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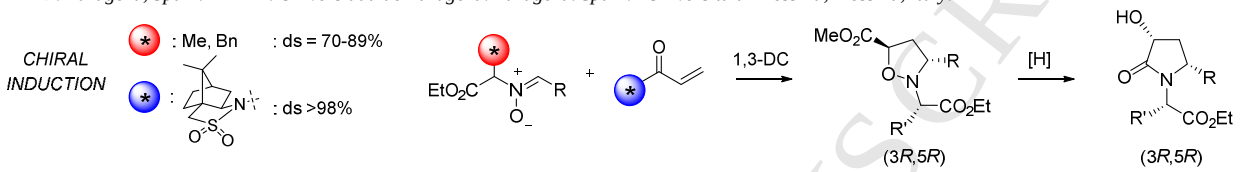

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Dedicated to Prof. Giovanni Romeo on occasion of his 70th birthday

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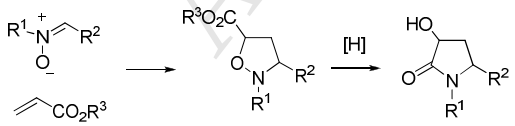
ABSTRACT

Diastereoselective asymmetric 1,3-dipolar cycloadditions of *N*-(alkoxycarbonylmethyl) nitrones derived from glycine, alanine and phenylalanine have been studied both experimental- and theoretically. Asymmetric induction is evaluated by either introducing a chiral group at the nitrone nitrogen atom or by using Oppolzer's sultam acrylamide. In both cases the sense of the asymmetric induction is the same, the (3*R*,5*R*)-isomer being preferentially obtained. The best results were observed with the chiral dipolarophile which afforded an only isomer in all cases. The obtained isoxazolidines are easily transformed into the corresponding 5-substituted-3-hydroxypyrrolidin-2-ones. DFT studies are in a qualitative agreement with the observed experimental results.

1. Introduction

The 1,3-dipolar cycloaddition between a nitrone and an alkene has been known for a long time as a powerful method for accessing to a variety of nitrogenated compounds[1] and the reaction has been extensively studied and reviewed.[2] The isoxazolidines obtained in the reaction are useful intermediates in organic synthesis.[3] In particular, 5-alkoxycarbonyl isoxazolidines obtained from the cycloaddition between nitrones and acrylates are precursors of 5-substituted 3-hydroxypyrrolidin-2-ones of synthetic interest (Scheme 1).[4]



Scheme 1. 1,3-Dipolar cycloadditions en route to 3-hydroxypyrrolin-2ones

Even though the reaction performs with high chemical yields, an inherent problem of the process is the induction of asymmetry when enantiomerically pure compounds are pursued. Catalytic approaches have been widely studied and excellent results have been obtained in several instances.[5] However, in some cases and depending on the required substrates, the catalytic approach, usually based on the use of chiral Lewis acids,[5,6] is not the best option because only enriched mixtures of enantiomers, difficult of being separated, are obtained. In such cases diastereoselective approaches are a good alternative providing homochiral compounds with excellent selectivities.[7] The asymmetric induction can be exerted by incorporating chiral groups either at the dipole or at the dipolarophile.[8] There are numerous examples of dipolar cycloadditions of nitrones bearing chiral groups at the nitrone carbon,[9] most of them derived from carbohydrates.[10] Chiral groups at the nitrone nitrogen atom have also been utilized and excellent results have been obtained when sugar moieties, susceptible of being further eliminated, have been employed.[11] Finally, the incorporation of chiral auxiliaries at the dipolarophile

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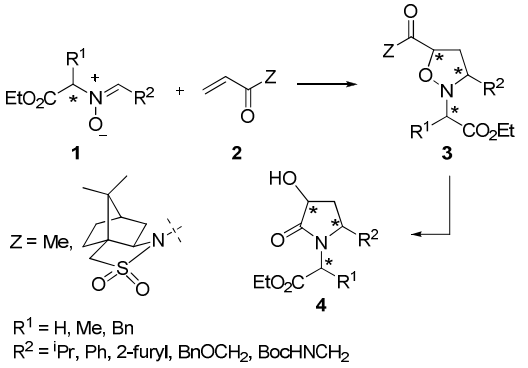
(by forming chiral esters and amides) has been widely studied[12] and among them the Oppolzer's sultam acrylamide has provided the best results.[13] In this context, we have recently reported a preliminary communication on the cycloaddition reaction between a glycine-derived nitrone and Oppolzer's sultam acrylamide en route to pyrrolidinyl PNA monomers.[14] Continuing our work in this area, we now report our latest efforts at expanding the scope of diastereoselective 1,3-dipolar cycloadditions of *N*-(alkoxycarbonylmethyl) nitrones **1**, which are precursors of 5-substsituted-3-hydroxy-*N*-substituted pyrrolidin-2-ones **4** through intermediate isoxazolidines **3**. A comparative study on the reactions between achiral nitrones **1** (Scheme 1, R^1=H) and Oppolzer's sultam acrylamide **2a**, and between chiral non-racemic nitrones **1** (Scheme 1, R^1=Me, Bn) and methyl acrylate **2b** (Scheme 2, Z = Me) is presented. DFT calculations are also discussed in order to rationalize the different asymmetric inductions observed experimentally.

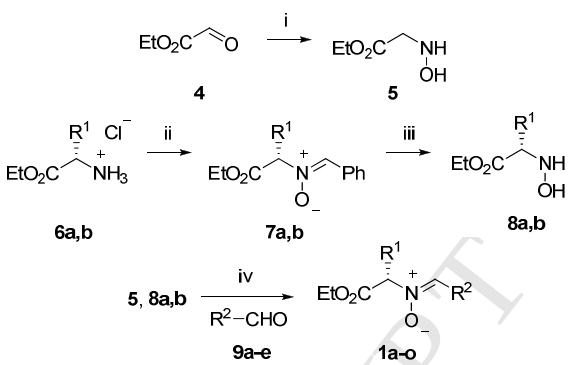


Scheme 2. Synthesis of 3-hydroxypyrrolidin-2-ones

2. Results and discussion

2.1. Experimental study

N-(Alkoxycarbonylmethyl) nitrones **1** were prepared following our previously reported procedure for achiral nitrones[14] consisting of condensation of the corresponding hydroxylamines and aldehydes (Scheme 3). The ethyl hydroxyglycinate **5a** was prepared from ethyl glyoxylate **4** by formation of the oxime and further reduction with borane in pyridine. Condensation of benzaldehyde with the corresponding α-aminoesters **6** afforded intermediate imines which were oxidized *in situ* with methyltrioxorhenium[15] to afford the *C*-phenyl nitrones **7**. Liberation of the free hydroxylamines from **7** could be made by acidic hydrolysis or transoximation with hydroxylamine hydrochloride. Finally, nitrones **1** were obtained by condensation of hydroxylamines **5** and **8** with the corresponding aldehydes **9** in the presence of magnesium sulfate as a drying agent (Scheme 2, Table 1). All the nitrones were obtained in good yields with the exception of those derived from *N*-Boc-glycinal **9e**, which showed to be unstable. Since nitrones **1e**, **1j** and **1o** could not be isolated, the corresponding cycloadditions were made by forming the nitrone *in situ* (see below).



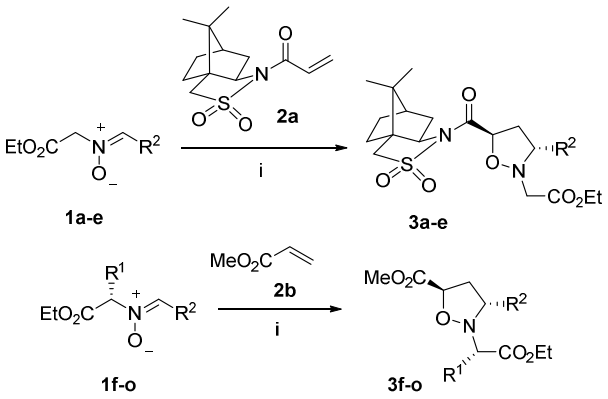
Scheme 3. Synthesis of *N*-(alkoxycarbonylmethyl) nitrones **1**. i) $H_2NHOH{\cdot}HCl$, $NaHCO_3$, 12 h, then $BH_3{\cdot}Py$. ii) Et_3N, PhCHO, 12 h, then $MeReO_3$, UHP, MeOH, $MgSO_4$. iii) $H_2NOH{\cdot}HCl$, MeOH (or HCl, H_2O), iv) $MgSO_4$, CH_2Cl_2, 4 h. (For R^1 and R^2 see Table 1)

Table 1. Synthesis of *N*-(alkoxycarbonylmethyl) nitrones (Scheme 2).

R^1	R^2	aldehyde	hydroxylamine	nitrone	yield (%)[a]
H	^{i}Pr	**9a**	**5**	**1a**	60
H	Ph	**9b**	**5**	**1b**	60
H	2-furyl	**9c**	**5**	**1c**	80
H	$BnOCH_2$	**9d**	**5**	**1d**	90
H	$BocHNCH_2$	**9e**	**5**	**1e**	----[b]
Me	^{i}Pr	**9a**	**8a**	**1f**	85
Me	Ph	**9b**	**8a**	**1g**	78
Me	2-furyl	**9c**	**8a**	**1h**	89
Me	$BnOCH_2$	**9d**	**8a**	**1i**	70
Me	$BocHNCH_2$	**9e**	**8a**	**1j**	----[b]
Bn	^{i}Pr	**9a**	**8b**	**1k**	87
Bn	Ph	**9b**	**8b**	**1l**	99
Bn	2-furyl	**9c**	**8b**	**1m**	90
Bn	$BnOCH_2$	**9d**	**8b**	**1n**	83
Bn	$BocHNCH_2$	**9e**	**8b**	**1o**	----[b]

[a] Isolated yield. [b] unstable; prepared *in situ* (see below)

The cycloaddition reactions were carried out in toluene as a solvent in a sealed tube (Scheme 4). The results are collected in Table 2. All the cycloadditions carried out utilizing *N*-acryloyl-(2*R*)-bornane-10,2-sultam **2a** as dipolarophile took place with complete regio- (3,5), diastereo- (*trans*) and enantioselectivities (3*R*,5*R*) and only one adduct was found in the crude isolated reaction mixtures. The 5-(*tert*-butoxycarbonylaminomethyl) adduct **3e** was obtained by mixing aldehyde **9e**, hydroxylamine **5** and **2a** under the same reaction conditions.



Scheme 4. Cycloaddition between nitrones and alkenes. i) toluene, sealed tube, 80 ºC, 16 h. (For R^1 and R^2 see see Table 2).

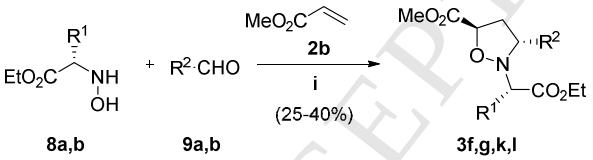
Table 2. Cycloadditions between nitrones **1** and dipolarophiles **2** (Scheme 4).

R^1	R^2	nitrone	alkene	isoxazolidine	d.r.[a]	yield (%)[b]
H	^{i}Pr	**1a**	**2a**	**3a**	>98:2:0:0[d]	50
H	Ph	**1b**	**2a**	**3b**	>98:2:0:0[d]	61
H	2-furyl	**1c**	**2a**	**3c**	>98:2:0:0[d]	80
H	$BnOCH_2$	**1d**	**2a**	**3d**	>98:2:0:0[d]	80
H	$BocHNCH_2$	**1e**[c]	**2a**	**3e**	>98:2:0:0[d]	75
Me	^{i}Pr	**1f**	**2b**	**3f**	72:10:9:9	55
Me	Ph	**1g**	**2b**	**3g**	82:10:8:0	83
Me	2-furyl	**1h**	**2b**	**3h**	80:15:5:0	77
Me	$BnOCH_2$	**1i**	**2b**	**3i**	70:20:10:0	68
Me	$BocHNCH_2$	**1j**[c]	**2b**	**3j**	80:10:10:0	45
Bn	^{i}Pr	**1k**	**2b**	**3k**	78:8:8:6	64
Bn	Ph	**1l**	**2b**	**3l**	89:6:5:0	82
Bn	2-furyl	**1m**	**2b**	**3m**	85:9:6:0	81
Bn	$BnOCH_2$	**1n**	**2b**	**3n**	85:9:6:0	54
Bn	$BocHNCH_2$	**1o**[c]	**2b**	**3o**	88:6:6:0	52

[a] Determined by NMR on the crude mixture [b] Isolated yield. [c] prepared *in situ*. [d] only one diastereomer was observed

When nitrones **1f-o**, bearing a chiral group at the nitrone nitrogen were used as dipoles in the cycloaddition reaction with methyl acrylate **2b**, lower diastereomeric ratios were found with respect to the use of the chiral dipolarophile **2a**. The (3*R*,5*R*)-isomer was also the preferred one but minor isomers were detected by NMR of the crude mixtures. After chromatographic purification the major isomer was isolated and characterized. Similarly to the obtention of isoxazolidine **3e**, the corresponding adducts **3j** and **3o** were obtained by mixing aldehyde **9e** and **2b** with hydroxylamines **8a** and **8b**, respectively, under the same reaction conditions. In general, nitrones bearing a benzyl group (**1k-1o**) gave better diastereomeric rations than those bearing a methyl group (**1f-1j**).

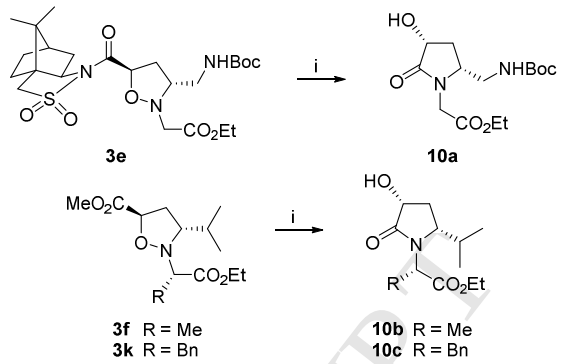
The reaction can also be carried out in a one-pot procedure as in the case of nitrones derived from *N*-Boc-glycinal **9e**. However, when we check such a protocol for the synthesis of isoxazolidines **3f,g** and **3k,l** (Scheme 5) considerably lower yields (25-40%) were observed; the diastereoselectivity was not affected so, it can be considered intrinsic of the cycloaddition reactions. Consequently, the multicomponent reaction in this case cannot be considered as an advantageous approach.



8a,b **9a,b** **3f,g,k,l**

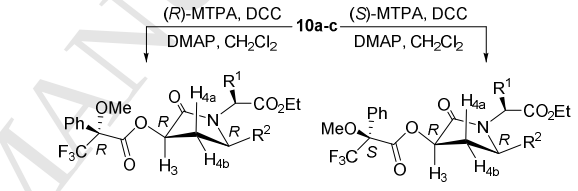
Scheme 5. Multicomponent synthesis of isoxazolidines. i) toluene, sealed tube, 60 ºC, 16 h. (For R^1 and R^2 see see Tables 1 and 2)

The synthetic utility of the isoxazolidines was demonstrated through the efficient conversion to the corresponding 3-hydroxypyrrolidin-2-ones **10** (Scheme 6). Catalytic hydrogenation of isoxazolidines **3f** and **3k** afforded in a quantitative yield pyrrolidin-2-ones **10a** and **10b**, respectively. The transformation of isoxazolidine **3e** into **10c** has been reported in our previous communication.[14]



Scheme 6. Synthesis of pyrrolidin-2-ones. i) H_2, $Pd(OH)_2$-C, 2000 psi, 48 h

The relative configuration of compounds **3** was assigned by conventional 1D and 2D NMR techniques. The absolute configurations were determined by preparing the corresponding Mosher esters of pyrrolidines **10**. In order to apply successfully the Kakisawa's rule[16] we prepared Mosher esters **11** and **12** derived from (R)- and (S)-Mosher acids, respectively (Scheme 6) and the ^{1}H NMR spectra were recorded to calculate differences in the chemical shift between the values corresponding to a pair of isomers.



11a-c **12a-c**

	R^1	R^2	δH_{4a}	δH_{4b}		R^1	R^2	δH_{4a}	δH_{4b}
11a	H	$BocNHCH_2$	2.62	1.72	**12a**	H	$BocNHCH_2$	2.67	1.94
11b	Me	^{i}Pr	2.44	1.67	**12b**	Me	^{i}Pr	2.49	1.67
11c	Bn	^{i}Pr	2.04	1.68	**12c**	Bn	^{i}Pr	2.11	1.50

$\Delta\delta = \delta_S - \delta_R$

	R^1	R^2	H_{4a}	H_{4b}
11a / 12a	H	$BocNHCH_2$	0.05	0.22
11b / 12b	Me	^{i}Pr	0.05	0.19
11c / 12c	Bn	^{i}Pr	0.07	0.18

Scheme 7. Mosher esters of compounds **10**.

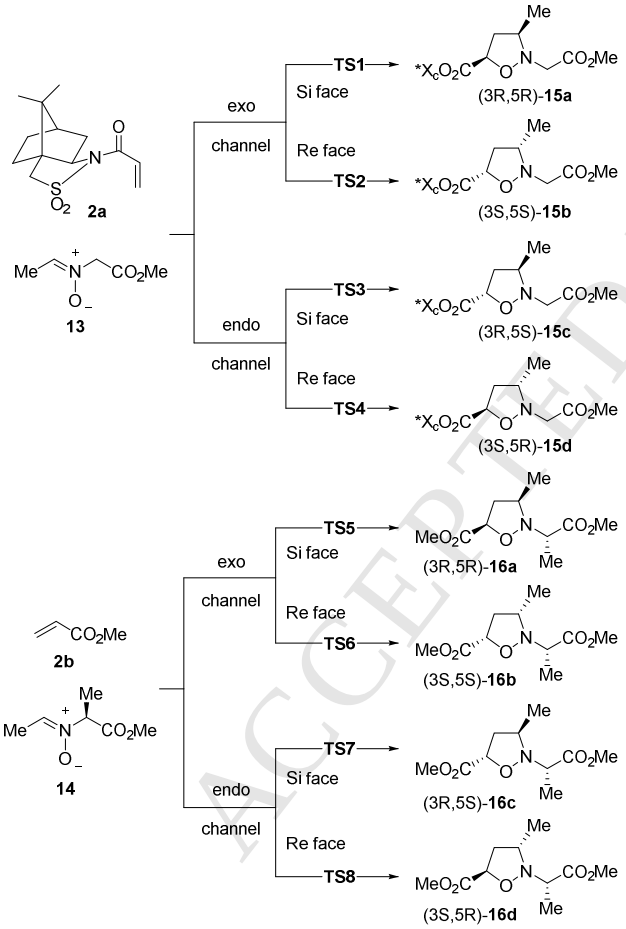
According to Kakisawa's rule[16] the methylene group (H_{4a} and H_{4b}) is selectively shielded by the phenyl group when the two groups are located on the same side of the plane containing H_3 and the carbonyl group (compounds **11**). By defining $\Delta\delta$ as indicated in Scheme 7 (δ_S and δ_R refers to chemical shifts of (S)- and (R)-MTPA esters, respectively) positive values indicate a 3*R* configuration, whereas negative values indicate a 3*S* configuration. According to the values illustrated in Scheme 6 it was confirmed a 3*R* configuration for compounds **10a-c**. This confirmation served to ascertain the absolute configuration of the major product of the cycloaddition, compounds **3** as (3*R*,5*R*).

2.2. Theoretical study

In order to rationalize the stereochemical course of the studied reactions we carried out theoretical studies of all the possible paths of reaction. All calculations were performed with the GAUSSIAN 09 package.[17] The hybrid density functional theory B3LYP[18] with the 6-31G(d) basis set[19] was employed for

geometry optimizations. This method has been successfully used in theoretical investigations of reactions involving dipolar cycloadditions of nitrones.[14]

To evaluate inclusion of diffuse functions and different functionals with a higher level basis set, single point calculations were carried out on the optimized structures using both B3LYP[18] and M06-2X[20] functionals with triple Z basis set 6-311+G(d). Geometry optimizations and vibrational analyses were performed without any constraint and all transition structures were characterized by analysis of the normal mode corresponding to its unique imaginary frequency. All the located transition states were confirmed to connect to reactants and products by intrinsic reaction coordinate (IRC) calculations.[21] Regarding the computational costs, the only changes made in the model is the use of *C*-methyl nitrones and methyl esters. The rest of the molecule has been preserved. Two model reactions have been studied (Scheme 8) corresponding to the cycloaddition with Oppolzer's sultam acrylamide and nitrones bearing chiral groups at the nitrogen atom. In both cases the four possible transition states corresponding to the obtention of 3,5-adducts through *endo* and *exo* attacks by the *Re* and *Si* faces have been considered.



Scheme 8. Model reactions studied at DFT level

In our previous communication, preliminary calculations at B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) level predicted in the case of cycloaddition with **2a**, a preferred *Si-endo* attack with very small energy differences (within the experimental error) with respect to the other transition states. However, such a transition state leads to the (3*R*,5*S*)-adduct, whereas the obtained adduct is that with (3*S*,5*R*) configuration in the model (actually, (3*R*,5*R*) in the real adduct.[22] In addition, energy differences between TSs lower than 1.0 kcal/mol do not justify the excellent diastereoselectivity observed in the reaction. Because of these reasons (failure in prediction) we decided to move to Thrular's functional M06-2X for performing more accurate calculations. It has been reported that B3LYP functionals, adequate for determining geometries, are not so precise in energy calculations and Thrular's functionals should provide more accurate energy values more in agreement with the experimental findings.[23]

We located (B3LYP/6-31G(d)) four transition states for the cycloaddition between nitrone **13** and **2a** (Figure 1) and four transition states for the reaction between nitrone **14** and **2b** (Figure 2). The energy values are given in Tables 3 and 4. All the transition states are concerted asynchronous as expected for a typical normal-demand 1,3-dipolar cycloaddition. The C-O forming bonds are in the range of 2.28-2.39 Å and the C-C forming bonds in the range of 2.04-2.11 Å. The geometry of the transition structures is rather similar independently of the position of the chiral auxiliary, with shorter C-O forming bonds for *exo* approaches. On the opposite, the shorter C-C forming bonds correspond to the *endo* approaches.

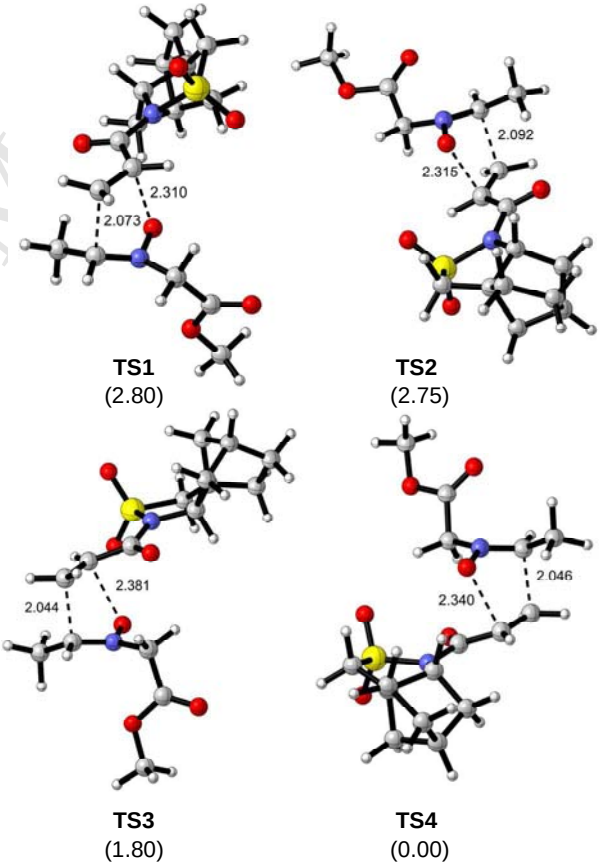


Figure 1. Transition structures (B3LYP/6-31G(d)) corresponding to the reaction between **13** and **2a**. **TS1**, **TS2**, **TS3** and **TS4** correspond to *Si exo*, *Re exo*, *Si endo* and *Re endo* approaches leading to (3*R*,5*R*)-, (3*S*,5*S*)-, (3*R*,5*S*)- and (3*S*,5*R*)-isomers. Relative energy values between TSs are calculated at M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level on theory and given in kcal/mol. Bond distances are given in Å.

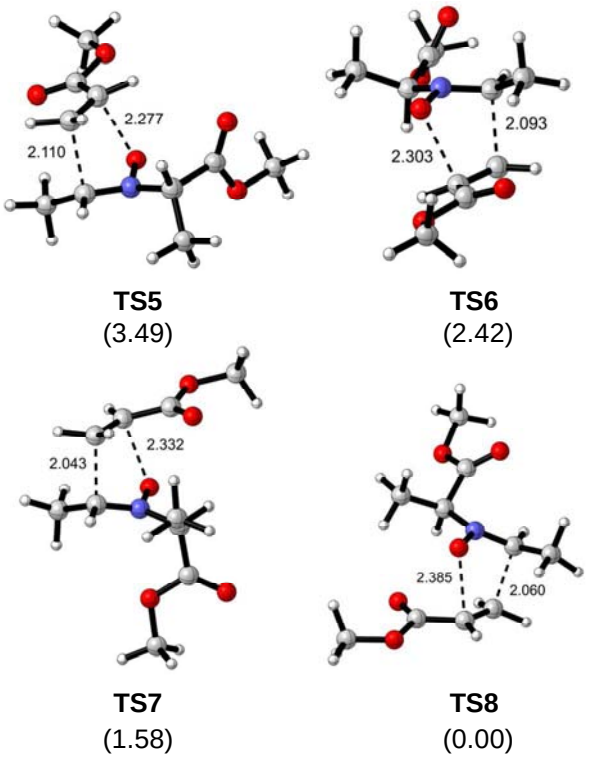


Figure 2. Transition structures (B3LYP/6-31G(d)) corresponding to the reaction between **14** and **2b**. **TS5**, **TS6**, **TS7** and **TS8** correspond to *Si exo*, *Re exo*, *Si endo* and *Re endo* approaches leading to (3*R*,5*R*)-, (3*S*,5*S*)-, (3*R*,5*S*)- and (3*S*,5*R*)-isomers. Relative energy values between TSs are calculated at M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level on theory and given in kcal/mol. Bond distances are given in Å.

Table 3. Calculated (M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) and B3LYP/6-311+G(d,p)//B3LYP/6-31G(d)) free (ΔG, hartrees) and relative energies (ΔΔG, kcal·mol^{-1}) of the stationery points corresponding to the reaction of nitrone **13** with **2a** (see Scheme 8).[a]

	B3LYP/6-311G(d,p) //B3LYP/6-31G(d)		M06-2X/6-311G(d,p) //B3LYP/6-31G(d)	
	ΔG	ΔΔG[b]	ΔG	ΔΔG[b]
2a	-1106.712249		-1106.397708	
13	-476.328878		-476.120257	
TS1	-1583.002915	23.98	-1582.489996	17.55
TS2	-1583.001658	24.77	-1582.490071	17.50
TS3	-1583.003196	23.80	-1582.491584	16.55
TS4	-1583.002396	24.30	-1582.494459	14.75
15a	-1583.049313	-5.14	-1582.558545	-25.46
15b	-1583.047860	-4.23	-1582.550269	-20.27
15c	-1583.048858	-4.85	-1582.555084	-23.29
15d	-1583.050002	-5.57	-1582.556095	-23.93

[a] **TS1** corresponds to *Si exo* approach leading to (3*R*,5*R*)-**15a**; **TS2** corresponds to *Re exo* approach leading to (3*S*,5*S*)-**15b**; **TS3** corresponds to *Si endo* approach leading to (3*R*,5*S*)-**15c**; **TS4** corresponds to *Re endo* approach leading to (3*S*,5*R*)-**15d**. [b]Referred to starting materials (**2a**+**13** = -1583.041127 and -1582.517965 hartree for B3LYP and M06-2X single point calculations, respectively).

Table 4. Calculated (M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) and B3LYP/6-311+G(d,p)//B3LYP/6-31G(d)) free (ΔG, hartrees) and relative energies (ΔΔG, kcal·mol^{-1}) of the transition structures corresponding to the reaction of nitrone **14** with **2b** (see Scheme 8).[a]

	B3LYP/6-311G(d,p) //B3LYP/6-31G(d)		M06-2X/6-311G(d,p) //B3LYP/6-31G(d)	
	ΔG	ΔΔG[b]	ΔG	ΔΔG[b]
2b	-306.475408			
14	-515.627400			
TS5	-822.065070	23.68	-821.713674	15.48
TS6	-822.067509	22.15	-821.715380	14.40
TS7	-822.067220	22.33	-821.716713	13.57
TS8	-822.069269	21.05	-821.719235	11.99
16a	-822.108544	-3.60	-821.772882	-21.68
16b	-822.111340	-5.35	-821.775567	-23.36
16c	-822.109955	-4.48	-821.775804	-23.51
16d	-822.111883	-5.69	-821.777319	-24.46

[a] **TS5** corresponds to *Si exo* approach leading to (3*R*,5*R*)-**16a**; **TS6** corresponds to *Re exo* approach leading to (3*S*,5*S*)-**16b**; **TS7** corresponds to *Si endo* approach leading to (3*R*,5*S*)-**16c**; **TS8** corresponds to *Re endo* approach leading to (3*S*,5*R*)-**16d**. [b]Referred to starting materials (**2b**+**14** = -822.102808 and -821.738335 hartree for B3LYP and M06-2X single point calculations, respectively).

The energy values were calculated through single point calculations using B3LYP and M06-2X functionals and triple Z basis sets including diffuse functions. As mentioned above, while the use of B3LYP functional does not predict correctly the stereochemical course of the reaction, the use of M06-2X functional indicated the lower transition states those corresponding to a *Re-endo* attack in both cases (**TS4** and **TS8**) leading to the corresponding (3*S*,5*R*)-isomers **15d** and **16d**. The barrier for the cycloaddition between **2a** and **13** is 14.75 kcal/mol and the barrier for the cycloaddition between **2b** and **14** is 11.99 kcal/mol. These results are in good agreement with the experimental observations. Moreover, the energy differences between transition states are sufficient to justify a good selectivity, even though it is not possible to evaluate in a quantitative way the observed diastereoselectivity.

3. Conclusions

Diastereoselective 1,3-dipolar cycloadditions of achiral *N*-(alkoxycarbonylmethyl) nitrones with Oppolzer's sultam acrylamide has been compared with the corresponding cycloadditions between *N*-(alkoxycarbonylmethyl) nitrones bearing a chiral group at the nitrone nitrogen and methyl acrylate. In all cases the regio- and diastereoselectvity is complete towards 3,5-*trans*-disubstituted isoxazolidines. Also, the asymmetric induction is the same leading to (3*R*,5*R*)-isomers; however whereas inclusion of chirality at the nitrogen atom in the nitrone moiety affords mixtures of isomers, the use of the Oppolzer's sultam acrylamide as dipolarophile furnishes only one isomer. In conclusion, and according to previously reported dipolar cycloadditions with such a dipolarophile[13] the Oppolzer's sultam is confirmed to be an excellent chiral auxiliary. For this sort of 1,3-dipolar cycloadditions it is more advisable to include the chiral group at the dipolarophile rather than at the nitrone nitrogen atom. Whereas DFT calculations at B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) level of theory are not capable of predicting correctly the stereochemical course of the reaction, the use of Thrular's functional ((M06-2X/6-311G+(d,p)//B3LYP/6-

31G(d)) provides energy values that are in good qualitative agreement with the observed asymmetric induction.

4. Experimental Section

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with either 5% ethanolic phosphomolybdic acid or Mostain solution. Column chromatography was carried out in a Buchi 800 MPLC system or a Combiflash apparatus, using silica gel 60 microns and with solvents distilled prior to use. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or 500 instruments in the stated solvent. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. Optical rotations were taken on a JASCO DIP-370 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer or with a Perkin-Elmer 2400 instrument.

*4.1. Ethyl hydroxyglycinate **5***

A solution of ethyl glyoxylate **4** (8.5 mL of a 50% solution in toluene, 43.2 mmol) in toluene (75 mL) was treated with hydroxylamine hydrochloride (3 g, 43.1 mmol) and sodium bicarbonate (7 g, 86.4 mmol) and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate evaporated under reduced pressure. The crude product was taken up in dichloromethane and washed with brine. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude oxime (3.53 g, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, 3H), 4.33 (q, 2H), 7.56 (s, 1H), 9.10 (bs, 1H)) which was dissolved in ethanol (60 mL), cooled to 0 °C and treated sequentially with borane in pyridine (18.7 mL, 149.6 mmol) and 7N HCl in EtOH. After stirring for 2 h at 0 °C the solvent is evaporated under reduced pressure and the residue is taken up in dichloromethane. Solid sodium carbonate is added and stirred for 15 min. The mixture is filtered and the filtrate evaporated to give the crude hydroxylamine (1.9 g, 55%; ^{1}H NMR (CDCl3, 400 MHz) δ 1.30 (t, 3H), 3.67 (s, 2H), 4.25 (q, 2H), 5.37 (br, 2H)), which is used in the next step without further purification.

*4.2. General Procedure for the Synthesis of Nitrones **7***

A suspension of the corresponding ester hydrochloride (15 mmol) in dichloromethane (25 mL) was treated with triethylamine (15 mmol); the resulting mixture was stirred vigorously for 2 h at ambient temperature under an argon atmosphere. Benzaldehyde (15 mmol) was added and stiring was maintained for additional 24 h at room temperature. The reaction mixture was filtered through a pad of Celite® and the filtrate was evaporated under reduced pressure to give crude imine, which was taken up in MeOH (20 mL) and treated sequentially with $MgSO_4$ (1.80 g, 15 mmol), methyl trioxorhenium (0.08 g, 0.28 mmol) and urea-hydrogen peroxide complex (4.25 g, 45 mmol). The resulting mixture was stirred for 7 h at ambient temperature, filtered and evaporated under reduced pressure to give the crude nitrones, which were used in the next step without further purification.

*4.2.1. (S,Z)-N-(1-ethoxy-1-oxopropan-2-yl)-1-phenylmethanimine oxide **7a***

(3.15 g, 95%); white foam. ^{1}H NMR ($CDCl_3$, 400 MHz) d 1.34 (t, 3H, J = 7.1 Hz), 1.78 (d, 3H, J = 7.0 Hz), 4.29 (q, 2H, J = 7.1 Hz), 4.75 (q, 1H, J = 7.0 Hz), 7.41-7.44 (m, 3H), 7.87-7.89 (m, 1H), 8.23-8.27 (m, 2H).

*4.2.2. (S,Z)-N-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)-1-phenylmethanimine oxide **7b***

(4.14 g, 93%); white foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H, J = 7.1 Hz), 3.41 (dd, 1H, J = 14.2, 4.6 Hz), 3.72 (dd, 1H, J = 14.2, 10.1 Hz), 4.31 (q, 2H, J = 7.1 Hz), 4.70 (dd, 1H, J = 10.1, 4.6 Hz), 7.14 (s, 1H), 7.22-7.29 (m, 5H), 7.41-7.43 (m, 3H), 8.16-8.19 (m, 2H)

*4.3. General Procedure for the Synthesis of Hydroxylamines **8***

To a cooled (0 °C) solution of hydroxylamine hydrochloride (3.16 g, 45.5 mmol) in MeOH (50 ml), NaOH (1.82 g, 45.4 mmol) and acetic acid (2.73 g, 2.7 mL, 45.4 mmol) were added sequentially. The resulting solution was stirred for 15 min at which time the corresponding nitrone (16 mmol) was added. The reaction mixture was heated under reflux for 16 h. After concentration under reduced pressure a 6N solution of KOH saturated with NaCl was added until pH = 7. The resulting mixture was extracted with EtOAc (3 x 60 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was used in the next step without further purification

*4.3.1. Ethyl N-hydroxy-L-alaninate **8a***

(1.11 g, 52%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.31 (m, 6H), 3.72 (q, 1H), 4.23 (q, 2H), 5.48 (bs, 1H).

*4.3.2. Ethyl N-hydroxy-L-phenylalaninate **8b***

(1.67 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz) d 1.12 (t, 3H, J = 7.1 Hz), 2.79 (dd, 1H, J = 13.8, 8.2 Hz), 2.88 (dd, 1H, J = 13.8, 6.2 Hz), 3.77 (dd, 1H, J = 8.2, 6.2 Hz), 4.08 (q, 2H, J = 7.1 Hz), 7.08-7.22 (m, 5H).

*4.4. General Procedure for the Synthesis of Nitrones **1***.

A solution of the corresponding aldehyde (5 mmol) and hydroxylamine (5 mmol) in dichlorometane (25 mL) was treated with magnesium sulfate (1 g, 13.3 mmol). The resulting mixture was stirred at ambient temperature for 4 h, filtrated and the filtrate evaporated to give the crude nitrone, which was purified by column chromatography.

*4.4.1. (Z)-N-(2-Ethoxy-2-oxoethyl)-2-methylpropan-1-imine oxide **1a***

Eluent: EtOAc. (0.520 g, 60 %); oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (d, 6H, J = 6.9 Hz) 1.30 (t, 3H, J = 7.2 Hz) 3.21 (ddd, 1H, J = 6.9, 7.3 Hz), 4.27 (q, 1H, J = 7.2 Hz), 4.50 (s, 2H),6.58 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7 19.2, 20.2, 26.7, 52.8, 66.5, 147.8, 165.9. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.47; H, 8.61; N, 8.22.

*4.4.2. (Z)-N-(2-Ethoxy-2-oxoethyl)-1-phenylmethanimine oxide **1b***

Eluent: hexane/EtOAc, 1:1. (0.622 g, 60 %); oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H), 4.30 (q, 2H), 4.73 (s, 2H), 7.43-7.45 (m, 4H), 8.24-8.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.9, 53.0, 67.9, 128.5, 128.9, 130.1, 131.1, 137.4, 166.2. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.88; H, 6.48; N, 6.53.

*4.4.3. (Z)-N-(2-Ethoxy-2-oxoethyl)-1-(furan-2-yl)methanimine oxide **1c***

Eluent: hexane/EtOAc, 1:1. (0.789 g, 80 %); oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, 3H), 4.29 (q, 2H), 4.67 (s, 2H), 6.58

(bs, 1H), 7.51(s, 1H), 7.60 (s, 1H), 7.84 (d, 1H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 14.1, 62.4, 66.4, 112.5, 116.5, 127.8, 144.3, 146.3, 165.4. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.91; H, 5.50; N, 6.89.

4.4.4. (Z)-2-(Benzyloxy)-N-(2-ethoxy-2-oxoethyl)ethan-1-imine oxide ***1d***

Eluent: hexane/EtOAc, 1:1. (1.13 g, 90 %); oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, J = 7.14 Hz), 4.18 (q, 2H, J = 7.14 Hz), 4.42-4.44 (m, 4H), 4.49 (s, 2H), 6.90 (t, 1H), 7.22-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 62.3, 65.6, 65.8, 73.6, 127.8, 127.9, 128.4, 137.1, 140.6, 165.0. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.23; H, 6.73; N, 5.42.

4.4.5. (S,Z)-N-(1-Ethoxy-1-oxopropan-2-yl)-2-methylpropan-1-imine oxide ***1f***

Eluent: hexane/EtOAc, 1:1. (0.796 g, 85 %); oil; $[\alpha]_D^{25}$ -27 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (dd, 6H, J = 9.9, 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.67 (d, 3H, J = 7.0 Hz), 3.21 (qd, 1H, J = 13.9, 6.9 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.52 (q, 1H, J = 7.0 Hz), 6.61 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 15.2, 18.5, 18.8, 25.9, 62.1, 71.6, 145.3, 168.0. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.81; H, 9.32; N, 7.19.

4.4.6. (S,Z)-N-(1-Ethoxy-1-oxopropan-2-yl)-1-phenylmethanimine oxide ***1g***

Eluent: hexane/EtOAc, 7:3. (0.863 g, 78 %); oil; $[\alpha]_D^{25}$ -23 (c 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H), 1.78 (d, 3H, J = 7.0 Hz) 4.23-4.30 (m, 2H), 4.74 (q, 1H, J = 7.0 Hz), 7.43-7.44 (m, 3H),7.47 (s, 1H), 8.25-8.27 (m, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 15.6, 62.3, 73.3, 128.6, 128.9, 130.2, 130.7, 135.0, 168.0 Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.90; H, 6.93; N, 6.17.

4.4.7. (S,Z)-N-(1-Ethoxy-1-oxopropan-2-yl)-1-(furan-2-yl)methanimine oxide ***1h***

Eluent: hexane/EtOAc, 7:3. (0.940 g, 89 %); oil; $[\alpha]_D^{25}$ -36 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H, J = 7.2 Hz), 1.77 (d, 3H, J = 7.0 Hz), 4.26 (q, 2H,), 4.72(q, 1H, J = 7.0 Hz), 6.57 (s, 1H,), 7.51 (s, 1H), 7.65 (s, 1H), 7.81 (d, 1H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 15.5, 62.3, 71.7, 112.4, 116.2, 125.7, 144.0, 144.1, 146.5, 167.8. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.65; H, 6.37; N, 6.85.

4.4.8. (S,Z)-2-(Benzyloxy)-N-(1-ethoxy-1-oxopropan-2-yl)ethan-1-imine oxide ***1i***

Eluent: hexane/EtOAc, 1:1. (0.929 g, 70 %); oil; $[\alpha]_D^{25}$ -8 (c 0.65 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, J = 7.14 Hz), 1.58 (d, 3H, J = 7.06 Hz), 4.17 (q, 2H, J = 7.14 Hz), 4.44 (dd, 2H), 4.49-4.51 (m, 3H), 6.94 (t, 1H), 7.22-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13-9, 15.3, 62.3, 65.8, 71.4, 73.7, 127.9, 128.0, 128.5, 137.1, 137.9, 167.5. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.06; H, 7.46; N, 5.07.

4.4.9. (S,Z)-N-(1-Ethoxy-1-oxo-3-phenylpropan-2-yl)-2-methylpropan-1-imine oxide ***1k***

Eluent: hexane/EtOAc, 2:1. (1.15 g, 87 %); oil; $[\alpha]_D^{25}$ -66 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J= 6.9 Hz), 1.29 (t, 3H, J = 7.1 Hz), 3.08 (qd, 1H, J = 13.9, 6.9 Hz), 3.25 (dd, 1H, J = 14.2, 4.2 Hz), 3.59 (dd, 1H, J = 14.2, 10.8 Hz), 4.26 (q, 2H, J = 7.1 Hz), 4.40 (dd, 1H, J = 10.8, 4.2 Hz), 6.20 (d, 1H, J = 7.3 Hz), 7.21-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 18.5, 18.7, 25.7, 34.6, 62.2, 78.0, 127.0, 128.6, 129.1, 136.3, 146.9, 166.8. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.58; H, 8.21; N, 5.49.

4.4.10. (S,Z)-N-(1-Ethoxy-1-oxo-3-phenylpropan-2-yl)-1-phenylmethanimine oxide ***1l***

Eluent: hexane/EtOAc, 1:1. (1.47 g, 99 %); oil; $[\alpha]_D^{25}$ -35 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H, J = 7.1 Hz), 3.41 (dd, 1H, J = 14.2, 4.6 Hz), 3.72 (dd, 1H, J = 14.2, 10.1 Hz), 4.31 (q, 2H, J = 7.1 Hz), 4.70 (dd, 1H, J = 10.1, 4.6 Hz),7.14 (s, 1H), 7.22-7.29 (m, 5H), 7.40-7.44 (m, 3H), 8.16-8.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 34.6, 62.2, 78.0, 127.0, 128.5, 128.6, 128.9, 129.1, 130.3, 135.4, 136.3, 146.9, 166.8. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.58; H, 6.63; N, 4.90.

4.4.11. (S,Z)-N-(1-Ethoxy-1-oxo-3-phenylpropan-2-yl)-1-(furan-2-yl)methanimine oxide ***1m***

Eluent: hexane/EtOAc, 4:1. (1.29 g, 90 %); oil; $[\alpha]_D^{25}$ -28 (c 0.43 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H), 3.37 (dd, 1H, J = 14.2, 4.9 Hz), 3.64 (dd, 14.2, 9.9 Hz), 4.23-4.29 (m, 2H,), 4.65 (dd, 1H, J = 9.9, 4.9 Hz), 6.54-6.55 (m, 1H,), 7.19-7.26 (m, 5H), 7.34 (s, 1H), 7.44 (s, 1H), 7.82 (d, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 35.1, 62.3, 78.7, 112.3, 116.2, 126.9, 127.2, 128.7, 128.9, 136.1, 144.0, 146.2, 166.7. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.04; H, 6.17; N, 4.66.

4.4.12. (S,Z)-2-(Benzyloxy)-N-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)ethan-1-imine oxide ***1n***

Eluent: hexane/EtOAc, 7:3. (1.42 g, 83 %); oil; $[\alpha]_D^{25}$ -39 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H), 3.22 (dd, 1H, J = 14.2, 4.8 Hz),3.48 (dd, 1H, J = 14.2, 10.6 Hz),4.14-4.24 (m, 2H), 4.27-4.38 (m, 4H), 4.44 (ddd, 1H, J = 10.6, 4.8 Hz), 6.59 (t, 1H), 7.13-7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 34.7, 62.4, 65.5, 73.4, 77.7, 127.2, 1279, 128.4, 128.7, 128.9, 135.9, 137.1, 139.9, 166.3. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.19; H, 6.54; N, 4.41.

4.5. General Procedure for the Cycloaddition Reactions

A solution of nitrone **1** (1 mmol) and the corresponding alkene (1 mmol) in toluene (15 mL) is place in a sealed tube and heated at 80 °C for 16 h at which time the solvent was evaporated and the crude product was purified by column chromatography.

4.5.1. Ethyl 2-((3R,5R)-5-((6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-3-isopropylisoxazolidin-2-yl)acetate ***3a***

Eluent: hexane/EtOAc, 4:1. (0.221 g, 50%); oil; $[\alpha]_D^{25}$ -25 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (s, 6H), 0.95 (s, 3H), 1.12 (s, 3H), 1.30 (t, 3H), 1.42-1.48 (m, 1H), 1.70-1.78 (m, 1H), 1.79-1.95 (m, 6H), 2.05-2.18 (m, 1H), 2.52 (t, 1H), 2.97 (q, 1H), 3.11 (d, 2H), 3.57 (d, 1H), 3.87-3.98 (m, 2H), 4.18-4.21 (m, 2H), 5.03 (t, 1H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 19.4, 19.9, 20.1, 20.4, 26.3, 29.9, 31.4, 35.6, 37.9, 44.2, 49.9, 52.5, 60.3, 62.4, 64.9, 71.1, 76.5, 168.9, 171.1. Anal. Calcd for $C_{21}H_{34}N_2O_6S$: C, 56.99; H, 7.74; N, 6.33; S, 7.24. Found: C, 56.84; H, 7.68; N, 6.51; S, 7.45.

4.5.2. Ethyl 2-((3R,5R)-5-((6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-3-phenylisoxazolidin-2-yl)acetate ***3b***

Eluent: hexane/EtOAc, 9:1. (0.291g, 61%); oil; $[\alpha]_D^{25}$ -35 (c 0.75 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 3H), 1.15 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz), 1.36-1.44 (m, 2H), 1.89-1.93 (m, 3H), 2.10 (dd, 1H, J = 13.8, 7.9 Hz), 2.18-2.24 (m, 1H), 2.80-2.84 (m, 2H), 3.45 (q, 2H, J = 13.8 Hz), 3.56 (d, 1H, J = 16.5

Hz), 3.78 (d, 1H, J = 16.5 Hz), 3.92 (dd, 1H, J = 7.9, 5.0 Hz), 4.08-4.18 (m, 3H), 5.31 (t, 1H), 7.28-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14-1, 19.9, 20.8, 26.4, 32.9, 38.4, 44.6, 47.8, 49.0, 532.9, 57.9, 60.8, 65.6, 69.2, 75.9, 127.8, 128.2, 128.7, 136.9, 169.1, 170.8. Anal. Calcd for $C_{24}H_{32}N_2O_6S$: C, 60.48; H, 6.77; N, 5.88; S, 6.73. Found: C, 60.52; H, 6.84; N, 5.72; S, 6.90.

*4.5.3. Ethyl 2-((3R,5R)-5-((6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo[c]isothiazole-1-carbonyl)-3-(furan-2-yl)isoxazolidin-2-yl)acetate **3c***

Eluent: hexane/EtOAc, 9:1. (0.373 g, 80%); oil; $[\alpha]_D^{25}$ -31 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 3H), 1.15 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.33-1.42 (m, 2H), 1.85-1.97 (m, 3H), 2.04-2.11 (m, 1H,), 2.15-2.21 (m, 1H), 2.73-2.83 (m, 1H), 2.97-3.05 (m, 1H), 3.47 (q, 2H, J = 13.7 Hz), 3.68- 3.77 (m, 1H), 3.91 (dd, 1H, J = 7.7, 5.0 Hz), 4.17 (q, 1H, J = 7.1 Hz), 4.32-4.36 (m, 1H), 5.29 (dd, 1H, J = 8.7, 4.8 Hz), 6.31-6.34 (m, 2H), 7.38-7.39 (m, 1H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.9, 20.8, 26.5, 29.7, 32.9, 38.3, 44.7, 47.9, 48.9, 53.0, 60.9, 65.5, 76.0, 108.8, 110.4, 142.8, 149.9, 168.7, 170.7. Anal. Calcd for $C_{22}H_{30}N_2O_7S$: C, 56.64; H, 6.48; N, 6.00; S, 6.87. Found: C, 56.73; H, 6.52; N, 5.84; S, 6.99.

*4.5.4. Ethyl 2-((3R,5R)-3-((benzyloxy)methyl)-5-((6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-methanobenzo-[c]isothiazole-1-carbonyl)isoxazolidin-2-yl)acetate **3d***

Eluent: hexane/EtOAc, 7:3. (0.417 g, 80%); oil; $[\alpha]_D^{25}$ -52 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (s, 3H), 1.13 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 1.34-1.43 (m, 2H), 1.87-1.92 (m, 3H), 1.98-2.09 (m, 1H), 2.13-2.19 (m, 1H), 2.54-2.58 (m, 2H), 3.39-3.51 (m, 3H), 3.53-3.63 (m, 2H), 3.85-3.97 (m, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.52 (q, 2H), 5.10 (t, 1H), 7.26-7.36 (m, 5H0; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.8, 20.8, 26.4, 32.9, 36.4, 38.3, 44.6, 47.8, 48.9, 52.9, 59.9, 60.7, 64.7, 65.4, 70.8, 73.3, 76.2, 127.6, 127.7, 128.4, 137.8, 169.3, 171.0. Anal. Calcd for $C_{26}H_{36}N_2O_7S$: C, 59.98; H, 6.97; N, 5.38; S, 6.16. Found: C, 60.12; H, 6.77; N, 5.48; S, 6.33.

*4.5.5. Ethyl 2-((3R,5R)-3-(((tert-butoxycarbonyl)amino)methyl)-5-((6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-3H-3a,6-meth-anobenzo[c]isothiazole-1-carbonyl)isoxazolidin-2-yl)acetate **3e***

Eluent: hexane/EtOAc, 3:2. (0.444 g, 75%); oil; $[\alpha]_D^{25}$ -73 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (s, 3H), 1.13 (s, 3H),1.27 (t, 3H, J = 6.9 Hz), 1.33-1.40 (m, 2H), 1.42 (s, 9H), 1.87-1.92 (m, 3H), 2.02-2.12 (m, 2H), 2.43-2.49 (m, 1H), 2.65 (dt, 1H, J = 7.1, 13.7 Hz), 3.08-3.15 (m, 1H), 3.19-3.25 (m, 1H), 3.41 (d, 1H, J = 13.8 Hz), 3.44-3.47 (m, 1H), 3.50 (d, 1H, J = 13.8 Hz) 3.56 (d, 1H, J = 16.5 Hz), 3.88 (dd, 1H), 3.96 (d, 1H, J = 16.5 Hz), 4.20 (q, 2H, J = 6.9 Hz), 5.05 (dd, 1H, J = 7.1, 8.0 Hz), 5.20 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.9, 20.9, 26.4, 28.4, 32.9, 38.2, 40.1, 42.2, 44.7, 47.8, 48.9, 52.9, 59.5, 60.9, 71.5, 77.5, 79.4, 85.5, 156.6, 168.9, 171.1. Anal. Calcd for $C_{24}H_{39}N_3O_8S$: C, 54.43; H, 7.42; N, 7.93; S, 6.05. Found: C, 54.49; H, 7.52; N, 7.96; S, 6.19.

*4.5.6. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxopropan-2-yl)-3-isopropylisoxazolidine-5-carboxylate **3f***

Eluent: hexane/EtOAc, 9:1. (0.109 g, 40%); oil; $[\alpha]_D^{25}$ -21 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.7 Hz) 1.27 (t, 3H, J = 7.1 Hz), 1.48 (d, 3H, J = 6.6 Hz), 1.70 (qd, 1H, J = 13.7, 6.8 Hz), 2.47 (ddd, 2H, J = 8.5, 4.7 Hz), 3.05 (ddd, 1H, J = 7.2, 6.8 Hz), 3.61 (q, 1H, J = 6.6 Hz), 3.65 (s, 3H), 4.17 (q, 2H, J = 7.1Hz), 4.48 (t, 1H, J = 8.5 Hz);; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 16.0, 18.7, 20.1, 30.8, 33.9, 52.2, 60.8, 64.5, 70.1, 77.2, 172.3, 172.9. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12;. Found: C, 57.28; H, 8.36; N, 5.27.

*4.5.7. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxopropan-2-yl)-3-phenylisoxazolidine-5-carboxylate **3g***

Eluent: hexane/EtOAc, 9:1. (0.209 g, 68%); oil; $[\alpha]_D^{25}$ +11 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, 3H), 1.34 (d, 3H, J = 6.7 Hz), 2.63 (ddd, 1H, J = 12.7, 8.9, 7.0 Hz), 2.74 (ddd, 1H, J = 12.7, 7.2, 5.6 Hz), 3.63 (q, 1H, J = 6.7 Hz), 3.71 (s, 3H), 3.82-3.91 (m, 2H), 4.25 (t, 1H, J = 7.1 Hz), 4.61 (dd, 1H, J = 8.9, 5.6 Hz), 7.21-7.27 (m, 3H), 7.32-7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 14.4, 42.5, 52.4, 60.8, 63.1, 66.4, 75.2, 127.6, 127.9, 128.6, 138.9, 171.7, 172.1. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.47; H, 6.79; N, 4.63.

*4.5.8. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxopropan-2-yl)-3-(furan-2-yl)isoxazolidine-5-carboxylate **3h***

Eluent: hexane/EtOAc, 9:1. (0.184 g, 62%); oil; $[\alpha]_D^{25}$ -2 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3H), 1.44 (d, 3H, J = 6.7 Hz), 2.74-2.80 (m, 2H), 2.89 (ddd, 1H, J = 13.5, 8.8, 4.8 Hz), 3.57-3.60 (m, 1H), 3.78 (s, 3H), 4.11 (q, 2H), 4.50 (dd, 1H, J = 7.4, 4.9 Hz), 4.74 (dd, 1H, J = 8.6, 6.8 Hz), 6.28 (d, 1H), 6.32-6.33 (m, 1H), 7.38-7.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 15.3, 38.7, 51.9, 52.4, 60.9, 74.8, 75.1, 108.5, 110.3, 142.5, 151.2, 171.8, 171.9.. Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.72; H, 6.39; N, 4.90.

*4.5.9. Methyl (3R,5R)-3-((benzyloxy)methyl)-2-((S)-1-ethoxy-1-oxopropan-2-yl)isoxazolidine-5-carboxylate **3i***

Eluent: hexane/EtOAc, 5:1. (0.169 g, 48%); oil; $[\alpha]_D^{25}$ -23 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H), 1.48 (d, 3H, J= 6.7 Hz), 2.51 (ddd, 1H, J = 12.4, 7.5 Hz), 2.62 (ddd, 1H, J = 12.4, 8.6 Hz), 3.39 (dd, 1H, J= 9.0, 7.2 Hz), 3.58-3.66 (m, 2H), 3.73-3.76(m, 4H), 4.12-4.24 (m, 2H), 4.49-4.56 (m, 3H), 7.28-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 16.4, 35.6, 52.2, 60.6, 61.0, 63.7, 71.2, 73.3, 75.9, 127.6, 128.3, 128.7, 130.7, 137.7, 171.5, 172.1. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.48; H, 6.95; N, 4.13.

*4.5.10. Methyl (3R,5R)-3-(((tert-butoxycarbonyl)amino)methyl)-2-((S)-1-ethoxy-1-oxopropan-2-yl)isoxazolidine-5-carboxylate **3j***

Eluent: hexane/EtOAc, 95:5. (0.130 g, 36%); oil; $[\alpha]_D^{25}$ -21 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H, J = 7.1 Hz), 1.41 (s, 9H), 1.49 (d, 3H, J = 6.6 Hz), 2.34 (ddd, 1H, J = 13.1, 8.9 Hz), 2.58 (ddd, 1H, J = 13.1, 7.8 Hz), 2.97-3.03 (m, 1H) 3.18-3.24 (m, 1H), 3.43-3.49 (m, 1H), 3.60 (q, 1H, J = 6.6 Hz), 3.74 (s, 3H) 4.18 (q, 2H, J = 7.1 Hz), 4.52 (t, 1H, J = 8.5 Hz) 5.23 (bs, 1H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 16.6, 28.4, 29.7, 35-0, 43.0, 52.4, 61.1, 63.9, 64.3, 77.3, 81.5, 158.2, 172.1, 172.5. Anal. Calcd for $C_{16}H_{28}N_2O_7$: C, 53.32; H, 7.83; N, 7.77. Found: C, 53.48; H, 7.91; N, 7.85.

*4.5.11. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)-3-isopropylisoxazolidine-5-carboxylate **3k***

Eluent: hexane/EtOAc, 4:1. (0.175 g, 50%); oil; $[\alpha]_D^{25}$ -15 (c 0.75 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (d, 3H, J = 6.7 Hz), 0.98 (d, 3H, J = 6.7 Hz) 1.06 (t, 3H, J = 7.1Hz), 1.68 (dt, 1H, J = 13.6, 6.8 Hz), 2.49-2.56 (m, 2H), 2.98-3.02 (m, 1H), 3.08 (dd, 1H, J = 13.1, 10.6 Hz), 3.58 (dd, 1H, J = 13.1, 4.3 Hz), 3.80 (s, 3H), 3.85 (q, 1H, J = 10.6, 4.3 Hz), 3.98 (q, 1H, J = 7.1 Hz), 4.56 (t, 1H, J = 8.4 Hz), 7.16-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 18.9, 19.8, 30.5, 34.0, 36.9, 52.2, 60.5, 70.4, 71.9, 77.4, 126.2, 128.1, 129.2, 137.2, 170.4, 172.9. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.22; H, 7.68; N, 4.26.

4.5.12. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)-3-phenylisoxazolidine-5-carboxylate ***3l***

Eluent: hexane/EtOAc, 9:1. (0.280 g, 73%); oil; $[\alpha]_D^{25}$ +36 (c 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H), 2.73 (ddd, 1H, J = 13.0, 8.7, 6.5 Hz), 2.85 (ddd, 1H, J = 13.0, 7.2, 5.9 Hz), 3.05 (dd, 1H, J = 13.3, 10.5 Hz), 3.37 (dd, 1H, J = 13.3, 4.3 Hz), 3.74-3.78 (m, 2H), 3.82 (s, 3H), 3.92 (dd, 1H, J = 10.5, 4.3 Hz), 4.40 (t, 1H), 4.70 (dd, 1H, J = 8.7, 5.9 Hz), 7.13-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 36.2, 42.6, 52.4, 60.6, 66.6, 70.9, 75.9, 126.5, 127.5, 127.8, 128.3, 128.5, 129.3, 137.2, 138.9, 170.2, 172.1. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.02; H, 6.47; N, 3.56.

4.5.13. Methyl (3R,5R)-2-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)-3-(furan-2-yl)isoxazolidine-5-carboxylate ***3m***

Eluent: hexane/EtOAc, 9:1. (0.258 g, 69%); oil; $[\alpha]_D^{25}$ +2 (c 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, 3H, J = 7.1 Hz), 2.80 (ddd, 1H, J =13.1, 7.5, 7.0 Hz), 2.91 (ddd, 1H, J = 13.1, 8.7, 4.6 Hz), 3.05 (dd, 1H, J = 13.1, 10.8 Hz), 3.34 (dd, 1H, J = 13.1, 4.2 Hz), 3.73-3.76 (m, 1H), 3.81 (s, 3H), 3.93 (q, 1H, J = 7.1 Hz), 4.58 (dd, 1H, J = 7.5, 4.6 Hz), 4.77 (dd, 1H, J = 8.7, 7.0 Hz), 6.29 (d, 1H, J = 3.2 Hz), 6.34 (dd, 1H, J = 1.9 Hz, J = 3.2 Hz), 7.13-7.24 (m, 5H), 7.41-7.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 36.6, 38.2, 52.4, 60.1, 60.7, 70.3, 75.9, 108.6, 110.5, 126.5, 128.2, 129.1, 136.9, 142.8, 151.3, 170.5, 172.0. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.29; H, 6.18; N, 3.90.

4.5.14. Methyl (3R,5R)-3-((benzyloxy)methyl)-2-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)isoxazolidine-5-carboxylate ***3n***

Eluent: hexane/EtOAc, 7:3. (0.197 g, 46%); oil; $[\alpha]_D^{25}$ +9 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, 3H), 2.49 (ddd, 1H, J = 12.8, 7.7 Hz), 2.61 (ddd, 1H, J = 12.8, 8.7 Hz), 2.99 (dd, 1H, J = 13.2, 10.5 Hz), 3.31 (dd, 1H, J = 9.4, 7.8 Hz),3.45 (dd, 1H, J = 13.2, 4.3 Hz), 3.51 (dd, 1H, J = 9.4, 5.5 Hz) 3.59 (ddd, 1H, J = 7.8, 5.5 Hz), 3.73 (s, 3H), 3.83-3.94 (m, 3H), 4.46 (d, 2H), 4.51 (t, 1H), 7.10, 7.29 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 34.9, 36.8, 52.4, 60.8, 63.3, 70.8, 71.1, 73.4, 76.7, 126.5, 127.7, 128.2, 128.4, 129.4, 137.1, 137.9, 170.6, 172.6. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.36; H, 6.94; N, 3.11.

4.5.15. Methyl (3R,5R)-3-(((tert-butoxycarbonyl)amino)methyl)-2-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)isoxazolidine-5-carboxylate ***3o***

Eluent: hexane/EtOAc, 9:1. (0.201 g, 46%); oil; $[\alpha]_D^{25}$ -7 (c 0.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 2.42 (ddd, 1H, J = 13.2, 9.0 Hz), 2.64 (ddd, 1H, J = 13.2, 7.8 Hz), 2.96-3.02 (m, 1H), 3.07 (dd, 1H, J = 13.3 10.3 Hz), 3.23-3.29 (m, 1H), 3.45-3.49 (m, 1H), 3.57 (dd, 1H, J = 13.3, 4.3 Hz), 3.81 (s, 3H), 3.83 (dd, 1H, J = 10.3, 4.3 Hz), 3.97 (q, 2H, J = 7.1 Hz), 4.61 (t, 1H, J = 8.5 Hz), 5.15 (bs, 1H), 7.18-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 28.1, 37.1, 42.6, 52.3, 60.6, 64.1, 71.0, 77.3, 78.6, 126.3, 128.0, 129.1, 136.7, 155.5, 170.1, 172.8. Anal. Calcd for $C_{22}H_{32}N_2O_7$: C, 60.54; H, 7.39; N, 6.42. Found: C, 60.67; H, 7.26; N, 6.51.

4.6. General Procedure for the Synthesis of 3-hydroxypyrrolidin-2-ones ***10***

A solution of cycloadduct (0.75 mmol) in ethanol (12 mL) is treated with $Pd(OH)_2$-C (28 mg, 0.19 mmol) and stirred at ambient temperature for 48 h under a pressure of 100 atm of hydrogen. The reaction mixture is filtered and the solvent evaporated to afford the crude product which was purified by column chromatography.

4.6.1. ethyl 2-((3R,5R)-5-(((tert-butoxycarbonyl)amino)methyl)-3-hydroxy-2-oxopyrrolidin-1-yl)acetate ***10a***

Eluent: EtOAc. (0.220 g, 93%); oil; $[\alpha]_D^{25}$ +59 (c 0.9 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H, J = 7.0 Hz), 1.42 (s, 9H),1.77 (dt, 1H, J = 7.2, 13.4 Hz), 2.52 (ddd, 1H, J = 7.2, 8.5, 13.4 Hz), 3.30-3.41 (m, 2H), 3.77-3.83 (m, 1H), 3.98 (m, 1H), 4.16-4.22 (m, 2H), 4.37 (q, 2H, J = 7.0 Hz), 5.27 (bs, 2H, ex. D_2O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 28.4, 30.8, 41.1, 42.6, 55.2, 61.7, 68.9, 79.8, 156.2, 168.8, 175.9 Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.09; H, 7.51; N, 8.96.

4.6.2. Ethyl (S)-2-((3R,5R)-3-hydroxy-5-isopropyl-2-oxopyrrolidin-1-yl)-3-phenylpropanoate ***10b***

Eluent: hexane/EtOAc, 4:1. (0.228 g, 95%); oil; $[\alpha]_D^{25}$ +10 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.7 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.33 (d, 3H, J=7.0 Hz), 1.75-1.89 (m, 3H), 2.51 (ddd, 1H, J = 7.4, 6.1 Hz), 3.45 (q, 1H, J = 7.0 Hz), 4.18 (q, 1H, J = 7.2 Hz), 4.53 (dd, 1H, J = 7.4, 3.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 17.0, 19.5, 19.9, 29.0, 30.9, 54.2, 60.9, 61.0, 70.2, 174.8, 175.2. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.49; H, 7.74; N, 4.50.

4.6.3. Ethyl (S)-2-((3R,5R)-3-hydroxy-5-isopropyl-2-oxopyrrolidin-1-yl)propanoate ***10c***

Eluent: hexane/EtOAc, 4:1. (0.173 g, 95%); oil; $[\alpha]_D^{25}$ -2 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.7 Hz), 1.11 (t, 3H, J = 7.1 Hz), 1.69-1.83 (m, 3H), 2.48 (ddd, 1H, J = 7.4, 6.1, 3.0 Hz), 2.89 (dd, 1H, J = 13.4, 7.7 Hz), 3.02 (dd, 1H, J = 13.4, 6.0 Hz), 3.61 (dd, 1H, J = 7.7, 6.0 Hz), 4.04 (q, 2H, J = 7.1 Hz), 4.43 (dd, 1H, J = 8.0, 3.4 Hz), 7.14-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 17.0, 19.8, 29.5, 31.4, 40.6, 60.8, 61.1, 61.4, 69.7, 126.7, 128.3, 129.2, 136.6, 174.5, 174.9. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.37; H, 8.58; N, 5.83

4.7. General Procedure for the Synthesis of Mosher Esters ***11*** *and* ***12***

To a solution of the pyrrolidin-2-one (0.5 mmol) in anhydrous dichloromethane (15 mL), the corresponding Mosher acid (1.24 mmol), DCC (0.309 g, 1.5 mmol) and DMAP (12 mg, 0.1 mmol) are sequentially added. The resulting mixture is stirred at ambient temperature for 12 h at which time the solvent is eliminated under reduced pressure. The crude product is purified by column chromatography to provide the pure Mosher ester.

4.7.1. (3R,5R)-5-(((tert-butoxycarbonyl)amino)methyl)-1-(2-ethoxy-2-oxoethyl)-2-oxopyrrolidin-3-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***11a***

Eluent: hexane/EtOAc, 7:3. (0.186 g, 70%); oil; $[\alpha]_D^{25}$ +22 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H), 1.38 (s ,9H), 2.33-2.36 (m, 1H), 2.63 (ddd, 1H, J= 13.8, 8.8, 7.3 Hz), 3.15-3.19 (m, 1H), 3.30-3.35 (m, 1H), 3.64 (s, 3H), 3.82-3.87 (m, 1H), 4.04 (d, 1H), 4.17 (d, 1H), 4.18-4.23 (m, 2H), 4.82 (bs, 1H), 5.66 (dd, 1H, J = 8.8, 7.2 Hz), 7.40-7.42 (m, 3H), 7.59-7.61 (m, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 28.0, 28.4, 29.8, 41.5, 43.3, 55.4, 55.9, 61.9, 71.2, 80.2, 83.2, 121.6, 124.5, 127.3, 128.7, 129.7, 131.4, 156.3, 165.9, 168.6, 170.2. Anal. Calcd for $C_{24}H_{31}F_3N_2O_8$: C, 54.13; H, 5.87; F, 10.70; N, 5.26. Found: C, 54.34; H, 5.69; N, 5.36.

4.7.2. (3R,5R)-1-((S)-1-ethoxy-1-oxopropan-2-yl)-5-isopropyl-2-oxopyrrolidin-3-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***11b***

Eluent: hexane/EtOAc, 7:3. (0.156 g, 68%); oil; $[\alpha]_D^{25}$ +32 (c 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, 3H, J = 6.7 Hz), 0.86 (d, 3H, J = 6.9 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.43 (d, 3H, J = 7.2 Hz), 1.67 (ddd, 1H, J = 13.9, 6.4 Hz), 2.05 (dtd, 1H, J = 6.9, 6.7, 3.4 Hz), 2.44 (ddd, 1H, J = 13.9, 9.4, 7.6 Hz), 3.62 (s, 3H), 3.66 (ddd, 1H, J = 7.6, 6.4, 3.4 Hz), 4.16- 4.27 (m, 3H), 5.59 (dd, 1H, J = 9.4, 6.4 Hz), 7.39-7.41 (m, 3H), 7.58-7.61 (m, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 13.9, 14.6, 18.7, 24.8, 28.2, 50.9, 55.7, 59.9, 61.5, 71.1, 124.6, 127.3, 128.4, 129.6, 132.0, 165.9, 169.4, 170.0. Anal. Calcd for $C_{22}H_{28}F_3NO_6$: C, 57.51; H, 6.14; F, 12.40; N, 3.05. Found: C, 57.78; H, 5.95; N, 3.19.

4.7.3. (3R,5R)-1-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)-5-isopropyl-2-oxopyrrolidin-3-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***11c***

Eluent: hexane/EtOAc, 7:3. (0.193 g, 72%); oil; $[\alpha]_D^{25}$ -36 (c 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.62 (d, 3H, J = 6.9 Hz), 0.66 (d, 3H, J= 6.7 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.50 (ddd, 1H, J = 13.7, 6.4 Hz), 1.83 (dtd, 1H, J = 6.8, 6.7, 3.5 Hz), 2.04 (ddd, 1H, J = 13.7, 9.2, 7.5 Hz), 2.36 (ddd, 1H, J = 7.5, 6.4, 3.5 Hz), 3.33-3.42 (m, 2H), 3.63 (s, 3H),3.97 (dd, 1H, J = 10.1, 5.8 Hz), 4.15-4.26 (m, 2H), 5.49 (dd, 1H, J = 9.2, 6.4 Hz), 7.17-7.19 (m, 2H), 7.27-7.33 (m, 3H), 7.38-7.40 (m, 3H), 7.58- 7.61 (m, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 13.9, 18.6, 25.1, 27.7, 34.2, 55.7, 57.5, 61.6, 61.8, 71.0, 127.0, 127.3, 128.4, 128.7, 129.0, 129.6, 132.0, 137.7, 166.0, 168.9, 169.1. Anal. Calcd for $C_{28}H_{32}F_3NO_6$: C, 62.80; H, 6.02; F, 10.64; N, 2.62. Found: C, 62.99; H, 5.92; N, 2.75.

4.7.4. (3R,5R)-5-(((tert-butoxycarbonyl)amino)methyl)-1-(2-ethoxy-2-oxoethyl)-2-oxopyrrolidin-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***12a***

Eluent: hexane/EtOAc, 7:3. (0.186 g, 70%); oil; $[\alpha]_D^{25}$ +24 (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H), 1.42 (s, 9H), 1.94 (ddd, 1H, J = 13.8, 7.7 Hz), 2.67 (ddd, 1H, J= 13.6, 9.0, 7.3 Hz), 3.25-3.29 (m, 1H), 3.42-3.48 (m, 1H), 3.54 (s, 3H), 3.84-3.89 (m, 1H), 4.02 (d, 1H), 4.12-4.23 (m, 3H), 5.10 (bs, 1H), 5.56 (dd, 1H, J = 9.0, 8.2 Hz), 7.40-7.42 (m, 3H), 7.58-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 28.0, 28.2, 29.7, 41.2, 43.1, 55.1, 55.5, 61.8, 71.6, 80.0, 121.6, 124.5, 127.7, 128.4, 129.7, 131.4, 156.3, 165.9, 168.6, 170.2. Anal. Calcd for $C_{24}H_{31}F_3N_2O_8$: C, 54.13; H, 5.87; F, 10.70; N, 5.26. Found: C, 54.35; H, 5.96; N, 5.07.

4.7.5. (3R,5R)-1-((S)-1-ethoxy-1-oxopropan-2-yl)-5-isopropyl-2-oxopyrrolidin-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***12b***

Eluent: hexane/EtOAc, 7:3. (0.159 g, 69%); oil; $[\alpha]_D^{25}$ -4 (c 0.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, 3H, J = 6.7 Hz), 0.93 (d, 3H, J = 6.9 Hz),1.20 (t, 3H, J = 7.1 Hz), 1.43 (d, 3H, J = 7.1 Hz), 1.86 (ddd, 1H, J = 13.8, 7.0 Hz), 2.12 (dtd, 1H, J = 6.9, 6.7, 3.4 Hz), 2.49 (ddd, 1H, J = 13.8, 9.4 Hz), 3.52 (s, 3H), 3.69 (ddd, 1H, J = 7.1, 3.5 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.26 (q, 1H, J = 7.1 Hz), 5.53 (dd, 1H, J = 9.4, 7.0 Hz), 7.39-7.41 (m, 3H), 7.58-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 13.9, 14.6, 18.7, 24.9, 28.2, 50.9, 55.4, 59.7, 61.5, 71.4, 124.5, 127.8, 128.4, 129.7, 131.4, 165.8, 169.4, 170.0. Anal. Calcd for $C_{22}H_{28}F_3NO_6$: C, 57.51; H, 6.14; F, 12.40; N, 3.05. Found: C, 57.69; H, 5.98; N, 3.16.

4.7.6. (3R,5R)-1-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)-5-isopropyl-2-oxopyrrolidin-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ***12c***

Eluent: hexane/EtOAc, 7:3. (0.193 g, 72%); oil; $[\alpha]_D^{25}$ -74 (c 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (d, 3H, J = 6.9 Hz),0.82 (d, 3H, J= 6.7 Hz), 1.18 (t, 3H, J = 7.2 Hz), 1.68 (ddd, 1H, J = 13.7, 7.0 Hz), 1.89 (dtd, 1H, J = 6.9, 6.7, 3.4 Hz), 2.11 (ddd, 1H, J = 13.7,9.3 Hz), 2.37 (ddd, 1H, J = 7.0, 3.4 Hz), 3.31-3.41 (m, 2H), 3.52 (s, 3H), 3.98 (dd, 1H, J = 9.7, 6.3 Hz), 4.12-4.24 (m, 2H), 5.49 (dd, 1H, J = 9.3, 7.0 Hz), 7.17-7.19 (m, 2H), 7.27-7.33 (m, 3H), 7.40-7.41 (m, 3H), 7.58- 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 18.6, 25.2, 27.7, 34.2, 55.4, 57.4, 61.4, 61.6, 71.4, 127.0, 127.8, 128.4, 128.7, 129.0, 129.6, 131.4, 137.7, 165.9, 168.9, 169.1. Anal. Calcd for $C_{28}H_{32}F_3NO_6$: C, 62.80; H, 6.02; F, 10.64; N, 2.62. Found: C, 62.97; H, 5.95; N, 2.69.

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