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Access to α-Substituted Amino Acid Derivatives via 1,3-Dipolar Cycloaddition of α-Amino Ester Derived Nitrones

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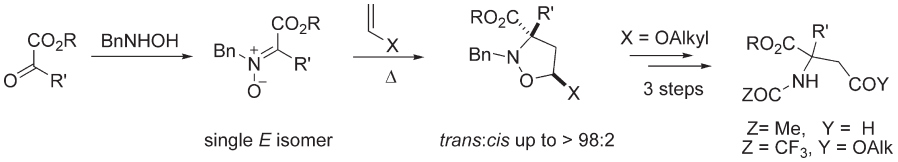
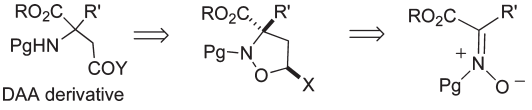


Amino acid derived nitrones were conveniently synthesized in good-to-excellent yields by condensation of α-ketoesters with *N*-benzylhydroxylamine. The cycloaddition reactions of these nitrones with different alkenes were investigated under thermal solvent-free conditions. Considering conversions, yields, and selectivities, alkyl vinyl ethers have proven to be valuable partners to achieve this transformation, which creates a tetrafunctionalized stereogenic quaternary center. From the adducts derived from vinyl ethers, a three-step access to highly functionalized α-substituted amino acid derivatives is described.

Introduction

Conformationally constrained amino acids are extremely useful building blocks in synthetic organic chemistry and the pharmaceutical industry to create novel peptides. Their incorporation into peptide chains could induce conformational restrictions and enhance properties with respect to natural active peptides and proteins. Among these conformational restrictions, the use of α,α-disubstituted amino acids (DAA) has shown to be one of the most promising strategies. For this purpose, a range of procedures that allow the synthesis of the desired DAA in enantiomerically pure form has been developed.[1] However, to our knowledge, 1,3-dipolar cycloaddition (1,3-DC) involving α-amino acid derived nitrones and alkenes has never been used to afford such molecules, although isoxazolidine adducts[2,3] could be valuable precursors for DAA derivatives (γ-amino alcohols, β-amino ketones, aldehydes, and esters) (Scheme 1).[4]

SCHEME 1. α,α-Disubstituted α-Amino Acid (DAA) Synthesis: Nitrone Route



We have recently revisited[5] the one-step preparation of *N*-benzyl aspartate nitrones **1** by Michael addition of *N*-benzylhydroxylamine to dialkylacetylenedicarboxylate **2** and extensively studied their 1,3-DC reaction with alkenes, leading to high yields under thermal conditions.[6] Interestingly, isoxazolidines **3** were obtained with excellent *trans* selectivities when vinyl ethers were used as dipolarophiles (X = OR″), especially in the case of *tert*-butyl vinyl ether (Scheme 2).

(1) For recent reviews, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (c) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (d) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (e) Park, K. H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629. (f) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron* **2000**, *11*, 645. (g) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.

(2) For reviews of cycloaddition of nitrones, see: (a) Padwa, A.; Ed. In *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vols. 1−2. (b) Deshong, P.; Lander, S. W.; Jr.; Leginus, J. M.; Dicken, C. M. In *Advances in Cycloaddition*; Curran, D. P.; Ed.; JAI press: Greenwich, CT, 1988; Vol. 1, pp 87−128. (c) Carruther, W. *Cycloaddition Reaction in Organic Synthesis*; Pergamon Press: Oxford, 1990. (d) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I.; Eds.; Pergamon Press: Oxford, 1991; Vol 5, pp 239−270. (e) Gotheft, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.

(3) (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Syntheses*; VCH: New York, 1988; Vol. 20. (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

(4) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; John Wiley and Sons: Hoboken, NJ, 2003.

(5) Winterfeld, E.; Krohn, W.; Stracke, H. U. *Chem. Ber.* **1969**, *102*, 2346.

(6) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett.* **2008**, *10*, 4493.

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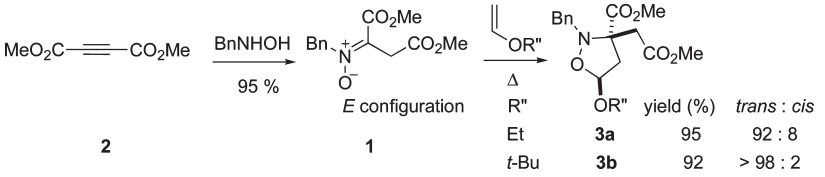
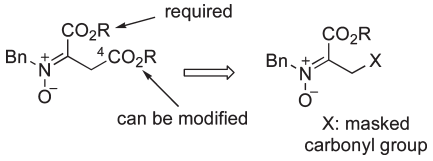
SCHEME 2. Synthesis and 1,3-DC of *N*-Benzyl Aspartate Nitrones 1[6]



SCHEME 3. Aspartate Nitrones Differentiated at C-4



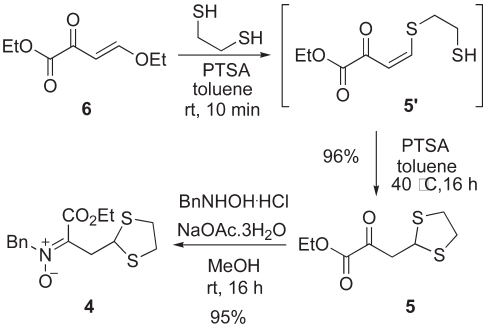
These results encouraged us (i) to define a general access to ketone-derived nitrones (Scheme 1) bearing various R′ groups and to reinvestigate the stereochemical outcome of their 1,3-DC reaction with alkenes, in respect to the nitrone geometry, and (ii) to explore the ability of isoxazolidines such as **3** to undergo a ring-opening reaction based on cleavage of the N−O bond. These two goals are the purpose of this paper.

Results and Discussion

C-4-Differentiated Aspartate Nitrone: Synthesis and 1,3-Dipolar Cycloaddition with Alkenes. As first extension, starting from the results obtained previously with aspartic nitrone **1**,[6] we studied the extension of this pathway to aspartate-like nitrones bearing two differentiated carboxy functions. We considered that the transformation of the ester function at C-4 would not deeply alter the electronic nature of the nitrone moiety (Scheme 3). We decided to replace the ester function at the C-4 position by a protected form of an aldehyde function. The dithiolane group[7] provides not only a robust aldehyde protection that could be deprotected by different methods[7,8] but also a versatile functionalizable center.[9]

Nitrone **4** was obtained in excellent yield and high purity by condensing α-ketoester **5** with *N*-benzylhydroxylamine[10] in an acetate-buffered methanol solution (Scheme 4). α-Ketoester **5** could be conveniently prepared by a one-pot reaction between alkoxymethylidenepyruvate **6** and ethane-1,2-dithiol via an addition/dehydroalkoxylation/cyclization cascade reaction.

SCHEME 4. Synthesis of Carboxy-Differentiated Nitrone 4



As expected, nitrones **4** and **1**[6] displayed similar features: first, both nitrones exist at rt in $CDCl_3$ solution as the sole *E*-isomer as shown by ^1H NMR (only one set each of ^1H and ^{13}C NMR was observed, and no NOESY correlation between CH_{2Bn} and $CH_{2\alpha}$ protons could be observed). The rationale for the stability of the *E*-isomer of nitrone **1**[6] is also valid for **4** as the *E*-isomer appears to be more stable because its structure could avoid two unfavorable interactions encountered in the *Z*-isomer (Figure 1).

Moreover, compared to nitrone **1**,[6] the nitrone **4** displayed similar reactivity under the same thermal uncatalyzed conditions in 1,3-DC with different acyclic alkenes **7a**−**i**, including simple alkenes **7a**, functional alkenes **7b**−**d**, electron-deficient alkenes **7e,f**, and electron-rich alkenes **7g**−**i** (Table 1).

As shown in Table 1, compared to the previously described isoxazolidines **3**,[6] the isoxazolidines **8a**−**i** were obtained in similar yields (88−95%) and with the same degree of regio- and stereoselectivity. Again, cycloadditions involving electron-deficient dipolarophiles **7e,f** proceeded most rapidly, leading to completion of the reaction after only 4−16 h at 80 °C (entries 5 and 6). Simple alkene **7a** and electron-rich alkenes **8g**−**i** reacted notably more slowly (entries 1 and 7−9). Compared to its acetate ester **7c** (entry 3) or to its homologue **7d** (entry 5), allyl alcohol **7b** displayed a notably high reactivity, leading to a total conversion after only 10 h at 80 °C (entry 2). As previously suggested,[6] this enhanced reactivity is probably due to the hydrogen bonding between OH group of **7b** and ester oxygens of **4** (or **1**) in the transition state that could favor their approach and lower activation barrier. When the OH group locates further from reaction site as in **7d**, this interaction would be less effective.

Extension to Other α-Substituted α-Nitrone Esters. Encouraged by the marked *trans* selectivities of the cycloaddition with vinyl ethers in both series (**1**/**4**), we extended our study to other α-ester nitrones α-substituted by various alkyl chains. Different α-substituted ester nitrones **9a**−**d** were prepared by condensation between *N*-benzylhydroxylamine and the corresponding α-keto esters.[10] Interestingly, these new nitrones, obtained in good-to-excellent yields (Table 2),

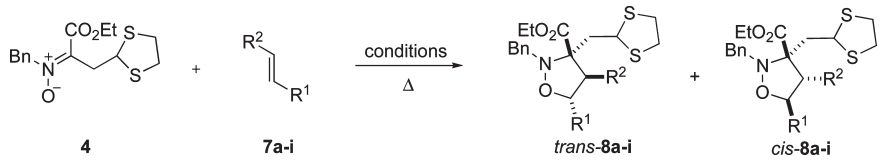
(7) (a) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New York, 2006; pp 482−500. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme, Stutgart, 2004; pp 77−93 and references therein.

(8) (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077. (b) Liu, J.; Wong, C. H. *Tetrahedron Lett.* **2002**, *43*, 4037. (c) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502.

(9) (a) Smith, A. B. III; Xiang, M. *J. Am. Chem. Soc.* **2006**, *128*, 66. (b) Chen, Y.; L.; Leguijt, R.; Redlich, H.; Fröhlich, R. *Synthesis* **2006**, 421. (c) Smith, A. B.; Kim, D. S. *Org. Lett.* **2004**, *6*, 1493. (d) Mulzer, J.; Berger, M. *J. Org. Chem.* **2004**, *69*, 891. (e) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 3635. (f) Seebach, D.; Wilka, E. M. *Synlett* **1976**, 476.

(10) (a) Hara, J.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3871. (b) Toy, A.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3533. (c) Chiacchio, U.; Piperno, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1998**, *54*, 5695. (d) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Synthesis* **2009**, 3174.

TABLE 1. 1,3-DC of Nitrone 4a with Alkenes 7a−i



entry	alkene	R^1	R^2	eq of **7**/conditions	adduct	diastereomeric ratio[a]	yield (%)[b]
1	**7a**	*n*-C_5H_{11}	H	10/toluene, 110 °C, 76 h	**8a**	75:25	95
2	**7b**	CH_2OH	H	10/80 °C, 10 h	**8b**	61:39	93
3	**7c**	CH_2OAc	H	10/80 °C, 48 h	**8c**	64:36	95
4	**7d**	$(CH_2)_2OH$	H	10/100 °C, 72 h	**8d**	63:37	93
5	**7e**	CO_2Me	H	10/80 °C, 16 h	**8e**	62:38	88
6	**7f**	CO_2Et	CO_2Et	2/80 °C, 4 h	**8f**	73:27	92
7	**7g**	OAc	H	2/80 °C, 48 h	**8g**	81[c]:19	90
8	**7h**	OEt	H	10/80 °C, 72 h	**8h**	92[c]:8	91
9	**7i**	O-*t*-Bu	H	3/80 °C, 72 h	**8i**	> 98[c]:2	89

[a]Determined by ^{1}H NMR of the crude product. [b]Isolated yield. [c]*trans* configuration assigned for the major adduct.

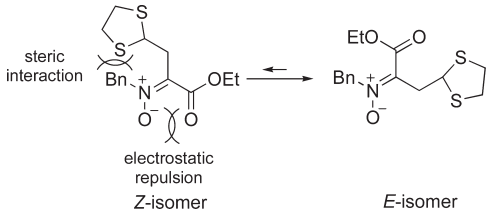
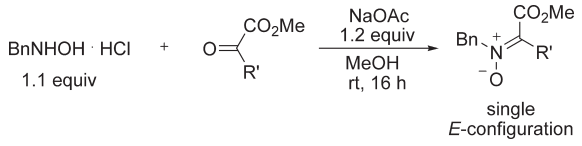


FIGURE 1. Stability comparison between *Z*-4 and *E*-4.

TABLE 2. Synthesis of α-Substituted Ester Nitrones 9a−d and 1,3-DC with Vinyl Ethers



entry	R′	nitrone	yield (%)
1	Me	**9a**	93
2	Et	**9b**	95
3	Bn	**9c**	83
4	$CH_2CH_2CO_2Me$	**9d**	94

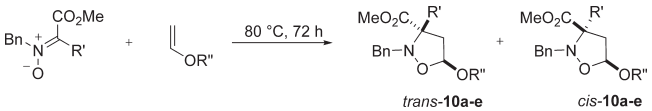
exhibited an exclusive *E* configuration as for nitrones **1** and **4** as shown by NMR.[11]

First, we tested the cycloaddition reactions of dipoles **9a−d** with ethyl vinyl ether, which led to significant *trans* selectivities in previous series (92:8 for R = CH_2CO_2Me and $CH_2CH(SCH_2)_2$).[12] In all cases, after 72 h at 80 °C in a sealed tube, the cycloaddition was found to have proceeded cleanly to give the desired adducts with total conversion and high yields (Table 3). Contrary to our expectation based on previous results observed with nitrones **1** and **4**, the reaction of these *E*-nitrones **9** exhibited varied degrees of *trans* selectivity, depending on the nature of the R′ group. When R′ is an alkyl group, the *trans*

(11) Only one set of ^{1}H NMR and ^{13}C NMR signals in $CDCl_3$ were observed for each nitrone. No NOESY correlation corresponding to the *Z*-isomer could be seen.

(12) See Scheme 1 (adduct **3**) and Table 1, entry 8 (adduct **8h**).

TABLE 3. 1,3-DC of α-Substituted Ester Nitrones 9a−d with Vinyl Ethers



entry	R′	R″[a]	adduct	*trans*:*cis* ratio	yield (%)[b]
1	Me	Et	**10a**	75:25	96
2	Et	Et	**10b**	79:21	97
3	Bn	Et	**10c**	87:13	63
4	$CH_2CH_2CO_2Me$	Et	**10d**	91:9	95
5	$CH_2CH_2CO_2Me$	*t*-Bu	**10e**	92:8	85

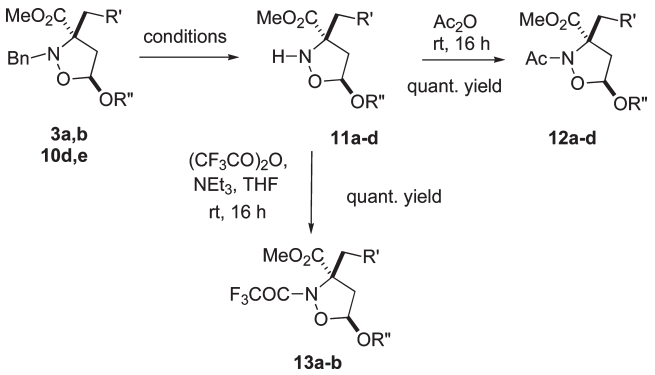
[a]10 equiv of ethyl vinyl ether or 3 equiv of *tert*-butyl vinyl ether. [b]Yields of isolated adduct.

selectivity increased with the size of the group, from 75:25 for **10a** (R = Me, entry 1) to 87:13 for **10c** (R = Bn, entry 3). In contrast, a good *trans* selectivity was obtained in the glutamic series (91:9, entry 4), comparable to previous ones. This *trans* selectivity was not significantly improved by changing the vinyl ether (92:8, entry 5).

Transformation of Isoxazolidines 3−10 into DAA Derivatives. We extensively studied the unprecedented transformation of adducts **3**,**10** into DAA derivatives via N−O bond cleavage. In the case of 5-heterosubstituted isoxazolidines, the direct reductive cleavage is commonly known as not convenient since this ring-opening process affords unstable *β*-amino aldehydes. As a valuable alternative, the *N*-quaternization-mediated ring-opening of 3-monosubstituted 5-heterosubstituted isoxazolidines (X = OR, NR_2, Scheme 1) has been described as an effective method to cleave the N−O bond *via* *β*-elimination (disproportionation pathway).[13] The thermal

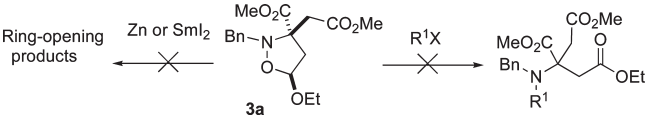
(13) (a) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, St. M. *J. Org. Chem.* **1982**, *47*, 4397. (b) Murahashi, S.-I.; Kodera, Y.; Hosomi, T. *Tetrahedron Lett.* **1988**, *29*, 5949. (c) Casuscelli, F.; Chiacchio, U.; Rescifina, A.; Romeo, G.; Romeo, R.; Tomassini, S.; Uccella, N. *Tetrahedron* **1995**, *51*, 2979. (d) Meske, M. *J. Prakt. Chem.* **1997**, *339*, 426. (e) Bayon, P.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron* **1998**, *54*, 15691. (f) Defoin, A.; Chevrier, C. *Synthesis* **2003**, *8*, 1221. (e) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *J. Org. Chem.* **2008**, *73*, 2621. (f) Nguyen, T. B.; Vuong, T. M. H.; Martel, A.; Dhal, R.; Dujardin, G. *Tetrahedron: Asymmetry* **2008**, *19*, 2084.

TABLE 4. Selective *N*-Debenzylation/Reprotection of Isoxazolidines 3a,b and 10d,e



entry	adduct	R′	R″	conditions	product	yield (%)
1	**3a**	CO_2Me	Et	H_2 (3 atm), Pd (10%)/C, EtOH, rt, 16 h	**11a**	40
2	**3a**	CO_2Me	Et	HCO_2H, Pd (10%)/C, MeOH, rt, 16 h	**11a**	91
3	**3b**	CO_2Me	*t*-Bu	HCO_2H, Pd (10%)/C, MeOH, rt, 16 h	**11b**	85
3	**10d**	CH_2CO_2Me	Et	HCO_2H, Pd (10%)/C, MeOH, rt, 16 h	**11c**	62
3	**10e**	CH_2CO_2Me	*t*-Bu	HCO_2H, Pd (10%)/C, MeOH, rt, 16 h	**11d**	76

SCHEME 5. DAA Compounds via Direct Ring-Opening of Isoxazolidine 3a



procedures using alkylating agents (BnBr, MeI, Me_2SO_4, ...) with or without external base added in the reaction medium (DABCO, Et_3N, NaH, ...) were previously applied to 5-oxa-[13a−d] and 5-aza-isoxazolidines[13e,f] to afford β-amino acid esters or β-amino imides respectively in high yields. Application of these literature procedures to the model substrate **3a** led in all cases to unsatisfactory results, even after modification. Indeed, the solvent-free conditions using BnBr in excess, with or without base, at different temperatures (up to 150 °C) resulted in the recovery of the unchanged starting adduct (Scheme 5). Using a strong alkylating agent such as BnOTf in chlorinated solvents was also unsuccessful. Only Me_2SO_4 could display some reactivity with this substrate. However, in this case, unidentified products were obtained, presumably due to the formation of quaternary amine salt and subsequent undesired reactions. The high steric hindrance on the nitrogen atom due to adjacent bulky quarternary carbon could prevent attack of the electrophile.

On the basis of these disappointing results, we decided to reinvestigate the reductive pathway. First, we wondered whether the reductive cleavage of the N−O bond could be directly applied in the particular case of the adduct **3a**, considering that bulkiness of the expected aminoaldehyde around the nitrogen site could avoid side reactions. The first trials were performed using zinc as reducing agent in different acidic media or SmI_2[14] at different temperatures between rt and 50 °C (Scheme 5). Unfortunately, all of these conditions resulted in the recovery of the starting adduct.[15]

Different palladium-catalyzed hydrogenolysis conditions were next tested. Interestingly, when the reaction was conducted under hydrogen atmosphere (3 bar), the *N*-benzyl group was selectively removed without N−O cleavage despite moderate yield (40%) (Table 4, entry 1). The yield could be greatly improved (up to 91%) by using formic acid as hydrogen source (Table 4, entry 2). Product **11a** thus obtained proved to be stable under these conditions and could be stored at 4 °C for up to 3 months without noticeable degradation. This selective *N*-deprotection was successfully extended to isoxazolidines **3b** and **10d,e** with good yields (Table 4, entries 3−5).

This result allowed a *N*-reprotection of isoxazolidines **11a−d** that could conveniently weaken the N−O bond toward reductive cleavage conditions and that could stabilize simultaneously the ring-opening product. For this purpose, an *N*-acyl protecting group seemed to be a good choice. Indeed, its electron withdrawing effect could activate it for reductive cleavage while reducing the nucleophilicity of the resulting nitrogen site and thus avoiding side reactions with the aldehyde function. Isoxazolidines **11a−d** were converted cleanly into acetamide**s 12a−d** with a quantitative yield by treatment with neat Ac_2O at rt followed by vacuum evaporation of volatile products. The corresponding trifluoroacetamide**s 13a,b** could be also obtained in quantitative yields using trifluoroacetic anhydride and NEt_3 in THF at rt.

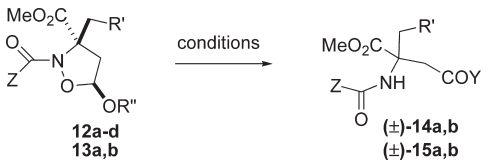
At last, we investigated the access to ring-opening products from these *N*-acyl derivatives. All our attempts to reduce the N−O bond by hydrogenolysis were unsuccessful. To our delight, when acetamide **12a** was treated with $Mo(CO)_6$[16] (2 equiv) in wet acetonitrile, the corresponding

(14) (a) Pearson, C. P.; Rinehart, K. L.; Sugano, M.; Costerison, J. R. *Org. Lett.* **2000**, *2*, 2901. (b) Westermann, B.; Walter, A.; Florke, U.; Altenbach, H. J. *Org. Lett.* **2001**, *3*, 1375. (c) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, *31*, 3351.

(15) Reaction was followed on the basis of the disappearance of the characteristic blue color of the SmI_2 in THF. No color change was observed after 24 h, and the adduct **3a** could be recovered unchanged.

(16) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

TABLE 5. DAA Compounds *via* Ring-Opening of *N*-Acyl-isoxazolidine 12a−d and 13a,b



12a-d
13a,b

(±)-14a,b
(±)-15a,b

		R′	R″	Z	conditions	product	Y	yield (%)
1	**12a**	CO_2Me	Et	Me	$Mo(CO)_6$ (1 equiv), MeCN/H_2O[a], reflux, 2 h	**14a**	H	10
2	**12a**	CO_2Me	Et	Me	$Mo(CO)_6$ (1 equiv), MeCN/H_2O, reflux, 16 h	**14a**	H	40
3	**12a**	CO_2Me	Et	Me	$Mo(CO)_6$ (2 equiv), MeCN/H_2O, reflux, 72 h	**14a**	H	91
4	**12a**	CO_2Me	Et	Me	SmI_2 (2 equiv), THF, rt, 10 min	**14a**	H	76
5	**12c**	CH_2CO_2Me	Et	Me	$Mo(CO)_6$ (2 equiv), MeCN/H_2O, reflux, 42 h[b]	**14b**	H	60
6	**12d**	CH_2CO_2Me	*t*-Bu	Me	$Mo(CO)_6$ (2 equiv), MeCN/H_2O, reflux, 96 h[c]	**14b**	H	30
7	**13a**	CO_2Me	*t*-Bu	CF_3	$Mo(CO)_6$ (2 equiv), MeCN/H_2O, reflux, 96 h[c]			-[d]
8	**13a**	CO_2Me	*t*-Bu	CF_3	SmI_2 (2.5 equiv), THF, rt, 10 min	**15a**	O*t*-Bu	75
9	**13b**	CH_2CO_2Me	*t*-Bu	CF_3	SmI_2 (2.5 equiv), THF, rt, 10 min	**15b**	O*t*-Bu	81

[a]10:3 volume ratio. [b]Complete conversion of the starting material. [c]Incomplete conversion of the starting material. [d]Recovery of starting material.

1,3-amidoaldehyde (±)-**14a** was cleanly obtained in excellent yield (91%) after extended reaction time (Table 5, entries 1−3). SmI_2 could be used instead of $Mo(CO)_6$ with shortened reaction time (10 min), but the product (±)-**14a** was found to be contaminated by a small amount of unidentified products (Table 5, entry 4). The 1,3-acetamidoaldehyde (±)-**14a** displays a fair stability under standard storing conditions. The optimal conditions used to afford (±)-**14a** from (±)-**12a** were applied successfully to the homologous diester (±)-**12c**, leading to the acetamidoaldehyde (±)-**14b** in 60% yield (Table 5, entry 5). The presence of a bulky *tert*-butoxy group at the C-5 position decreased significantly the yield of (±)-**14b** (Table 5, entry 6). SmI_2-mediated reactions failed in our hands when applied to acetamides **12c** and **12d**. In contrast to acetamides, trifluoroacetamides **13a** and **13b** were found to be unreactive in the presence of $Mo(CO)_6$ (Table 5, entry 7). Surprisingly, SmI_2 was efficient to transform these trifluoroacetamides **13a** and **13b** into the corresponding esters (±)-**15a** and (±)-**15b**. These triesters are of synthetic interest thanks to the orthogonality of the *tert*-butyl ester relative to the methyl ones. Study of the dramatic influence that the *N*-acyl substituant displays on the reactivity toward $Mo(CO)_6$ and on the outcome of the N−O reaction under SmI_2-mediated reactions is currently under investigation.

Conclusion

We have reported the high-yielding synthesis of ester nitrones substituted at the α-position by various functionalized or simple alkyl side chains (R′). This simple and efficient method allows access to an extended range of polyfunctional nitrones displaying a common pure *E*-configuration. The thermal 1,3-dipolar cycloaddition of these nitrones with different alkenes gave high yields of isoxazolidine adducts up to a multigram scale (20 g). Aspartic mono ester nitrone **4** gave the same degree of stereoselectivities as its diester analogue **1**, with high *trans* selectivities observed when alkyl vinyl ethers were used as dipolarophile (up to >98:2). For other α-substituted ester nitrones **9a−d**, variable *trans* selectivities were observed with ethyl vinyl ether, increasing with the bulkiness and functionality of the substituent R′. The *trans*-selectivities regularly obtained with glutamic nitrone **9d** (Scheme 1, R′ = -$(CH_2)_2CO_2Me$), and with modified or unmodified aspartic based nitrones **4** and **1** (R′ = -$CH(SCH_2)_2$ or CH_2CO_2Me) prompt us to currently investigate the asymmetric version of these reactions.[17] The interest in such 5-oxa-isoxazolidines was exemplified by the first examples of their transformation into densely functionalized α-substituted α-amino acid derivatives by a three-step sequence *N*-debenzylation/*N*-acylation/N−O bond cleavage. We believe that this pathway *via* nitrone cycloaddition could open a new interesting route to new biologically active molecules containing a polyfunctionalized quaternary center.

Experimental Section

Ethyl 3-(1,3-Dithiolan-2-yl)-2-oxopropanoate (5). To a stirred solution of ketoester **6**[18] (3.44 g, 20 mmol) and ethane-1,2-dithiol (1.88 g, 20 mmol) in toluene (20 mL) was added *p*-toluenesulfonic acid (190 mg, 1 mmol) at room temperature. After 5 min, a white precipitate was formed (this precipitate could be isolated via filtration and analyzed by ^1H and ^{13}C NMR as **5′**). The solution was stirred at 40 °C for 16 h, then cooled to rt, diluted with toluene (80 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), and dried over $MgSO_4$. The solvent was removed under vacuum to give the product **5** (4.22 g, 96%), suitable for further nitrone formation. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.86 (t, J = 7.1 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.43 (d, J = 7.1 Hz, 1H), 3.28−3.22 (m, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR 100 MHz ($CDCl_3$) δ 191.2, 159.9, 62.4, 49.6, 45.9, 38.3, 13.7. HRMS (CI+NH_3) calcd for $C_8H_{13}O_3S_2$ [M + H^+]: 221.0306, found 221.0309.

(*Z*)-Ethyl 4-(2-Mercaptoethylthio)-2-oxobut-3-enoate (5′). Colorless needles from toluene; mp 96 °C (dec). ^1H NMR (200 MHz, $CDCl_3$) δ 5.78 (d, J = 10.4 Hz, 1H), 5.58 (d, J = 10.4 Hz, 1H), 3.44−3.23 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR 100 MHz ($CDCl_3$) δ 191.4, 164.9, 139.0, 113.3, 62.4, 49.6, 45.6, 39.4, 14.0. HRMS (CI+NH_3) calcd for $C_8H_{13}O_3S_2$ [M + H^+]: 221.0306, found 221.0314.

(17) Preliminary results in this field involving 1,3-DC of chiral enol ethers or alternatively 1,3-DC of chiral aspartic nitrones has been already reported in this series (see ref 6).

(18) (a) Tietze, L. F.; Meier, H.; Voss, E. *Synthesis* **1988**, 274. (b) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763.

(*E*)-*N*-(3-(1,3-Dithiolan-2-yl)-1-ethoxy-1-oxopropan-2-ylidene)-(phenyl)methanamine Oxide (4). A mixture of **5** (11.0 g, 50 mmol), BnNHOH·HCl (8.77 g, 55 mmol), $NaOAc·3H_2O$ (8.16 g, 60 mmol), and MeOH (100 mL) was stirred at rt for 16 h and then concentrated under vacuum. The white semisolid residue was dissolved in a mixture of CH_2Cl_2 (100 mL) and H_2O (20 mL). The organic phase was separated, washed with H_2O (20 mL × 3), dried ($MgSO_4$), and concentrated under vacuum to afford a viscous residue. Purification of this material by column chromatography on silica gel (300 g) with dichloromethane (R_f = 0.52, CH_2Cl_2) yielded 15.4 g (95%) of nitrone **4** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.37 −7.30 (m, 3H), 5.70 (s, 2H), 5.06 (t, J = 7.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.29−3.18 (m, 6H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR 100 MHz ($CDCl_3$) δ 162.0, 138.8, 133.8, 128.6, 128.4, 128.3, 67.6, 61.8, 48.0, 38.2, 38.0, 14.0. HRMS (CI+NH_3) calcd for $C_{15}H_{20}NO_3S_2$ [M + H$^+$]: 326.0885, found 326.0882.

General Procedure for the Cycloaddition between Nitrone 4 and Alkenes 7a−i. A solution of nitrone **4** (325 mg, 1 mmol) in alkene (2−10 equiv; see Table 1) under argon in a sealed tube was stirred at indicated temperature until completion (TLC; for experimental conditions, see Table 1). The reaction mixture was then concentrated under vacuum to remove excess alkene. The crude adducts **8** were purified by column chromatography on silica gel (Et_2O in cyclohexane).

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzyl-5-hexylisoxazolidine-3-carboxylate (8a). From **4** and **7a**. Purification by flash chromatography (Et_2O/cyclohexane 1:6) afforded the title compound as a colorless oil (415 mg, 95%). R_f = 0.8 (Et_2O). Diastereomeric ratio: 75:25. Major adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.16 (m, 5H), 4.57 (t, J = 6.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.15−4.08 (m, 1H), 4.05 (d, J = 14.7 Hz, 1H), 3.74 (d, J = 14.7 Hz, 1H), 3.32−3.15 (m, 4H), 3.29 (dd, J = 12.1, 8.3 Hz, 1H), 2.62 (dd, J = 14.1, 7.1 Hz, 1H), 2.26 (dd, J = 14.4, 6.6 Hz, 1H), 1.98 (dd, J = 12.1, 5.8 Hz, 1H), 1.72−1.63 (m, 1H), 1.49−1.39 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.31−1.20 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.9, 138.4, 128.1, 128.0, 126.7, 76.7, 72.9, 61.2, 55.3, 49.4, 43.1, 42.6, 38.8, 38.4, 36.0, 31.7, 29.1, 26.0, 22.5, 14.3, 14.0. Some characteristic NMR signal of the minor adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (t, J = 6.3 Hz, 1H), 4.00 (d, J = 14.4 Hz, 1H), 3.72 (d, J = 14.4 Hz, 1H), 3.32−3.15 (m, 4H), 2.57 (dd, J = 14.4, 6.3 Hz, 1H), 2.51 (dd, J = 12.4, 8.1 Hz, 1H), 1.72−1.63 (m, 1H), 1.49−1.39 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.31−1.20 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR 100 MHz ($CDCl_3$) δ 171.5, 138.1, 129.0, 128.1, 126.7, 72.6, 61.2, 55.4, 49.2, 42.9, 42.6, 38.8, 38.5, 29.1, 26.2, 22.5, 14.3, 14.0. HRMS (CI+NH_3) calcd for $C_{18}H_{26}NO_4S_2$ [M + H$^+$]: 438.2137, found 438.2129.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzyl-5-(hydroxymethyl)-isoxazolidine-3-carboxylate (8b). From **4** and **7b**. Purification by flash chromatography (Et_2O/cyclohexane 1:2) afforded the title compound as a colorless oil (356 mg, 93%). R_f = 0.5 (Et_2O). Diastereomeric ratio: 61:39. Major adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 5H), 4.59 (t, J = 6.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.29−4.23 (m, 1H), 4.00 (d, J = 14.4 Hz, 1H), 3.60 (d, J = 14.4 Hz, 1H), 3.62−3.52 (m, 2H), 3.35−3.15 (m, 4H), 2.96 (dd, J = 12.4, 8.3 Hz, 1H), 2.63 (dd, J = 14.1, 7.0 Hz, 1H), 2.25 (dd, J = 14.1, 7.0 Hz, 1H), 2.19 (dd, J = 12.4, 5.8 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H,); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.3, 138.0, 128.2, 128.0, 127.1, 76.3, 72.7, 65.3, 61.4, 55.6, 49.4, 42.6, 38.9, 38.3, 37.9, 14.3. Minor adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 5H), 4.63 (t, J = 6.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.23−4.17 (m, 1H), 4.11 (d, J = 14.7 Hz, 1H), 3.78 (d, J = 14.7 Hz, 1H), 3.80−3.78 (m, 1H), 3.70−3.64 (m, 1H), 3.35−3.05 (m, 4H), 2.78 (dd, J = 12.9, 6.6 Hz, 1H), 2.62 (dd, J = 14.4, 6.8 Hz, 1H), 2.53 (dd, J = 12.9, 6.8 Hz, 1H), 2.38 (dd, J = 14.4, 6.8 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.3, 138.0, 128.2, 128.0, 127.1, 76.3, 72.7, 65.3, 61.4, 55.6, 49.4, 42.6, 38.9, 38.3, 37.9, 14.3; ^{13}C NMR 100 MHz ($CDCl_3$) δ 171.5, 137.7, 128.3, 128.2, 127.1, 77.2, 72.4, 62.6, 61.6, 55.3, 49.0, 42.4, 38.5, 38.3, 37.7, 14.2. HRMS (CI+NH_3) calcd for $C_{18}H_{26}NO_4S_2$ [M + H$^+$]: 266.1028, found 266.1034.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-5-(acetoxymethyl)-2-benzylisoxazolidine-3-carboxylate (8c). From **4** and **7c**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (404 mg, 95%). R_f = 0.6 (Et_2O). Diastereomeric ratio: 64:36. Major adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 4.55 (t, J = 6.8 Hz, 1H), 4.41−4.35 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.15 (dd, J = 11.6, 7.6 Hz, 1H), 4.11 (d, J = 14.9 Hz, 1H), 4.04 (dd, J = 11.4, 4.0 Hz, 1H), 3.70 (d, J = 14.9 Hz, 1H), 3.32−3.15 (m, 4H), 3.01 (dd, J = 12.4, 8.3 Hz, 1H), 2.61 (dd, J = 14.4, 6.8 Hz, 1H), 2.22 (dd, J = 14.4, 6.8 Hz, 1H), 2.06 (dd, J = 12.4, 6.1 Hz, 1H), 2.01 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.9, 170.7, 137.8, 128.1, 127.8, 126.9, 73.6, 72.3, 65.9, 61.4, 55.1, 49.2, 42.6, 39.3, 38.8, 38.4, 20.8, 14.3. Minor adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 4.58 (t, J = 6.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.30−4.25 (m, 2H), 4.20 (dd, J = 11.1, 7.3 Hz, 1H), 4.02 (d, J = 14.7 Hz, 1H), 3.80 (d, J = 14.7 Hz, 1H), 3.32−3.15 (m, 4H), 2.68−2.53 (m, 3H), 2.31 (dd, J = 14.4, 6.8 Hz, 1H), 2.04 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.7, 170.3, 137.8, 128.3, 128.1, 127.0, 73.9, 72.3, 64.9, 61.5, 55.4, 49.1, 38.9, 38.8, 38.5, 20.8, 14.2. HRMS (CI+NH_3) calcd for $C_{20}H_{28}NO_5S_2$ [M + H$^+$]: 426.1409, found 426.1309.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzyl-5-(2-hydroxyethyl)isoxazolidine-3-carboxylate (8d). From **4** and **7d**. Purification by flash chromatography (Et_2O/cyclohexane 1:1) afforded the title compound as a colorless oil (368 mg, 93%). R_f = 0.5 (Et_2O). Diastereomeric ratio: 63:37. Major adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.16 (m, 5H), 4.58 (t, J = 6.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.39−4.31 (m, 1H), 4.08 (d, J = 14.1 Hz, 1H), 3.62 (d, J = 14.1 Hz, 1H), 3.63−3.57 (m, 2H), 3.34−3.15 (m, 4H), 3.05 (dd, J = 12.4, 8.1 Hz, 1H), 2.66 (dd, J = 14.1, 6.8 Hz, 1H), 2.27 (dd, J = 14.1, 6.8 Hz, 1H), 2.10 (dd, J = 12.4, 6.3 Hz, 1H), 1.86 (broadband, 1H), 1.88−1.80 (m, 1H), 1.74−1.67 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.4, 137.6, 128.5, 127.3, 75.7, 72.6, 61.3, 60.8, 55.8, 49.3, 42.8, 42.6, 38.8, 38.4, 37.9, 14.3.

Minor adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.16 (m, 5H), 4.62 (dd, J = 7.1, 6.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.25−4.18 (m, 1H), 4.00 (d, J = 14.4 Hz, 1H), 3.73 (d, J = 14.4 Hz, 1H), 3.73−3.65 (m, 2H), 3.34−3.15 (m, 4H), 2.65 (dd, J = 12.6, 7.1 Hz, 1H), 2.59 (dd, J = 14.7, 6.3 Hz, 1H), 2.57 (dd, J = 12.6, 8.3 Hz, 1H), 2.36 (dd, J = 14.7, 7.1 Hz, 1H), 1.98−1.88 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.61 (broadband, 1H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.4, 137.6, 128.5, 128.3, 127.3, 75.3, 72.5, 61.4, 60.4, 55.6, 49.1, 42.6, 41.7, 38.8, 38.5, 35.7, 14.3. HRMS (CI+NH_3) calcd for $C_{21}H_{32}NO_5$ [M + H$^+$]: 398.1460, found 398.1461.

3-Ethyl 5-Methyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzylisoxazolidine-3,5-dicarboxylate (8e). From **4** and **7e**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (362 mg, 88%). R_f = 0.6 (Et_2O). Diastereomeric ratio: 62:38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.21 (m, 5H, Ph, both isomers), 4.57−4.53 (m, 2H, both isomers), 4.35−4.20 (m, 2H, both isomers), 4.15 (d, J = 15.2 Hz, 1H) and 3.73 (d, J = 15.2 Hz, 1H) of the same isomer, 4.06 (d, J = 14.7 Hz, 1H) and 3.90 (d, J = 14.7 Hz, 1H) of the same isomer, 3.72 (s, 3H, CO_2Me) and 3.74 (s, 3H, CO_2Me), 3,32−3.16 (m, 4H, CH_2S), 3.28 (dd, J = 12,6, 3.8 Hz, 1H) and 3.15 (dd, J = 12,9, 5.3 Hz, 1H), 2.78 (dd, J = 12,9, 10.1 Hz, 1H) and 2.63 (dd, J = 12.6, 6.1 Hz, 1H, H^{3b}), 2.62 (dd, J = 14.4, 7.1 Hz, 1H) and 2.60 (dd, J = 14.1, 7.1 Hz, 1H), 2.26 (dd, J = 6.8, 5.1 Hz, 1H) and 2.23 (dd, J = 6.6, 4.8 Hz, 1H), 1.35

and 1.30 (t, J = 7.1 Hz, 3H, $CH_{3\ Et}$); ^{13}C NMR 100 MHz ($CDCl_3$) δ 172.7 (C=O), 170.9 (C=O), 170.0 (C=O), 169.9 (C=O), 137.5 ($2C_{q.\ Ar}$), 128.3, 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.7 (CH_{Ar}), 127.1 (CH_{Ar}), 126.9 (CH_{Ar}), 74.0 and 73.9 (C^5), 72.4 and 71.9 (C_q-N), 61.6 and 61.5 ($CH_{2\ Et}$), 55.6 and 55.2 ($CH_{2\ Bn}$), 52.1 ($CH_{3\ ester}$), 49.0 and 49.1 (S-CH-S), 42.6 and 42.5 (CH_2), 40.1 and 39.8 (CH_2), 38.7 (CH_2S), 38.5 (CH_2S), 38.4 (CH_2S), 38.3 (CH_2S), 14.2 and 14.0 (CH_3). HRMS (CI+NH_3) calcd for $C_{21}H_{32}NO_5$ [M + H^+]: 412.1252, found 412.1238.

Triethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzylisoxazolidine-3,4,5-tricarboxylate (8f). From **4** and **7f**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (457 mg, 92%). R_f = 0.6 (Et_2O). Diastereomeric ratio: 73:27. Major adduct: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.33−7.29 (m, 2H), 7.25−7.22 (m, 1H), 4.98 (d, J = 5.1 Hz, 1H), 4.77 (dd, J = 6.7, 5.7 Hz, 1H), 4.50 (d, J = 5.1 Hz, 1H), 4.31−4.15 (m, 6H), 4.15 (d, J = 15.4 Hz, 1H), 3.59 (d, J = 15.4 Hz, 1H), 3.30−3.12 (m, 4H), 2.80 (dd, J = 15.7, 5.7 Hz, 1H), 2.64 (dd, J = 15.7, 6.7 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 171.4, 169.2, 168.4, 136.6, 128.1, 127.7, 127.0, 75.6, 74.2, 62.4, 61.5, 61.4, 56.6, 55.6, 48.6, 40.7, 38.7, 38.6, 14.0, 14.1, 14.2. Minor adduct: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.33−7.29 (m, 2H), 7.25−7.22 (m, 1H), 4.92 (d, J = 7.2 Hz, 1H), 4.84 (dd, J = 7.3, 4.5 Hz, 1H), 4.53 (d, J = 7.1 Hz, 1H), 4.31−4.15 (m, 8H), 3.30−3.12 (m, 4H), 2.54 (dd, J = 15.2, 4.5 Hz, 1H), 2.45 (dd, J = 15.2, 7.3 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 169.8, 169.5, 168.7, 137.1, 128.4, 128.1, 127.1, 78.2, 75.7, 62.3, 61.9, 61.7, 56.6, 56.5, 48.6, 42.0, 38.9, 38.3, 14.1, 14.0, 13.8. HRMS (CI+NH_3) calcd for $C_{23}H_{32}NO_7S_2$ [M + H^+]: 498.1620, found 498.1608.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-5-acetoxy-2-benzylisoxazolidine-3-carboxylate (8g). From **4** and **7g**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (370 mg, 90%). R_f = 0.6 (Et_2O). Diastereomeric ratio: 81:19. Major adduct (*trans*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 6.32 (dd, J = 6.3, 3.3 Hz, 1H), 4.56 (t, J = 7.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 15.2 Hz, 1H), 3.71 (d, J = 15.2 Hz, 1H), 3.30 (dd, J = 13.4, 6.6 Hz, 1H), 3.34−3.16 (m, 4H), 2.61 (dd, J = 14.1, 7.1 Hz, 1H), 2.50 (dd, J = 13.4, 3.3 Hz, 1H), 2.29 (dd, J = 14.1, 7.1 Hz, 1H), 2.05 (s, 3H), 1.36 (*t*, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.5, 169.8, 137.3, 128.1, 128.0, 127.0, 95.0, 73.9, 61.6, 55.5, 49.0, 43.7, 42.5, 38.5, 38.4, 21.2, 14.2. Minor adduct (*cis*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 6.30 (dd, J = 6.6, 3.3 Hz, 1H), 4.57 (t, J = 7.1 Hz, 1H), 4.13−4.29 (m, 2H), 4.30 (d, J = 14.4 Hz, 1H), 4.04 (d, J = 14.4 Hz, 1H), 3.34−3.16 (m, 4H), 3.06 (dd, J = 14.4, 3.3 Hz, 1H), 2.95 (dd, J = 14.4, 6.6 Hz, 1H), 2.62 (dd, J = 14.1, 7.1 Hz, 1H), 2.41 (dd, J = 14.1, 6.1 Hz, 1H), 2.05 (s, 3H), 1.31 (*t*, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.2, 169.6, 137.5, 128.7, 128.3, 126.9, 95.6, 72.8, 62.0, 56.0, 48.7, 46.1, 42.3, 38.7, 38.5, 21.2, 13.9. HRMS (CI+NH_3) calcd for $C_{21}H_{32}NO_5$ [M + H^+]: 412.1252, found 412.1242.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzyl-5-ethoxyisoxazolidine-3-carboxylate (8h). From **4** and **7h**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (361 mg, 91%). R_f = 0.6 (Et_2O). Diastereomeric ratio: 92:8. Major adduct (*trans*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.39 (m, 2H), 7.31−7.26 (m, 2H), 7.24−7.20 (m, 1H), 5.15 (dd, J = 6.3, 3.5 Hz, 1H), 4.56 (t, J = 6.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.15 (d, J = 14.9 Hz, 1H), 3.68 (d, J = 14.9 Hz, 1H), 3.58 (dq, J = 9.9, 7.1 Hz, 1H), 3.39 (dq, J = 9.9, 7.1 Hz, 1H), 3.29−3.14 (m, 4H), 3.18 (dd, J = 13.1, 6.3 Hz, 1H), 2.60 (dd, J = 14.1, 6.8 Hz, 1H), 2.32 (dd, J = 14.1, 6.8 Hz, 1H), 2.32 (dd, J = 13.1, 3.5 Hz, 1H), 1.35 (*t*, J = 7.1 Hz, 3H), 1.12 (*t*, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.6, 137.9, 128.0, 127.9, 126.7, 100.1, 72.9, 63.7, 61.3, 55.4, 49.2, 44.0, 42.3, 38.7, 38.3, 15.0, 14.3. Some characteristic ^1H and ^{13}C NMR signals of the minor adduct (*cis*): ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (dd, J = 7.1, 5.8 Hz, 1H), 4.06 (d, J = 13.6 Hz, 1H), 2.98 (dd, J = 14.0, 3.5 Hz, 1H), 2.75 (dd, J = 14.0, 6.6 Hz, 1H), 2.58 (dd, J = 14.4, 7.1 Hz, 1H), 2.38 (dd, J = 14.4, 5.8 Hz, 1H), 1.29 (*t*, J = 7.1 Hz, 3H), 1.13 (*t*, J = 7.1 Hz, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 169.9, 138.2, 64.0, 56.6, 48.8, 42.5, 38.6, 38.5, 14.9, 13.9. HRMS (CI+NH_3) calcd for $C_{19}H_{28}NO_4S_2$ [M + H^+]: 398.1460, found 398.1462.

Ethyl 3-((1,3-Dithiolan-2-yl)methyl)-2-benzyl-5-*tert*-butoxyisoxazolidine-3-carboxylate (8i). From **4** and **7i**. Purification by flash chromatography (30−50% Et_2O in cyclohexane) afforded the title compound as a colorless oil (378 mg, 89%). R_f = 0.6 (Et_2O). Diastereomeric ratio >98:2. Sole detected adduct (*trans*): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.39 (m, 2H), 7.30−7.26 (m, 2H), 7.23−7.19 (m, 1H), 5.43 (dd, J = 5.6, 4.0 Hz, 1H), 4.55 (dd, J = 7.1, 6.8 Hz, 1H), 4.35−4.18 (m, 2H), 4.11 (d, J = 14.4 Hz, 1H), 3.65 (d, J = 14.4 Hz, 1H), 3.33−3.12 (m, 5H), 2.62 (dd, J = 14.1, 7.1 Hz, 1H), 2.33 (dd, J = 14.1, 6.8 Hz, 1H), 2.25 (dd, J = 13.1, 4.0 Hz, 1H), 1.35 (*t*, J = 7.1 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.9, 138.0, 128.5, 127.8, 126.7, 96.1, 74.5, 73.0, 61.2, 55.7, 49.4, 44.9, 42.7, 38.7, 38.3, 28.7, 14.3. HRMS (CI+NH_3) calcd for $C_{21}H_{32}NO_4S_2$ [M + H^+]: 426.1773, found 426.1739.

Nitrone 9a−d. These products were prepared after the procedure for **4**.

(*E*)-*N*-(1-Methoxy-1-oxopropan-2-ylidene)(phenyl)methanamine Oxide (9a). On 10 mmol scale. Purification by flash chromatography afforded the title compound as a colorless oil (1.93 g, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.37−7.20 (m, 3H), 5.70 (s, 2H), 3.83 (s, 3H), 3.61 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 137.5, 133.9, 128.6, 128.4, 128.3, 67.0, 52.5, 15.1. HRMS (CI+NH_3) calcd for $C_{11}H_{14}NO_3$ [M + H^+]: 208.0974, found 208.0977.

(*E*)-*N*-(1-Methoxy-1-oxobutan-2-ylidene)(phenyl)methanamine Oxide (9b). On 10 mmol scale. Purification by flash chromatography afforded the title compound as a colorless oil (2.10 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.37−7.31 (m, 3H), 5.64 (s, 2H), 3.83 (s, 3H), 2.74 (q, J = 7.3 Hz, 2H), 1.08 (t, J = 7,3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 142.3, 134.0, 128.6, 128.5, 128.3, 67.4, 52.5, 21.9, 8.9. HRMS (CI+NH_3) calcd for $C_{12}H_{16}NO_3$ [M + H^+]: 222.1130, found 222.1134.

(*E*)-*N*-(1-Methoxy-1-oxo-3-phenylpropan-2-ylidene)(phenyl)-methanamine Oxide (9c). On 5 mmol scale. Purification by flash chromatography afforded the title compound as a colorless oil (1.17 g, 83%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.24 (m, 10H), 5.71 (s, 2H), 4.07 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 139.7, 136.2, 133.9, 128.82, 128.75, 128.5, 128.4, 128.3, 126.6, 67.8, 52.7, 33.7. HRMS (CI+NH_3) calcd for $C_{17}H_{18}NO_3$ [M + H^+]: 284.1287, found 284.1284.

(*E*)-*N*-(1,5-Dimethoxy-1,5-dioxopentan-2-ylidene)(phenyl)-methanamine Oxide (9d). On 10 mmol scale. Purification by flash chromatography (Et_2O/cyclohexane, 1:1) afforded the title compound as a colorless oil (2.63 g, 94%). ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.37−7.30 (m, 3H), 5.67 (s, 2H), 3.84 (s, 3H), 3.63 (s, 3H), 3.00 (t, J = 7.3 Hz, 2H), 2.60 (t, J = 7.3 Hz, 2H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 172.9, 162.6, 139.4, 133.9, 128.7, 128.5, 128.4, 67.5, 52.6, 51.6, 28.4, 24.3. HRMS (CI+NH_3) calcd for $C_{14}H_{18}NO_5$ [M + H^+]: 280.1185, found 280.1185.

Adducts 10a−e. These products were prepared after the procedure for **8h**.

Methyl 2-Benzyl-5-ethoxy-3-methylisoxazolidine-3-carboxylate (10a). From **9a** (1 mmol) and ethyl vinyl ether. Purification by flash chromatography (Et_2O/cyclohexane, 1:3) afforded the title compound **10a** as a colorless oil (268 mg, 96%). Diastereomeric

ratio: 75:25. Major adduct (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.41 (m, 2H), 7.32−7.29 (m, 2H), 7.25−7.21 (m, 1H), 5.16 (dd, J = 6.3, 3.5 Hz, 1H), 4.12 (d, J = 14.7 Hz, 1H), 3.79 (d, J = 14.7 Hz, 1H), 3.78 (s, 3H), 3.65−3.57 (m, 1H), 3.44−3.34 (m, 1H), 3.16 (dd, J = 13.4, 6.3 Hz, 1H), 2.16 (dd, J = 13.1, 3.5 Hz, 1H), 1.50 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.0, 128.1, 128.0, 126.8, 101.6, 70.1, 63.9, 55.8, 52.0, 46.6, 19.6, 15.0. Minor adduct (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.44 (m, 2H), 7.32−7.29 (m, 2H), 7.25−7.21 (m, 1H), 5.10 (dd, J = 6.3, 3.0 Hz, 1H), 4.19 (d, J = 14.4 Hz, 1H), 3.88 (d, J = 14.4 Hz, 1H), 3.70 (s, 3H), 3.65−3.57 (m, 1H), 3.44−3.34 (m, 1H), 2.86 (dd, J = 13.6, 3.3 Hz, 1H), 2.45 (dd, J = 13.6, 6.3 Hz, 1H), 1.45 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 138.0, 128.3, 128.1, 126.8, 100.6, 69.3, 63.6, 55.8, 52.3, 47.3, 19.6, 14.9. HRMS (CI+NH_3) calcd for $C_{15}H_{22}NO_4$ [M + H$^+$]: 280.1549, found 280.1541.

Methyl 2-Benzyl-5-ethoxy-3-ethylisoxazolidine-3-carboxylate (10b). From **9b** (5 mmol) and ethyl vinyl ether. Purification by flash chromatography (Et_2O/cyclohexane, 1:3) afforded the title compound **10b** as a colorless oil (1.42 g, 97%). Diastereomeric ratio: 79:21. Major adduct (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.32−7.28 (m, 2H), 7.24−7.21 (m, 1H), 5.16 (dd, J = 6.3, 3.5 Hz, 1H), 4.15 (d, J = 14.2 Hz, 1H), 3.79 (s, 3H), 3.73 (d, J = 14.2 Hz, 1H), 3.63−3.55 (m, 1H), 3.43−3.35 (m, 1H), 3.14 (dd, J = 13.4, 6.3 Hz, 1H), 2.12 (dd, J = 13.4, 3.5 Hz, 1H), 2.05−1.96 (m, 1H), 1.76−1.68 (m, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.1, 128.0, 127.9, 126.7, 101.4, 74.9, 63.7, 55.6, 51.8, 44.1, 26.6, 14.9, 9.6. Minor adduct (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.32−7.28 (m, 2H), 7.24−7.21 (m, 1H), 5.11 (dd, J = 6.3, 3.5 Hz, 1H), 4.31 (d, J = 14.2 Hz, 1H), 3.97 (s, 3H), 3.71 (d, J = 14.2 Hz, 1H), 3.63−3.55 (m, 1H), 3.43−3.35 (m, 1H), 2.89 (dd, J = 13.9, 3.5 Hz, 1H), 2.55 (dd, J = 13.9, 6.3 Hz, 1H), 2.07−2.00 (m, 1H), 1.83−1.74 (m, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 138.1, 128.3, 127.9, 126.7, 102.3, 74.4, 63.8, 56.5, 52.1, 42.0, 26.7, 14.9, 9.6. HRMS (CI+NH_3) calcd for $C_{16}H_{24}NO_4$ [M + H$^+$]: 294.1705, found 294.1696.

Methyl 2,3-Dibenzyl-5-ethoxyisoxazolidine-3-carboxylate (10c). From **9c** (1 mmol) and ethyl vinyl ether. Purification by flash chromatography (Et_2O/cyclohexane, 1:3) afforded the title compound **10c** as a colorless oil (222 mg, 63%). Diastereomeric ratio: 87:13. Major adduct (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.35−7.31 (m, 2H), 7.29−7.22 (m, 4H), 7.20−7.18 (m, 4H), 5.11 (dd, J = 6.3, 3.8 Hz, 1H), 4.30 (d, J = 14.9 Hz, 1H), 3.82 (d, J = 14.9 Hz, 1H), 3.75 (s, 3H), 3.65−3.56 (m, 1H), 3.43−3.36 (m, 1H), 3.37 (d, J = 12.9 Hz, 1H), 2.96 (d, J = 12.9 Hz, 1H), 2.87 (dd, J = 13.4, 6.3 Hz, 1H), 2.32 (dd, J = 13.4, 3.8 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.0, 136.0, 129.7, 128.4, 128.1, 128.0, 126.9, 126.8, 101.3, 74.9, 63.9, 55.9, 51.9, 44.4, 39.5, 15.0. Minor adduct (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 2H), 7.35−7.18 (m, 6H), 7.29−7.22 (m, 4H), 7.13−7.10 (m, 2H), 5.18 (dd, J = 6.3, 3.8 Hz, 1H), 4.42 (d, J = 13.9 Hz, 1H), 4.05 (d, J = 13.9 Hz, 1H), 3.68 (s, 3H), 3.65−3.57 (m, 1H), 3.47 (d, J = 13.6 Hz, 1H), 3.43−3.34 (m, 1H), 3.00 (d, J = 13.6 Hz, 1H), 2.77 (dd, J = 14.1, 3.8 Hz, 1H), 2.63 (dd, J = 14.1, 6.3 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.2, 136.2, 130.0, 128.4, 128.1, 128.0, 126.91, 126.85, 102.7, 75.0, 64.1, 56.5, 52.2, 41.1, 39.3, 15.0. HRMS (CI+NH_3) calcd for $C_{21}H_{26}NO_4$ [M + H$^+$]: 356.1862, found 356.1848.

Methyl 2-Benzyl-5-ethoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (10d). From **9d** (5 mmol) and ethyl vinyl ether. Purification by flash chromatography (Et_2O/cyclohexane, 1:1) afforded the title compound **10d** as a colorless oil (1.67 g, 95%). Diastereomeric ratio: 91:9. Major adduct (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.38 (m, 2H), 7.32−7.28 (m, 2H), 7.24−7.20 (m, 1H), 5.14 (dd, J = 6.3, 3.3 Hz, 1H), 4.14 (d, J = 14.7 Hz, 1H), 3.85 (s, 3H), 3.70 (d, J = 14.7 Hz, 1H), 3.61−3.53 (m, 2H), 3.41−3.34 (m, 1H), 3.07 (dd, J = 13.4, 6.3 Hz, 1H), 2.45−2.38 (m, 2H), 2.30−2.22 (m, 1H), 2.19−2.12 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.6, 137.8, 127.94, 127.89, 126.8, 100.8, 72.6, 63.6, 55.3, 52.0, 51.6, 44.1, 29.6, 28.1, 14.9. Minor adduct (*cis*): ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 170.6, 138.1, 128.3, 127.9, 126.8, 102.8, 72.9, 64.0, 56.7, 52.3, 51.9, 43.1, 29.4, 27.3, 14.8. HRMS (CI+NH_3) calcd for $C_{18}H_{26}NO_6$ [M + H$^+$]: 352.1760, found 352.1769.

Methyl 2-Benzyl-5-*tert*-butoxy-3-(3-methoxy-3-oxopropyl)-isoxazolidine-3-carboxylate (10e). From **9d** (10 mmol) and *tert*-butyl vinyl ether. Purification by flash chromatography (Et_2O/cyclohexane, 1:1) afforded the title compound **10e** as an oil (3.22 g, 85%). Diastereomeric ratio: 92:8. Major adduct (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 2H), 7.30−7.25 (m, 2H), 7.22−7.17 (m, 1H), 5.42 (dd, J = 6.4, 3.7 Hz, 1H), 4.11 (d, J = 14.4 Hz, 1H), 3.78 (s, 3H), 3,66 (d, J = 14.1 Hz, 1H), 3.65 (s, 3H), 3.01 (dd, J = 13.1, 6.6 Hz, 1H), 2.43−2,12 (m, 4H), 2.09 (dd, J = 13.1, 3.7 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.9, 137.9, 128.4, 127.8, 126.7, 93.0, 74.4, 72.8, 55.6, 51.9, 51.6, 44.9, 29.7, 28.6, 26.8. Minor adduct (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 2H), 7.30−7.25 (m, 2H), 7.22−7.17 (m, 1H), 5.42 (m, 1H), 4.24 (d, J = 13.6 Hz, 1H), 3,99 (d, J = 13.6 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 2.83 (dd, J = 13.8, 4.3 Hz, 1H), 2.49−2,12 (m, 5H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 170.8, 138.2, 128.6, 127.8, 126.7, 97.9, 74.7, 73.0, 57.0, 52.1, 51.5, 43.4, 29.4, 28.6, 26.8. HRMS calcd for $C_{20}H_{29}NO_6$ [M$^+$]: 379.1995, found 379.2000.

***trans*-Methyl 5-Ethoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (11a).** Under argon, to a stirred solution of adduct **3a**[6] (5,00 g, 14.8 mmol) in methanol (10 mL) and Pd/C (10%, 1 g) was added dropwise formic acid (20 mL). After 16 h of stirring at rt, the reaction mixture was diluted with AcOEt (100 mL) and filtered over Celite. The filtrate was concentrated under reduced pressure. The viscous residue was partitioned between AcOEt (100 mL) and aqueous saturated $NaHCO_3$ (50 mL). The aqueous phase was separated and extracted with AcOEt (50 mL × 2). The combined AcOEt phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) (R_f = 0.50 with Et_2O) yielded **11a** as a pale yellow oil (3.32 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (broadband, 1H), 5.28 (dd, J = 5.6, 1.3 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.78−3.71 (m, 1H), 3.52−3.44 (m, 1H), 3.07 (d, J = 16.9 Hz, 1H), 2.98 (broadband, 1H), 2.88 (d, J = 16.9 Hz, 1H), 2.13 (d, J = 13.6 Hz, 1H), 1.20 (t, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.1, 104.5, 67.1, 63.5, 52.9, 52.0, 45.1, 39.5. HRMS (CI+NH_3) calcd for $C_{21}H_{32}NO_6$ [M + H$^+$]: 248.1134, found 248.1139.

***trans*-Methyl 5-*tert*-Butoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (11b).** Prepared following the procedure described for **11a** from **3b** (2.30 g, 6.3 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **11b** as a colorless oil (1.50 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (broadband, 1H), 5.58 (dd, J = 5.6, 1.3 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.09 (d, J = 15.9 Hz, 1H), 2.97 (broadband, 1H), 2.87 (d, J = 15.9 Hz, 1H), 2.05 (dd, J = 13.4, 1.1 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.0, 99.9, 75.1, 67.3, 52.8, 51.8, 45.8, 39.4, 28.6. HRMS (CI+NH_3) calcd for $C_{12}H_{22}NO_6$ [M + H$^+$]: 276.1447, found 276.1441.

***trans*-Methyl 5-Ethoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (11c).** Prepared following the procedure described for **11a** from **10d** (2.70 g, 7.6 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **11c** as a colorless oil (1.23 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (broadband, 1H), 5.24 (d, J = 4.5 Hz, 1H), 3.77

(s, 3H), 3.76−3.70 (m, 1H), 3.68 (s, 3H), 3.51−3.43 (m, 1H), 3.00 (dd, J = 13.6, 5.4 Hz, 1H), 2.41−2.36 (m, 2H), 2.28−2.20 (m, 2H), 2.00 (d, J = 13.6 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 172.6, 104.6, 70.2, 63.5, 52.7, 51.7, 45.6, 30.0, 29.9, 14.9. HRMS (CI+NH_3) calcd for $C_{11}H_{20}NO_6$ [M + H^+]: 262.1291, found 262.1295.

***trans*-Methyl 5-*tert*-Butoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (11d).** Prepared following the procedure described for **11a** from **10e** (1.89 g, 5.0 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **11d** as a colorless oil (1.1 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (broadband, 1H), 5.53 (dd, J = 5.6, 1.6 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.97 (dd, J = 13.4, 5.7, Hz, 1H), 2.46−2.32 (m, 2H), 2.28−2.16 (m, 2H), 1.92 (dd, J = 13.4, 1.5, Hz, 1H), 1,24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.7, 99.9, 75.1, 70.4, 52.7, 51.7, 46.6, 30.0, 29.9, 28.7. HRMS calcd for $C_{13}H_{23}NO_6$ [M^+]: 289.1525, found 289.1536.

***trans*-Methyl 2-Acetyl-5-ethoxy-3-(2-methoxy-2-oxoethyl)-isoxazolidine-3-carboxylate (12a).** A solution of **11a** (1.01 g, 4 mmol) in Ac_2O (3 mL) was stirred at rt for 16 h. The reaction mixture was then evaporated under reduced pressure (40 °C at 10 mmHg, then 50 °C at 0.01 mmHg) to afford acetamide **12a** as a pale yellow oil (1.16 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, J = 5.1 Hz, 1H), 3.78 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (d, J = 16.2 Hz, 1H), 3.57 (m, 1H), 3.11 (dd, J = 13.4 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H), 2.86 (dd, J = 13.4 Hz, J = 5.1 Hz, 1H), 2.10 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.8, 167.4, 101.6, 64.9, 64.3, 53.1, 51.7, 44.8, 37.8, 21.4, 15.0. HRMS (CI+NH_3) calcd for $C_{12}H_{20}NO_7$ [M + H^+]: 290.1240, found 290.1242.

***trans*-Methyl 2-Acetyl-5-*tert*-butoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (12b).** Prepared following the procedure described for **12a** from **11b** (0.55 g, 2.0 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **12b** as a colorless oil (0.64 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (dd, J = 5.1, 2.1 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.56 (d, J = 16.1 Hz, 1H), 2.98 (dd, J = 13.3, 2.1 Hz, 1H), 2.90 (d, J = 16.1 Hz, 1H), 2.82 (ddd, J = 13.3, 5.1, 0.8 Hz, 1H), 2.08 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.8, 167.4, 97.2, 75.9, 65.1, 52.9, 51.5, 45.2, 37.9, 28.5, 21.2. HRMS (CI+NH_3) calcd for $C_{14}H_{24}NO_7$ [M + H^+]: 318.1553, found 318.1556.

***trans*-Methyl 2-Acetyl-5-ethoxy-3-(3-methoxy-3-oxopropyl)-isoxazolidine-3-carboxylate (12c).** Prepared following the procedure described for **12a** from **11c** (0.50 g, 1.9 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **12c** as a colorless oil (0.57 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (dd, J = 5.6, 1.1 Hz, 1H), 3.82−3.77 (m, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.61−3.53 (m, 1H), 2.77 (dd, J = 13.6, 5.6 Hz, 1H), 2.70−2.58 (m, 1H), 2.53−2.41 (m, 1H), 2.41 (dd, J = 13.6, 1.1 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 171.6, 169.2, 100.3, 67.0, 63.9, 52.6, 51.3, 45.6, 29.4, 28.6, 21.5, 14.7. HRMS (CI+NH_3) calcd for $C_{13}H_{22}NO_7$ [M + H^+]: 304.1396, found 304.1389.

***trans*-Methyl 2-Acetyl-5-tert-butoxy-3-(3-methoxy-3-oxopropy)-isoxazolidine-3-carboxylate (12d).** Prepared following the procedure described for **12a** from **11d** (0.64 g, 2.2 mmol). Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **12d** as a colorless oil (0.72 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dd, J = 5.6, 2.2 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 2.75−2.59 (m, 3H), 2.50−2.41 (m, 2H), 2.33−2.27 (m, 1H), 2.10 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 171.6, 168.8, 96.0, 75.8, 67.0, 52.5, 51.2, 46.2, 29.5, 28.8, 28.4, 21.3. HRMS (FI) calcd for $C_{15}H_{25}NO_7$ [M^+]: 331.1631, found 331.1630.

***trans*-Methyl 5-*tert*-Butoxy-3-(2-methoxy-2-oxoethyl)-2-(2,2,2-trifluoroacetyl)isoxazolidine-3-carboxylate (13a).** To a solution of **11b** (0.25 g, 0.86 mmol) in THF (1 mL) were added Et_3N (0.15 mL, 1.3 mmol) and $(CF_3CO)_2O$ (0.07 mL, 1.2 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl satd (5 mL) and extracted with Et_2O. The organic phases were combined, washed with NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified over silica gel chromatography (Et_2O/cyclohexane, 1:1) to afford **13a** as a colorless oil (0.33 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dd, J = 5.1, 2.5 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.51 (d, J = 16.1 Hz, 1H), 3.01 (dd, J = 13.4, 2.5 Hz, 1H), 2.97 (d, J = 16.1 Hz, 1H), 2.87 (dd, J = 13.4, 5.1 Hz, 1H), 1.27 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 169.1, 151.7 (q, J = 39.2 Hz), 115.5 (q, J = 284.6 Hz), 99.1, 77.1, 67.1, 53.4, 51.8, 44.0, 37.0, 28.2. HRMS (CI+NH_3) calcd for $C_{14}H_{21}NO_7F_3$ [M + H^+]: 372.1270, found 372.1270.

***trans*-Methyl 5-*tert*-Butoxy-3-(3-methoxy-3-oxopropyl)-2-(2,2,2-trifluoroacetyl)isoxazolidine-3-carboxylate (13b).** To a solution of **11d** (0.52 g, 1.87 mmol) in THF (2 mL) were added Et_3N (0.39 mL, 2.80 mmol) and $(CF_3CO)_2O$ (0.37 mL, 2.62 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl satd (5 mL) and extracted with Et_2O. Organic phases were combined, washed with NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified over silica gel chromatography (Et_2O/cyclohexane, 1:1) to afforded **13b** as a colorless oil (0.72 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dd, J = 5.6, 3.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 2.75 (dd, J = 13.3, 5.6 Hz, 1H), 2.67−2.58 (m, 2H), 2.55−2.39 (m, 2H), 2.35 (dd, J = 13.3, 3.1 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.1, 152.9 (q, J = 39.1 Hz), 115.5 (q, J = 286.4 Hz), 98.3, 76.7, 69.2, 53.3, 51.7, 45.1, 28.9, 28.8, 28.3. HRMS (FD) calcd for $C_{15}H_{22}F_3NO_7$ [M^+]: 385.1348, found 385.1380.

(±)-Dimethyl 2-Acetamido-2-(2-oxoethyl)succinate ((±)-14a). A mixture of **12a** (289 mg, 1 mmol) and $Mo(CO)_6$ (528 mg, 2 mmol) in CH_3CN (10 mL) and H_2O (3 mL) was refluxed for 3 d and then concentrated under vacumm. The residue was partitioned in AcOEt (50 mL) and H_2O (10 mL). The aqueous phase was separated and extracted with AcOEt (50 mL × 2). The combined AcOEt phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography with Et_2O and then with AcOEt (R_f = 0.10 with Et_2O) yielded **(±)-14a** as a pale yellow oil (224 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (t, J = 1.3 Hz, 1H), 6.86 (broadband, 1H), 3.82 (dd, J = 17.4, 1.3 Hz, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 3.56 (d, J = 15.7 Hz, 1H), 2.95 (dd, J = 17.4, 1.3 Hz, 1H), 2.84 (d, J = 15.7 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 171.7, 170.0, 169.9, 57.9, 53.3, 51.8, 47.6, 39.5, 23.7. HRMS (CI+NH_3) calcd for $C_{10}H_{16}NO_6$ [M + H^+]: 246.0978, found 246.0982.

(±)-Dimethyl 2-Acetamido-2-(2-oxoethyl)pentanedioate ((±)-14b). A mixture of **12c** (303 mg, 1 mmol) and $Mo(CO)_6$ (528 mg, 2 mmol) in CH_3CN (10 mL) and H_2O (3 mL) was refluxed for 42 h and then concentrated under vacumm. The residue was partitioned in AcOEt (50 mL) and H_2O (10 mL). The aqueous phase was separated and extracted with AcOEt (50 mL × 2). Combined AcOEt phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded **(±)-14b** as a pale yellow oil (156 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 6.75 (broadband, 1H), 3.90 (dd, J = 18.3, 1.1 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.05 (d, J = 18.3 Hz, 1H), 2.79−2.71 (m, 1H), 2.37−2.29 (m, 1H), 2.21−2.13 (m, 1H), 2.08−2.00 (m, 1H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 172.8, 172.6, 169.6, 57.9, 59.3, 53.1, 51.7, 48.4, 30.2, 28.3, 23.7. HRMS (FI) calcd for $C_{11}H_{18}NO_6$ [M + H^+]: 260.1134, found 260.1135.

(±)-**1-*tert*-Butyl 2,3-Dimethyl 2-(2,2,2-trifluoroacetamido)-propane-1,2,3-tricarboxylate** ((±)-**15a**)**.** To a solution of **13a** (100 mg, 0.27 mmol) in THF (1 mL) was added a solution of SmI_2 in THF (4.5 mL, 4.5 mmol) under argon. After color change of the solution from deep blue to yellow in 10 min, NH_4Cl and Et_2O were added, and the aqueous phase was separated and extracted with Et_2O. Combined Et_2O phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded (±)-**15a** as a pale yellow oil (75 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (broadband, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 3.54 (d, J = 15.8 Hz, 1H), 3.44 (d, J = 15.4 Hz, 1H), 2.93 (d, J = 15.8 Hz, 1H), 2.83 (d, J = 15.4 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.1, 167.6, 156.1 (q, J = 37.3 Hz), 115.3 (q, J = 286.5 Hz), 82.2, 59.6, 53.7, 52.0, 40.6, 39.1, 27.7. HRMS (CI+NH_3) calcd for $C_{14}H_{21}NO_7F_3$ [M + H$^+$]: 372.1270, found 372.1269.

(±)-**1-*tert*-Butyl 2,4-Dimethyl 2-(2,2,2-trifluoroacetamido)-butane-1,2,4-tricarboxylate** ((±)-**15b**)**.** To a solution of **13b** (69 mg, 0.18 mmol) in THF (1 mL) was added a solution of SmI_2 in THF (4.5 mL, 4.5 mmol) under argon. After color change of the solution from deep blue to yellow in 10 min, NH_4Cl and Et_2O were added, and the aqueous phase was separated and extracted with Et_2O. Combined Et_2O phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography (Et_2O/cyclohexane, 1:1) yielded (±)-**15b** as a pale yellow oil (56 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (broadband, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.48 (d, J = 16.5 Hz, 1H), 2.94 (d, J = 16.4 Hz, 1H), 2.80−2.71 (m, 1H), 2.33−2.24 (m, 1H), 2.19−2.11 (m, 2H),1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.8, 168.4, 155.9 (q, J = 37.3 Hz), 115.3 (q, J = 286.8 Hz), 82.1, 61.7, 53.3, 51.9, 40.5, 29.6, 28.4, 27.8. HRMS (CI+NH_3) calcd for $C_{15}H_{23}NO_7F_3$ [M + H$^+$]: 386.1427, found 386.1421.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.