (d, C-7), 55.6 and 55.7 (q, C-15), 56.7 and 60.2 (d, C-3), 70.3 and 70.4 (d, C-8), 73.7 and 76.2 (t, C-10), 84.0 (s, C-5), 110.3 and 114.4 (s, C-1), 117.9 and 118.0 (t, C-12), 133.7 and 133.8 (d, C-11), 143.2 and 143.5 (s, C-2), 149.4 and 151.1 (s, C-13), 153.5 and 153.6 (s, C-14), 166.4 and 166.6 (s, C-4) ppm. Minor diastereomers (11%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, $^3J_{9,8}$ = 6.2 Hz, 3 H, 9-H), 1.49 and 1.52 (s, 9 H, 6-H), 2.82 and 2.88 (dd, $^3J_{7,8}$ = 6.7, $^3J_{7,3}$ = 1.2 Hz, 1 H, 7-H), 3.95 (s, 3 H, 15-H), 4. 51 (s, 1 H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 and 28.0 (q, C-6), 43.4 (t, C-10), 52.5 (d, C-8), 54.7 (q, C-15), 56.0 (d, C-3), 69.4 and 71.5 (d, C-8), 73.3 (t, C-10), 82.2 and 83.8 (s, C-5), 108.0 (s, C-1), 117.2 (t, C-12) ppm. $C_{17}H_{23}F_3N_2O_7$ (410.34): calcd. C 48.11, H 5.46, N 6.60; found C 48.45, H 5.95, N 6.78. HRMS (CI): calcd. for $C_{17}H_{24}F_3N_2O_7$ $[M + H]^+$ 425.1536; found 425.1525.

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