Nucleophilic Addition of Nitrones to Ketones: Development of a New Catalytic Asymmetric Nitrone-Aldol Reaction

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Abstract: A new organic reaction has been discovered in which nitrones react with carbonyl compounds in an aldol-type reaction to give functionalized β-hydroxynitrones. The α-carbon atom of the nitrone undergoes a nucleophilic addition reaction to electron-deficient ketones, such as α-ketoesters, α,β-diketones, and trifluoromethyl ketones, to afford the products in moderate to good yields. The scope and potential of the reaction have been investigated and developed. The reaction can also be catalyzed by secondary amines. The use of chiral cyclic amines, such as L-proline leads to optically active β-hydroxynitrones in moderate yield and with moderate to high enantiomeric excess. The reaction mechanism was studied by kinetic measurements, intermediate and product analysis, and determination of the absolute configuration of the product; based on these investigations a mechanism for the new reaction is proposed.

Keywords: aldol reaction • amines • asymmetric catalysis • enantioselectivity • nitrones

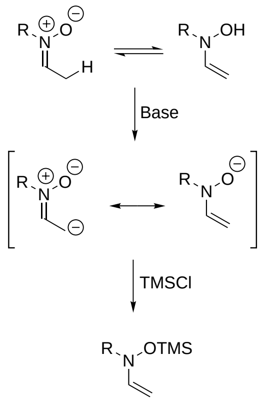
Introduction

Nitrones are important compounds in organic synthesis and they are known to undergo two fundamental reactions: 1,3-dipolar cycloaddition reactions with alkenes and addition of nucleophiles. The 1,3-dipolar cycloaddition reaction is probably the most important of these, and the isoxazolidine products have been widely used for the preparation of a variety of different highly functionalized molecules.[1] This reaction has recently been intensively investigated due to the interest in developing catalytic asymmetric 1,3-dipolar cycloadditions of nitrones.[2] The nucleophilic addition to nitrones is the other important reaction of this class of dipoles and this approach has mainly been used for the formation of new C–C bonds.[3]

In the present paper, we report a new fundamental reaction of nitrones. In this new C–C bond forming process, the nitrone acts as a nucleophile that adds to electrophiles such as carbonyl compounds.

Nitrones with an α-proton can be in equilibrium with the N-hydroxylenamine tautomer as outlined in Scheme 1. This nitrone–*N*-hydroxylenamine tautomerism is analogous to keto–enol and imine–enamine tautomerism. The formation of the *N*-hydroxylenamine from the nitrone can be initiated by deprotonation by a base as shown in Scheme 1. The formation of the *N*-hydroxylenamine from the nitrone thus generates a nucleophilic carbon atom, which may add to carbonyl compounds, for example. This reaction can be considered as the nitrone analogue of the aldol reaction, that is, a nitrone-aldol reaction.

Previous investigations of the nucleophilicity of nitrones are very limited. It has been shown that the *N*-hydroxylenamine tautomer of nitrones can be trapped by silylation of the nitrone oxygen atom to give the *O*-TMS-hydroxylenamine (Scheme 1).[4] However, the reactivity of this species was not studied. Others have studied the mechanism of the dimerization of *C*-alkyl nitrones,[5] and they proposed the *N*-hydroxylenamine as a key intermediate in this reaction. In two independent studies it was shown that at elevated temperature and under very harsh reaction conditions, nitrones undergo condensation with benzaldehyde to give an α,β-unsaturated nitrone.[6]



Scheme 1. Nitrone-hydroxylenamine tautomers and silylation of the nitronate.

This paper presents a new reaction of nitrones **1** with ketones **2** in which β-hydroxynitrones **3** are formed (Scheme 2). The development of the new nitrone-aldol-type reaction will be discussed in detail. These studies include the basis for the reaction, its scope and mechanism, and finally the development of an enantioselective organo-catalyzed reaction leading to optically active β-hydroxynitrones with moderate to high enantiomeric excess.

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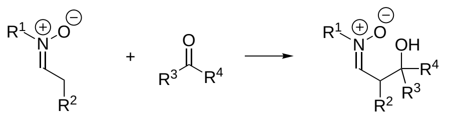
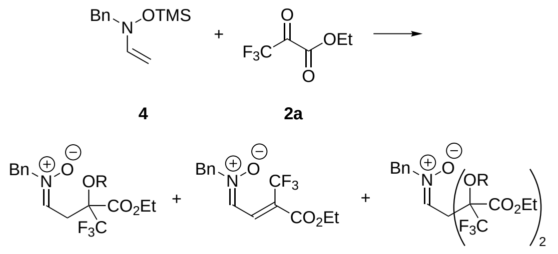


1 **2** **3**

Scheme 2. Nucleophilic addition of nitrones to ketones: the nitrone-aldol reaction.

Results and Discussion

The present work was initiated by investigations of the reaction of protected *N*-hydroxylenamines **4** with ethyl 1,1,1-trifluoropyruvate (**2a**) (Scheme 3). When different protected *N*-hydroxylenamines **4** reacted with aldehydes and ketones the expected TMS-protected product **3′** was formed in low conversion in a mixture with alcohol **3**. In several cases, the elimination product **5** and the double addition product **6** were also isolated. The formation of the latter compound probably takes place by a nucleophilic reaction of the α-carbon atom in **3** with a second equivalent of **2a** to form a new C–C bond.



4 **2a**

3 : R = H
3': R = TMS

5 **6**

Scheme 3. Reaction of the TMS-protected hydroxylenamine **4** with ketone **2a**.

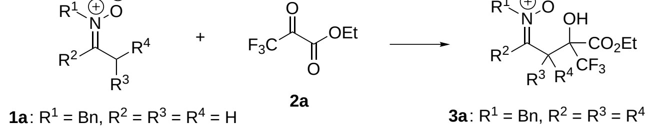
This observation led us to explore the possibility of performing the direct addition of nitrones to carbonyl compounds, since it has been proposed that the dimerization of nitrones with an aliphatic α-C–H proceeds through spontaneous enolization of nitrones.[5] It turned out that the *N*-benzyl-*C*-methylnitrone (**1a**) reacts with activated carbonyl compounds such as ethyl 1,1,1-trifluoropyruvate (**2a**) by a direct nucleophilic reaction to give the addition product **3a** in good yield (Scheme 4). Various reaction conditions were tested and it was found that a fast, but less selective reaction took place in THF compared to the reaction performed in CH_2Cl_2 in which product **3a** was formed in good yield. The reaction between nitrones with an α-proton and **2a** turned out to be general and Table 1 shows the results for the direct nitrone-aldol reaction of various nitrones **1a**–**h** with **2a**.

Table 1. Nitrone-aldol reactions of nitrones **1a**–**h** with ethyl 1,1,1-trifluoropyruvate (**2a**) in CH_2Cl_2 at room temperature.

Entry	Nitrone	Equiv **2a**	Reaction time [h]	Product	Yield [%][a]
1	**1a**	1	24	**3a**	63
2	**1a**	3	15	**3a**	70[b]
3	**1b**	1	22	**3b**	40
4	**1c**	3	96	**3c**	86[c]
5	**1d**	2	120	**3d**	71[c]
6	**1e**	3	> 120	**3e**	< 5
7	**1f**	2	22	**3f**	31
8	**1g**	1.2	72	**3g**	34[d]
9	**1h**	1.2	120	**3h**	< 5

[a] Isolated yield. [b] The double addition product was isolated in 5 % yield after the addition of a second equivalent of **2a**. [c] Diastereomeric ratio 3:2. [d] Diastereomeric ratio 4:1.

N-Benzyl-*C*-methylnitrone (**1a**) and *N*-*tert*-butyl-*C*-methylnitrone (**1b**), both with the α-proton on a primary carbon atom, react with ethyl 1,1,1-trifluoropyruvate (**2a**) to give **3a** and **3b** in 63 % and 40 % yield, respectively (Table 1, entries 1 and 3). If three equivalents of **2a** are used, the yield of **3a** increases slightly to 70 %; however, in addition to product **3a**, the double addition product similar to **6** (Scheme 3) was also formed in 5 % yield (entry 2). Reactions between **1c** or **1d**, both with the α-proton on a secondary carbon atom, and **2a** proceeded smoothly to afford the 86 and 71 % yield of **3c** and **3d**, respectively. In both cases the products have a diastereomeric ratio of 3:2 (entries 4 and 5). The nitrone **1e**, derived from 2-methyl propionaldehyde, did not react with **2a** (entry 6), which might be explained by the fact that the α-proton is attached to a tertiary carbon atom making deprotonation more difficult compared to the other nitrones studied. The low reactivity of nitrone **1e** was further supported by a slow deprotonation reaction, as a very slow deuterium exchange of the α-proton was observed when **1e** was mixed with CF_3COOD (15 equiv) in $CDCl_3$. The acetophenone-derived nitrone **1f** reacts with **2a** to give the addition product **3f** in moderate yield (entry 7), and a similar result is obtained for the cyclic nitrone **1g** (entry 8). Thus, nitrones derived from ketones can also be applied in this reaction. The difference in reactivity for the two cyclic nitrones **1g** and **1h** is notable (entries 8 and 9). The ring in **1h** might be too strained to allow the formation of the *N*-hydroxylenamine. The present reaction gives an easy approach to trifluoromethylhydroxy compounds which have found application in various fields.[7]



2a

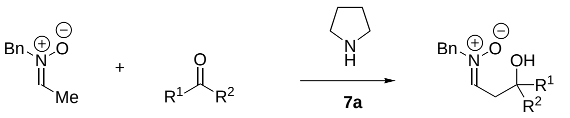
1a: R^1 = Bn, R^2 = R^3 = R^4 = H
1b: R^1 = *t*Bu, R^2 = R^3 = R^4 = H
1c: R^1 = Bn, R^2 = R^3 = H, R^4 = Me
1d: R^1 = Bn, R^2 = R^3 = H, R^4 = Et
1e: R^1 = Bn, R^2 = H, R^3 = R^4 = Me
1f : R^1 = Bn, R^2 = Ph, R^3 = R^4 = H
1g: R^1 = Bn, R^2, R^3 = -$(CH_2)_4$-, R^4 = H
1h: R^1 = Bn, R^2, R^3 = -$(CH_2)_3$-, R^4 = H

3a: R^1 = Bn, R^2 = R^3 = R^4 = H
3b: R^1 = *t*Bu, R^2 = R^3 = R^4 = H
3c: R^1 = Bn, R^2 = R^3 = H, R^4 = Me
3d: R^1 = Bn, R^2 = R^3 = H, R^4 = Et
3e: R^1 = Bn, R^2 = H, R^3 = R^4 = Me
3f : R^1 = Bn, R^2 = Ph, R^3 = R^4 = H
3g: R^1 = Bn, R^2, R^3 = -$(CH_2)_4$-, R^4 = H
3h: R^1 = Bn, R^2, R^3 = -$(CH_2)_3$-, R^4 = H

Scheme 4. Reaction of nitrones **1a**–**h** with ketone **2a**.

To develop a catalytic variant of the present reaction, a series of experiments was performed. Application of Brønsted and Lewis acids as catalysts did not improve the reaction rate significantly, but these reagents often resulted in decomposition of the desired products. However, the presence of a secondary cyclic amine such as pyrrolidine (**7a**) (20 mol%) led to a significant enhancement of the reaction rate. The reaction of *N*-benzyl-*C*-methylnitrone (**1a**) with ethyl 1,1,1-trifluoropyruvate (**2a**) in the presence of **7a** gave product **3a** in high yield after only 4 h, whereas 24 h were required to obtain **3a** in only moderate yield in the absence of **7a** (Table 1, entry 1). Based on ^{1}H NMR spectroscopic experiments, the initial rate of formation of **3a** was estimated to be 6 μM s^{-1} and 18 μM s^{-1} in the absence and presence of **7a**, respectively. Other primary and secondary amines were also tested as catalysts. Isopropyl amine and diisopropyl amine did not increase the reaction rate, and *N*-methyl aniline led to formation of the Friedel–Crafts product by reaction with **2a**.[8]

Pyrrolidine (**7a**) was therefore found to be an effective catalyst for the nucleophilic addition of nitrones to carbonyl compounds (Scheme 5). Furthermore, with this catalyst the reaction could be performed with carbonyl compounds other than the highly activated carbonyl compound ethyl 1,1,1-trifluoropyruvate (**2a**). The results for the reactions of *N*-benzyl-*C*-methylnitrone (**1a**) with a series of different ketones **2a**–**h** catalyzed by **7a** (20 mol%) are shown in Table 2. It should be noted that for substrates other than **2a** no reaction takes place in the absence of catalyst **7a**. The more activated ketones, trifluoroacetophenone (**2b**) and diethyl ketomalonate (**2c**) afforded the fastest reactions in the presence of catalyst **7a**, and gave the addition products (**3i** and **3j**) in 84 and 63% yields, respectively (entries 2 and 3). Slower reactions were obtained for the reactions between **1a** and α-ketoesters **2d** and **2e**, and due to the fact that **1a** undergoes a slow dimerization reaction, the isolated yields of **3k** and **3l** were moderate (entries 4 and 5). Nitrone **1a** reacts with 2,3-butanedione (**2f**) to give **3m** in 45% yield (entry 6), while the reaction with 1-phenyl-1,2-propanedione (**2g**) gives two regioisomers **3n** and **3o** in a total yield of 49% and in a 3:1 ratio (entry 7). 1,9-Decadien-5,6-dione (**2h**) was less reactive and product **3p** could only be obtained in 30% yield after 72 h.



1a

2a: $R^1 = CF_3$, $R^2 = CO_2Et$
2b: $R^1 = CF_3$, $R^2 = Ph$
2c: $R^1 = R^2 = CO_2Et$
2d: $R^1 = CO_2Et$, $R^2 = Ph$
2e: $R^1 = CO_2CH_2CH{=}CH_2$, $R^2 = Ph$
2f: $R^1 = COMe$, $R^2 = Me$
2g: $R^1 = COMe$, $R^2 = Ph$
2h: $R^1 = CO(CH_2)_2CH{=}CH_2$, $R^2 = (CH_2)_2CH{=}CH_2$

3a: $R^1 = CF_3$, $R^2 = CO_2Et$
3i: $R^1 = CF_3$, $R^2 = Ph$
3j: $R^1 = R^2 = CO_2Et$
3k: $R^1 = CO_2Et$, $R^2 = Ph$
3l: $R^1 = CO_2CH_2CH{=}CH_2$, $R^2 = Ph$
3m: $R^1 = COMe$, $R^2 = Me$
3n: $R^1 = COMe$, $R^2 = Ph$
3o: $R^1 = COPh$, $R^2 = Me$
3p: $R^1 = CO(CH_2)_2CH{=}CH_2$, $R^2 = (CH_2)_2CH{=}CH_2$

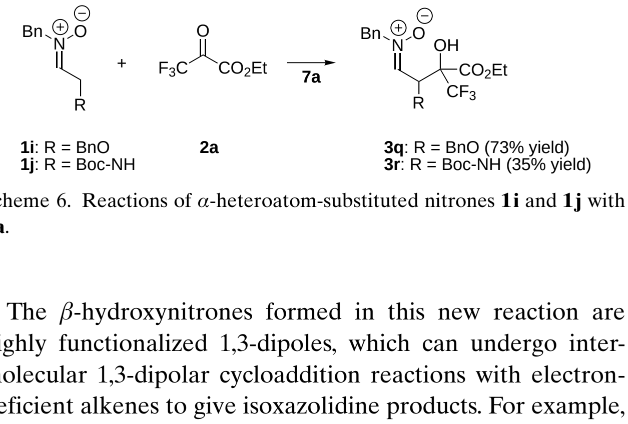
Scheme 5. The pyrrolidine-catalyzed nitrone-aldol reaction.

Table 2. The reaction of *N*-benzyl-*C*-methylnitrone (**1a**) with various carbonyl compounds **2a**–**h** catalyzed by pyrrolidine (**7a**) (20 mol%).

Entry	Ketone [equiv]	Reaction time [h]	Conversion of **2a** [%]	Product	Yield [%][a]
1	**2a** (1.1)	4	>95	**3a**	74
2	**2b** (1.2)	27	>95	**3i**	84
3	**2c** (1.5)	24	>95	**3j**	63
4	**2d** (2.0)	48	>95	**3k**	46
5	**2e** (2.0)	96	90	**3l**	44
6	**2f** (2.0)	48	>95	**3m**	45
7	**2g** (2.0)	48	90	**3n**+**3o**	49[b]
8	**2h** (1.5)	72	70	**3p**	30

[a] Isolated yield. [b] Combined yield of regioisomers; ratio **3n**:**3o** = 3:1.

To expand the scope of the reaction further, we synthesized two heteroatom-substituted nitrones **1i** and **1j** and subjected these to reaction with ethyl 1,1,1-trifluoropyruvate (**2a**) (Scheme 6). The *N*-benzyl nitrone **1i** derived from benzyloxyacetaldehyde[9] undergoes pyrrolidine-catalyzed reaction with **2a** to give the highly functionalized nitrone **3q** in 73% yield and a diastereomeric ratio of 3:2. The *N*-benzyl nitrone **1j** derived from *N*-Boc-aminoacetaldehyde is found to be less reactive, and **3r** is formed in only 35% yield.



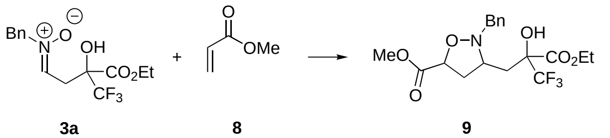
1i: R = BnO
1j: R = Boc-NH

2a

3q: R = BnO (73% yield)
3r: R = Boc-NH (35% yield)

Scheme 6. Reactions of α-heteroatom-substituted nitrones **1i** and **1j** with **2a**.

The β-hydroxynitrones formed in this new reaction are highly functionalized 1,3-dipoles, which can undergo intermolecular 1,3-dipolar cycloaddition reactions with electron-deficient alkenes to give isoxazolidine products. For example, nitrone **3a** reacts with methyl acrylate (**8**) to give the cycloaddition product **9** in 77% yield after 1 h (Scheme 7). The diastereomeric ratio of **9** was found to be 15:9:5:3 corresponding to an *endo*:*exo* selectivity of 5:3, and a facial selectivity of 3:1 for both the *endo* and *exo* isomers.



3a

8

9
(77% yield)

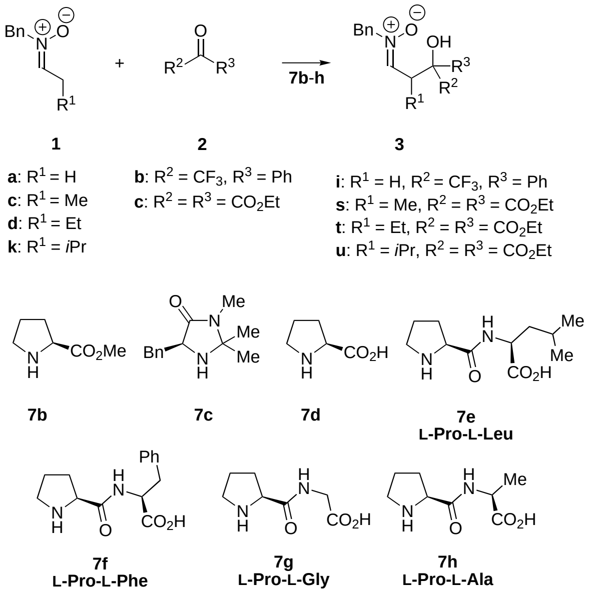
Scheme 7. 1,3-Dipolar cycloaddition reactions of nitrone-aldol adduct **3a** with methyl acrylate (**8**).

It is known that nitrones containing a double bond can undergo intramolecular 1,3-dipolar cycloadditions.[10] This led us to prepare the ketones **2e** and **2h** (Scheme 3),[11] but unfortunately, the desired tandem 1,3-dipolar cycloaddition reaction did not proceed.

The structure of **3b** obtained by reaction of **1b** and **2a** has been determined by X-ray crystallography (Figure 1). The structure of **3b** is stabilized by a hydrogen bond from the proton of the hydroxyl group to the nitrone oxygen atom leading to a seven-membered ring.

The structure of the major diastereomer of the 1,3-dipolar cycloaddition adduct **9** has also been determined (Figure 1). A *trans* relationship between the two substituents on C1 and C3 of the isoxazolidine ring originates from an *endo*-transition state structure in the 1,3-dipolar cycloaddition.

As an extension to the successful use of pyrrolidine (**7a**) as a catalyst for the nitrone-aldol reaction, chiral amines[12] such as **7b** and **7c** were investigated as chiral catalysts for the same reaction (Scheme 8). The catalytic effect of methyl L-prolinate (**7b**) on the reaction of *N*-benzyl-*C*-methylnitrone (**1a**) with ethyl 1,1,1-trifluoropyruvate (**2a**) was found to be similar to **7a** (i.e., a racemic product was obtained), while the sterically more hindered and commonly applied chiral organo-catalyst **7c**[12s] failed to increase the reaction rate. Unfortunately, the two chiral catalysts **7b** and **7c** or their hydrochloride salts induced only sparse enantioselectivity in the reaction.



Scheme 8. Organo-catalyzed asymmetric reactions of nitrones with ketones.

Other chiral organo-catalysts **7d**–**h** have also been tested for the nitrone-aldol reaction in an attempt to obtain optically active products (Scheme 8). The results for the reaction of *N*-benzyl-*C*-methylnitrone (**1a**) with trifluoroacetophenone (**2b**) in the presence of the different catalysts are presented in Table 3 (entries 1–5). It appears that L-proline **7d** and the dipeptide L-Pro-L-Leu (**7e**) are the best chiral catalysts. The optically active nitrone **3i** was obtained in up to 30% *ee* (entries 1 and 2). It turned out that the use of α-substituted nitrones in the presence of catalytic L-proline in reactions with diethyl ketomalonate (**2c**) led to an improvement in enantioselectivity as shown in Table 3. The *N*-benzyl nitrone derived from propionaldehyde (**1c**) reacts with **2c** to give β-hydroxynitrone **3s** in 55% isolated yield and with 76% *ee* (entry 7). The *N*-benzyl nitrones **1d** and **1k** derived from butyraldehyde and isovaleraldehyde also react with **2c** to give the corresponding nitrones in 48 and 15% yield and in 80 and 80% *ee*, respectively (entries 7 and 8). It should be noted that when aldehydes are used in these reactions the initially formed β-hydroxynitrone eliminates water to give the corresponding α,β-unsaturated compound.

Table 3. Catalytic enantioselective nitrone-aldol reaction of various nitrones with activated carbonyl compounds catalyzed by chiral amines **7d**–**h**.

Entry	Nitrone	Ketone	Catalyst[a]	Product	Yield [%][b]	*ee* [%][e]
1[c]	**1a**	**2b**	**7d**	**3i**	50	30
2[d]	**1a**	**2b**	**7e**	**3i**	46	29
3[d]	**1a**	**2b**	**7f**	**3i**	22	9
4[d]	**1a**	**2b**	**7g**	**3i**	86	21
5[d]	**1a**	**2b**	**7h**	**3i**	81	20
6[c]	**1c**	**2c**	**7d**	**3s**	55	76
7[c]	**1d**	**2c**	**7d**	**3t**	48	80
8[c]	**1k**	**2c**	**7d**	**3u**	15	80

[a] It should be noted that the catalysts have limited solubility. [b] Isolated yield. [c] Solvent: CH_2Cl_2. [d] Solvent: DMSO. [e] Enantiomeric excess was measured by HPLC with CHIRALPAC AD or AS columns.

In an attempt to obtain information about the reaction mechanism, a series of kinetic measurements was carried out.

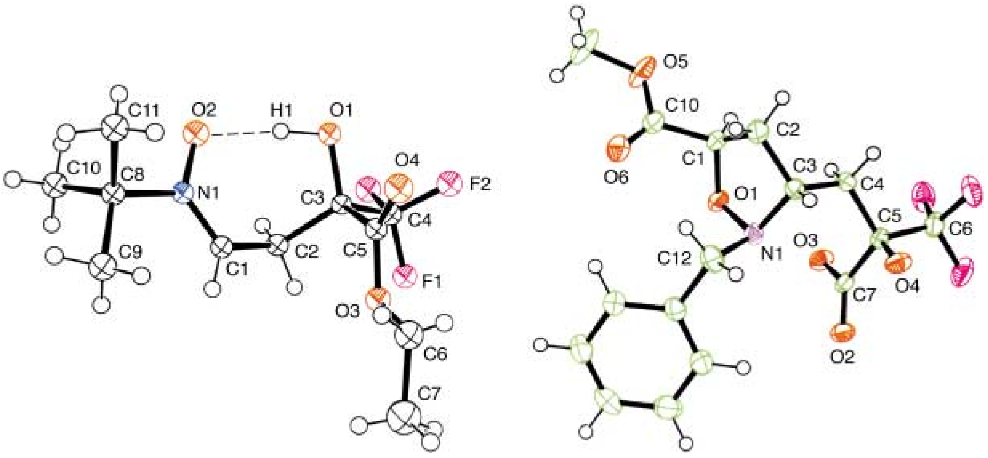


Figure 1. The X-ray structures of **3b** (left) and **9** (right).

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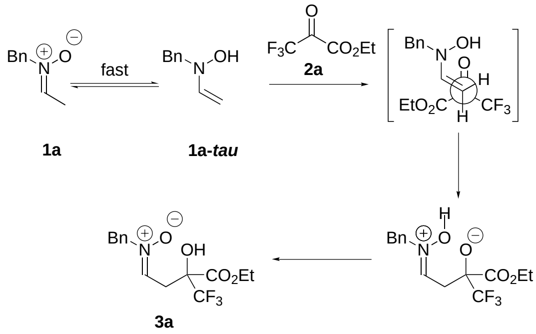
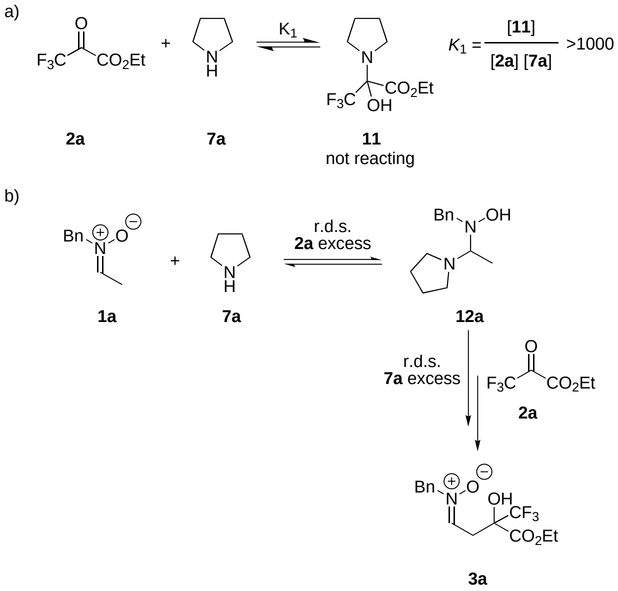
In the absence of a secondary cyclic amine catalyst such as pyrrolidine (**7a**), the rate of formation of **3a** from *N*-benzyl-*C*-methylnitrone (**1a**) and ethyl 1,1,1-trifluoropyruvate (**2a**) had first-order dependency on the concentration of both substrates (i.e., $v = k[\mathbf{1a}][\mathbf{2a}]$). These results indicate that under these reaction conditions, the first step is a fast equilibration between nitrone **1a** and the *N*-hydroxylenamine **1a-*tau*** (see Scheme 9). In the following step, **1a-*tau*** reacts with **2a** in the rate-determining step (r.d.s.). Proton transfer from the *N*-hydroxylenamine to the alkoxy-oxygen atom finally forms product **3a**. It should be noted that in the absence of a cyclic secondary amine catalyst only the most electron-deficient carbonyl compounds undergo reaction.



Scheme 9. A proposed mechanism for the reaction of nitrones with ketones in the absence of a catalyst.

Addition of secondary amines such as pyrrolidine, piperidine, or L-proline to the reaction mixture leads to a more complex kinetic picture. For example, the ratio between pyrrolidine (**7a**) and ethyl 1,1,1-trifluoropyruvate (**2a**) becomes very important. Two kinetically different domains exist, one in which **7a** is in excess relative to **2a** (i.e., $[\mathbf{7a}] > [\mathbf{2a}]$), and a second in which the ketone is in excess (i.e., $[\mathbf{2a}] > [\mathbf{7a}]$). In the former case the rate of formation of the β-hydroxynitrone **3a** has a first-order dependency on the concentration of both substrates (i.e., $v = k[\mathbf{1a}][\mathbf{2a}]$), whereas the concentration of **7a** seems to be insignificant as long as it is in excess. However, in the latter case, an unexpected relationship between reaction rate and concentration of **2a** was found. In the region over which the rate of formation of **3a** has first-order dependency on the nitrone concentration, the dependency of the ketone concentration is -1, that is, $v = k[\mathbf{1a}]/[\mathbf{2a}]$. Under these conditions the concentration of **7a** seems to have little influence on the reaction rate. To understand this observation, two mixtures (**1a**+**7a** and **2a**+**7a**) were studied by ^{1}H NMR spectroscopy. When nitrone **1a** and **7a** were mixed ($[\mathbf{1a}] > [\mathbf{7a}]$) the dimerization of the nitrone was more rapid than in the absence of **7a**. However, the product of the nucleophilic addition of the amine to the nitrone could not be detected, which resembles findings reported in the literature,[13] in which formation of the addition product between a nitrone and allyl amines is believed to be the first step in the formation of 1,2,5-oxadiazinanes.

When pyrrolidine (**7a**) and ethyl 1,1,1-trifluoropyruvate (**2a**) are mixed in a 1:1 ratio, complete conversion into the hemi-aminal **11** is observed by ^{1}H NMR spectroscopy (Scheme 10a). We anticipate that **11** is *not* involved in the addition reaction (see below). However, addition of **1a** to this reaction mixture leads to the formation of β-hydroxynitrone **3a**, that is, the desired reaction occurs, indicating that the formation of **11** must be reversible. The equilibrium constant (K_1) for formation of **11** must be high. This equilibrium is the key to understanding the observed reaction kinetics.



Scheme 10. Intermediates in the pyrrolidine-catalyzed nitrone-aldol reaction.

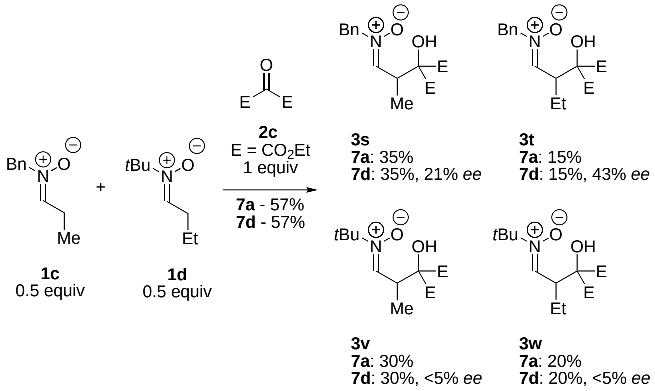
The abovementioned dependency on the concentration of **2a** can be explained by the mechanism proposed in Scheme 10b. A short-lived reactive intermediate **12a**, which could not be detected by ^{1}H NMR spectroscopy, is formed between **1a** and **7a** and further reaction of this intermediate with **2a** leads to product **3a** and pyrrolidine (**7a**). It is not obvious how **12a** reacts with **2a**, and indeed later we will outline how a second intermediate is in fact formed before reaction with **2a** (see below). Due to the equilibrium with **11**, the concentration of pyrrolidine is very low when the ketone is in excess. A consequence of this low pyrrolidine concentration is that the r.d.s. is the formation of **12a**. As soon as **12a** is formed, it rapidly reacts with **2a** which is in high concentration. Since the formation of **12a** is the r.d.s., an increase of the ketone concentration (lower pyrrolidine concentration) gives a slower reaction rate as observed.

When pyrrolidine (**7a**) is in excess, the ketone concentration is low, and the r.d.s becomes the last step. The intermediate **12a** is in equilibrium with nitrone **1a** and **7a**. An increase of the concentration of **7a** will thus also increase the concentration of **12a**. However, the concentration of **2a** is decreased due to the equilibrium with **11**, and the overall rate is therefore unchanged. Increasing the concentration of either

1a or **2a** leads to a higher reaction rate as observed. The fact that ketones other than **2a** only react in the presence of **7a**, can be explained by an increased reactivity of intermediate **12a** relative to **1a**-***tau***.

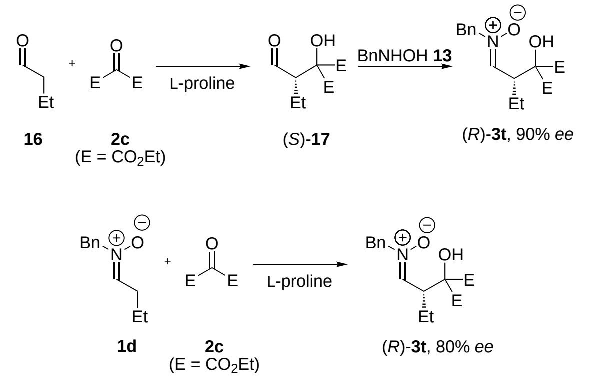
The good enantioselectivities obtained in reactions catalyzed by L-proline (**7d**) led us to anticipate that the stereogenic center in **7d** is close to the reaction center. Based on the kinetic investigations and a series of investigations (see below) we propose the mechanism outlined in Scheme 11 for the catalytic enantioselective reaction of nitrones with the carbonyl compounds in the presence of catalyst **7d**. The first step in the reaction is the addition of **7d** to the nitrone to form the aminal **12b**, which upon elimination of benzylhydroxylamine (**13**) gives a chiral enamine **14**. We propose that the enantioselectivity is induced by the reaction of **14** with the carbonyl compound **2c** (see below). The zwitterionic aldol product **15** then reacts with **13** to form a second aminal **16**, from which the catalyst L-proline (**7d**) is eliminated and the optically active β-hydroxynitrone **3s** is obtained.

To provide evidence for the mechanism proposed in Scheme 11, we added a mixture of the nitrones **1c** and **1d** to diethyl ketomalonate (**2c**) and catalytic pyrrolidine (**7a**) or L-proline (**7d**). If the hydroxylamine is free in solution during the reaction, the crossover products **3t** and **3v** would also be formed in addition to the expected products **3s** and **3w** (Scheme 12). Both the reaction of **1c** and **1d** with **2d** catalyzed by **7a** and **7d** gave the expected products **3s** and **3w** together with the crossover products **3t** and **3v**. It also appears from the results in Scheme 12 that the ratio of the four products is the same for the two catalysts. These experiments therefore support a mechanism involving the enamine-type intermediate **14** as shown in Scheme 11. However, it should also be noted that the enantiomeric excess of **3s** (21% *ee*) obtained in this mixed reaction is much lower than that obtained (76% *ee*) in the reaction between **1c** and **2c** in the presence of catalytic **7d** (Table 3, entry 6).



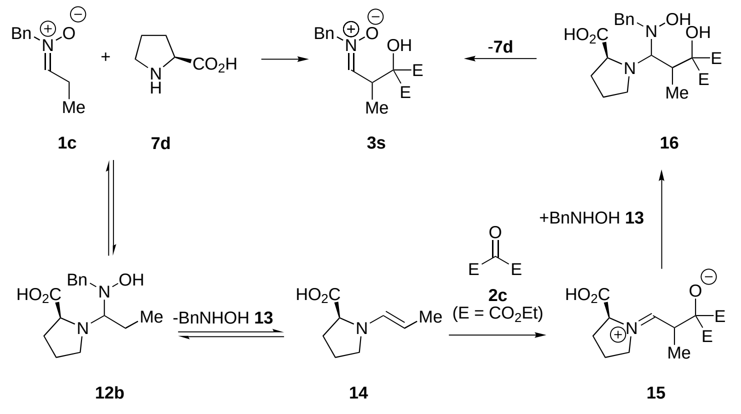
Scheme 12. Crossover experiment showing that the hydroxylamine moieties in **1d** and **1e** have become partially exchanged during the reaction.

Further support for the enamine intermediate **14** in the present nitrone-aldol reaction has been obtained from experiments used for the assignment of the absolute configuration of the products as presented in Scheme 13. Reaction of butanal (**16**) with diethyl ketomalonate (**2c**) in the presence of L-proline (**7d**) gives the aldol adduct **17**.[12f] The absolute configurations of this type of product have been assigned as (*S*) based on conversion of **17** into optically active β-hydroxycarboxylic acids of known absolute configuration. Reaction of **17** with benzylhydroxylamine (**13**) gives the optically active β-hydroxynitrone (*R*)-**3t** with 90% *ee* (Scheme 8 and 13). The direct L-proline-catalyzed reaction of nitrone **1d** which is derived from butanal (**16**), with **2c** also gives the (*R*) enantiomer of the optically active β-hydroxynitrones **3t**, as found by comparing HPLC retention times (Scheme 8 and 13).



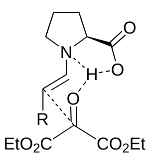
Scheme 13. Derivation of the absolute configuration of the nitrone-aldol product **3t** from an aldehyde (*S*)-**17** of known configuration.

The formation of the new stereocenter in the present reaction is thus directed by the approach of the activated carbonyl compound **2c** to the enamine intermediate **14**. Based on the absolute configuration of the product we propose that the approach of **2c** to the enamine intermediate **14** is directed by the interaction of the incoming carbonyl oxygen atom with the proton of the carboxylic acid of L-proline as outlined in Scheme 14. This is supported by the fact that reactions catalyzed by methyl L-prolinate (**7b**) give racemic products. The reaction step in Scheme 14 creates a new chiral



Scheme 11. Proposed mechanism for the organo-catalyzed reaction of nitrones with activated ketones.

carbon atom in the reaction leading to intermediate **15** (Scheme 11). Addition of the hydroxylamine to **15** produces aminal **16** (Scheme 11) and elimination of the catalyst in the final step produces optically active β-hydroxynitrone.



Scheme 14. Proposed approach of the ketone **2c** to the enamine intermediate **14**.

Conclusion

A new catalytic aldol-type reaction of nitrones with activated carbonyl compounds has been developed. The reaction proceeds for nitrones with a methyl or methylene substituent in the α-position to give functionalized β-hydroxynitrones. Cyclic secondary amines such as pyrrolidine and L-proline are excellent catalysts for the nitrone-aldol reaction leading to racemic and optically active β-hydroxynitrones, respectively. High yields and enantioselectivities are obtained for the catalytic asymmetric reactions. Kinetic measurements, intermediate and product analysis, and the absolute configuration of the optically active β-hydroxynitrone product have revealed that the reaction proceeds via an enamine intermediate, which is formed by the addition of the catalyst to the nitrone followed by elimination of the hydroxylamine. Reaction of this enamine intermediate with an activated carbonyl compound in an aldol-type reaction is followed by exchange of the proline catalyst with hydroxylamine to give the β-hydroxynitrone products. This new nitrone-aldol reaction demonstrates that nitrones can react not only as 1,3-dipoles and electrophiles, but also as nucleophiles.

Experimental Section

General methods: All reactions were carried out under a nitrogen atmosphere with anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products was carried out by flash chromatography (FC) on Merck silica gel 60 (230–400 mesh) when necessary. TLC was performed on Merck silica gel 60 F_{254} aluminium plates and visualized with blue stain. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. The enantiomeric excess (*ee*) of each product was determined by HPLC or GC/GC-MS. Daicel Chiralpak AD or AS columns were used for the *ee* determination by HPLC.

Materials: All substrate nitrones are known compounds. Preparation of nitrones from aldehydes[14] and ketones[15] were therefore performed according to literature methods.

Kinetic experiments: All kinetic data were obtained by using ^{1}H NMR spectroscopy on reactions preformed in $CDCl_3$ (0.6 mL). In general 0.12 mmol (0.2 M) of starting materials were used and the actual concentrations were estimated from integration of selected signals under the assumption that no byproducts were formed (i.e., an internal standard was not used).

General procedures

Method A. Reactions of nitrones with ethyl 1,1,1-trifluoropyruvate (2a): The nitrone (0.6 mmol) and **2a** (102 mg, 0.6 mmol) were mixed in dry CH_2Cl_2 (2–3 mL) in a Schlenk tube with a magnetic stirring bar. The reaction was monitored by TLC with Et_2O as the eluent; the products have R_f values higher than the substrate nitrone. The product was isolated by FC on silica (eluent: pentane/Et_2O/EtOAc gradient of increasing polarity).

Method B. Organo-catalyzed reactions: The ketone (1.5 equiv), nitrone (0.6 mmol, 1 equiv), and the cyclic amine (0.2 equiv) were mixed in dry CH_2Cl_2 (2–3 mL) in a Schlenk tube with a magnetic stirring bar and the products were isolated as described in Method A.

Benzyl-(2-benzyloxyethylidene)amine *N*-oxide (1i): $MgSO_4$ (2–3 g), $NaHCO_3$ (1 g), and CH_2Cl_2 (15 mL) were mixed in a 50 mL round-bottomed flask with a magnetic stirring bar. *N*-Benzylhydroxylamine hydrochloride (3.13 mmol, 0.5 g) was added followed by benzyloxyacetaldehyde (0.99 equiv). Within 1 min gas evolution occurs (CO_2). After 5 min the white suspension of *N*-benzylhydroxylamine hydrochloride disappears and the reaction is complete. After 15 min the solution is filtered and evaporated to dryness in vacuo. The crude product can be recrystallized from a pentane/Et_2O mixture. Note that the use of higher boiling solvents might lead to substantial dimerization of the nitrone and cause a loss of material. ^{1}H NMR: $\delta = 4.40$ (m, $^{3}J(\mathrm{H,H}) = 4.4$ Hz, 2H), 4.46 (s, 2H), 4.79 (s, 2H), 6.71 (t, $^{3}J(\mathrm{H,H}) = 4.4$ Hz, 1H), 7.19–7.33 (m, 10H); ^{13}C NMR: $\delta =$ 66.43, 69.25, 74.05, 128.27, 128.33, 128.78, 129.31, 129.47, 129.92, 132.30, 137.38, 137.57; MS (TOF ES^{+}): *m*/*z*: 278 $[M+Na]^{+}$; HRMS: *m*/*z*: calcd for $C_{16}H_{17}NNaO_2$: 278.1157; found: 278.1154.

Benzyl-(3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxybutylidene)amine *N*-oxide (3a): ^{1}H NMR: $\delta = 1.22$ (t, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 3H), 3.10 (dd, $^{3}J(\mathrm{H,H}) = 5.8$ Hz, $^{2}J(\mathrm{H,H}) = 15.6$ Hz, 1H), 3.15 (dd, $^{3}J(\mathrm{H,H}) = 5.8$ Hz, $^{2}J(\mathrm{H,H}) = 15.6$ Hz, 1H), 4.21 (m, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 2H), 4.88 (s, 2H), 6.75 (s, 1H), 6.86 (t, $^{3}J(\mathrm{H,H}) = 6.0$ Hz, 1H), 7.36 (m, 5H); ^{13}C NMR: $\delta = 14.05$, 30.97, 63.56, 69.18, 78.29 (q, $^{2}J(\mathrm{C,F}) = 29$ Hz), 123.48 (q, $^{1}J(\mathrm{C,F}) = 285$ Hz), 129.28, 129.48, 129.52, 132.23, 134.35, 168.54; MS (TOF ES^{+}): *m*/*z*: 342 $[M+Na]^{+}$; HRMS: *m*/*z*: calcd for $C_{11}H_{18}F_3NNaO_4$: 342.0929; found: 342.0926.

***tert*-Butyl-(3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxybutylidene)amine *N*-oxide (3b)**: ^{1}H NMR: $\delta = 1.29$ (t, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 3H), 1.40 (s, 9H), 3.12 (dd, $^{3}J(\mathrm{H,H}) = 5.6$ Hz, $^{2}J(\mathrm{H,H}) = 15.0$ Hz, 1H), 3.17 (dd, $^{3}J(\mathrm{H,H}) =$ 5.8 Hz, $^{2}J(\mathrm{H,H}) = 15.0$ Hz, 1H), 4.28 (q, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 2H), 7.03 (t, $^{3}J(\mathrm{H,H}) = 5.8$ Hz, 1H), 7.62 (s, 1H); ^{13}C NMR: $\delta = 14.17$, 27.99, 31.11, 63.19, 70.31, 79.48 (q, $^{2}J(\mathrm{C,F}) = 29$ Hz), 123.62 (q, $^{1}J(\mathrm{C,F}) = 285$ Hz), 130.45, 168.66; MS (TOF ES^{+}): *m*/*z*: 308 $[M+Na]^{+}$; HRMS: *m*/*z*: calcd for $C_{11}H_{18}F_3NNaO_4$: 308.1086; found: 308.1081.

Benzyl-(3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxy-2-methylbutylidene)amine *N*-oxide (3c): Major diastereomer: ^{1}H NMR: $\delta = 1.12$ (d, $^{3}J(\mathrm{H,H}) =$ 6.8 Hz, 3H), 1.32 (t, $^{3}J(\mathrm{H,H}) = 7.0$ Hz, 3H), 3.78 (dq, $^{3}J(\mathrm{H,H}) = 7.0$, 6.8 Hz, 1H), 4.33 (m, 2H), 4.90 (s, 2H), 5.67 (br s, 1H), 6.84 (d, $^{3}J(\mathrm{H,H}) = 6.8$ Hz, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR: $\delta = 10.57$, 14.14, 30.52, 34.89, 64.10, 69.75, 78.80 (q, $^{2}J(\mathrm{C,F}) = 29$ Hz), 123.51 (q, $^{1}J(\mathrm{C,F}) = 286$ Hz), 129.25, 129.38, 129.45, 132.49, 137.69, 168.68; MS (TOF ES^{+}): *m*/*z*: 333 $[M+Na]^{+}$; HRMS: *m*/*z*: calcd for $C_{15}H_{18}F_3NNaO_4$: 356.1086; found: 356.1087.

Minor diastereomer: ^{1}H NMR: $\delta = 1.18$ (t, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 3H), 1.24 (d, $^{3}J(\mathrm{H,H}) = 5.6$ Hz, 3H), 3.88 (dq, $^{3}J(\mathrm{H,H}) = 7.0$, 6.8 Hz, 1H), 4.08 (dq, $^{2}J(\mathrm{H,H}) = 10.4$ Hz, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 1H), 4.19 (dq, $^{2}J(\mathrm{H,H}) = 10.4$ Hz, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 1H), 4.85 (s, 2H), 5.30 (br s, 1H), 6.66 (d, $^{3}J(\mathrm{H,H}) =$ 7.2 Hz, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR: $\delta = 11.07$, 13.97, 29.94, 35.53, 63.93, 69.95, 78.80 (q, $^{2}J(\mathrm{C,F}) = 29$ Hz), 123.51 (q, $^{1}J(\mathrm{C,F}) = 286$ Hz), 129.22, 129.38, 129.45, 132.67, 137.69, 168.66.

Benzyl-(3-ethoxycarbonyl-2-ethyl-4,4,4-trifluoro-3-hydroxybutylidene)amine *N*-oxide (3d): Major diastereomer: ^{1}H NMR: $\delta = 0.85$ (t, $^{3}J(\mathrm{H,H}) =$ 7.4 Hz, 3H), 1.32 (t, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 3H), 1.44 (ddq, $^{2}J(\mathrm{H,H}) = 13.8$, $^{3}J(\mathrm{H,H}) = 4.0$, 7.4 Hz, 1H), 1.87 (ddq, $^{2}J(\mathrm{H,H}) = 13.8$, $^{3}J(\mathrm{H,H}) = 10.8$, 7.4 Hz, 1H), 3.62 (ddd, $^{3}J(\mathrm{H,H}) = 4.0$, 7.4, 10.8 Hz, 1H), 4.33 (m, 2H), 4.93 (s, 2H), 5.81 (br s, 1H), 6.76 (d, $^{3}J(\mathrm{H,H}) = 8.0$ Hz, 1H), 7.40 (m, 5H); ^{13}C NMR: $\delta = 12.08$, 14.16, 19.98, 41.78, 63.77, 69.91, 80.61 (q, $^{2}J(\mathrm{C,F}) =$ 27 Hz), 123.60 (q, $^{1}J(\mathrm{C,F}) = 286$ Hz), 129.31, 129.54, 129.67, 132.36, 137.02, 168.61.

Minor diastereomer: ^{1}H NMR: $\delta = 0.88$ (t, $^{3}J(\mathrm{H,H}) = 7.6$ Hz, 3H), 1.21 (t, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 3H), 1.64 (ddq, $^{2}J(\mathrm{H,H}) = 14.2$, $^{3}J(\mathrm{H,H}) = 11.2$, 7.6 Hz, 1H), 1.81 (ddq, $^{2}J(\mathrm{H,H}) = 14.2$, $^{3}J(\mathrm{H,H}) = 4.0$, 7.6 Hz, 1H), 3.82 (ddd, $^{3}J(\mathrm{H,H}) = 4.0$, 8.0, 11.2 Hz, 1H), 4.08 (dq, $^{2}J(\mathrm{H,H}) = 10.8$, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 1H), 4.18 (dq, $^{2}J(\mathrm{H,H}) = 10.8$, $^{3}J(\mathrm{H,H}) = 7.2$ Hz, 1H), 4.89 (s, 2H), 5.76 (br s, 1H), 6.62 (d, $^{3}J(\mathrm{H,H}) = 7.6$ Hz, 1H), 7.37–7.43 (m, 5H); ^{13}C NMR: $\delta = 12.08$, 14.43, 20.35, 42.20, 63.66, 70.00, 80.61(q, $^{2}J(\mathrm{C,F}) = 27$ Hz), 123.60

(q, ^{1}J(C,F) = 286 Hz), 129.31, 129.54, 129.67, 132.53, 137.45, 168.61; MS (TOF ES^{+}): *m*/*z*: 370 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{16}H_{20}F_3NNaO_4$: 370.1242; found: 370.1241.

Benzyl-(3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxy-1-phenylbutylidene)amine *N*-oxide (3f): ^{1}H NMR: $\delta = 0.98$ (t, ^{3}J(H,H) = 7.0 Hz, 3H), 3.35 (d, ^{3}J(H,H) = 13.6 Hz, 1H), 3.82 (dq, ^{2}J(H,H) = 11.2 Hz, ^{3}J(H,H) = 7.2 Hz, 1H), 3.84 (d, ^{3}J(H,H) = 13.6 Hz, 1H), 3.98 (dq, ^{2}J(H,H) = 11.2 Hz, ^{3}J(H,H) = 7.2 Hz, 1H), 4.88 (d, ^{2}J(H,H) = 14 Hz, 1H), 4.95 (d, ^{2}J(H,H) = 14 Hz, 1H), 7.14–7.21 (m, 4H), 7.25–7.31 (m, 3H), 7.35–7.43 (m, 3H), 8.37 (brs, 1H); ^{13}C NMR: $\delta = 13.84$, 38.59, 62.81, 64.59, 79.56 (q, ^{2}J(C,F) = 29 Hz), 123.69 (q, ^{1}J(C,F) = 285 Hz), 128.02, 128.15, 128.77, 129.08, 129.47, 130.66, 133.47, 134.42, 148.61, 168.05; MS (TOF ES^{+}): *m*/*z*: 395 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{20}H_{20}F_3NNaO_4$: 418.1242; found: 418.1243.

Benzyl-(2-(1-ethoxycarbonyl-2,2,2-trifluoro-1-hydroxyethyl)-cyclohexylidene)amine *N*-oxide (3g): Mixture of diastereomers: ^{1}H NMR: $\delta = 1.25$ (t, ^{3}J(H,H) = 7.0 Hz), 1.23–1.44 (m, 2H), 1.61–1.71 (m, 1H), 1.72–1,87 (m, 3H), 2.52–2.71 (m, 2H), 3.97 (dd, ^{3}J(H,H) = 5.6, 8.8 Hz, 1H; minor diastereomer), 4.25 (dt, ^{3}J(H,H) = 6.0, 2H), 4.38 (t, ^{3}J(H,H) = 6.8, 1H; major diastereomer), 5.10 (2H, Bn; minor diastereomer), 5.14 (d, ^{2}J(H,H) = 14.6, 1H; Bn major diastereomer), 5.20 (d, ^{2}J(H,H) = 14.6, 1H; Bn major diastereomer), 7.30–7.43 (m, 5H), 8.18 (brs, 1H); ^{13}C NMR: $\delta =$ 14.07 (14.00), 20.63 (21.92), 23.35 (24.34), 25.19 (25.98), 28.03 (29.46), 40.61 (44.18), 63.14 (64.12), 64.68 (64.93), 82.25 (q, ^{2}J(C,F) = 28 Hz), 123.81 (q, ^{2}J(C,F) = 285 Hz), 127.54, 128.68, 129.22, 133.32, 154.01, 168,38 (167,79); MS (TOF ES^{+}): *m*/*z*: 396 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{18}H_{22}F_3NNaO_4$: 396.1399; found: 396.1399.

Benzyl-(4,4,4-trifluoro-3-hydroxy-3-phenylbutylidene)amine *N*-oxide (3i): The enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/*i*PrOH 90:10; flow rate 1.0 mL min^{-1}; $\tau_{major} = 9.6$ min; τ $_{minor} = 13.2$ min). ^{1}H NMR: $\delta = 3.19$ (dd, ^{3}J(H,H) = 6.2 Hz, ^{2}J(H,H) = 14.8 Hz, 1H), 3.44 (dd, ^{3}J(H,H) = 6.2 Hz, ^{2}J(H,H) = 14.8 Hz, 1H), 4.73 (d, ^{2}J(H,H) = 14.4 Hz, 1H), 4.78 (d, ^{2}J(H,H) = 14.4 Hz, 1H), 6.72 (t, ^{3}J(H,H) = 6.0 Hz, 1H), 7.03–7.06 (m, 2H), 7.26–7.38 (m, 6H), 7.58–7.61 (m, 2H), 7.95 (brs, 1H); ^{13}C NMR: $\delta = 34.22$, 68.88, 78.68 (q, ^{2}J(C,F) = 27 Hz), 125.32 (q, ^{1}J(C,F) = 285 Hz), 126.76, 128.60, 128.88, 129.05, 129.25, 129.38, 132.02, 136.32, 138.18; MS (TOF ES^{+}): *m*/*z*: 346 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{17}H_{16}F_3NNaO_2$: 346.1031; found: 346.1035.

Benzyl-(3,3-bis(ethoxycarbonyl)-3-hydroxypropylidene)amine *N*-oxide (3j): ^{1}H NMR: $\delta = 1.16$ (t, ^{3}J(H,H) = 7.2 Hz, 6H), 3.12 (d, ^{3}J(H,H) = 6.9 Hz, 2H), 4.14 (m, ^{3}J(H,H) = 7.2 Hz, 4H), 4.84 (s, 2H), 6.08 (s, 1H), 6.89 (t, ^{3}J(H,H) = 6.0 Hz, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR: $\delta = 14.13$, 33.48, 62.71, 69.16, 78.91, 129.11, 129.21, 129.37, 132.69, 135.58, 169.81; MS (TOF ES^{+}): *m*/*z*: 346 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{16}H_{21}NNaO_6$: 346.1267; found: 346.1270.

Benzyl-(3-ethoxycarbonyl-3-hydroxy-3-phenylpropylidene)amine *N*-oxide (3k): ^{1}H NMR: $\delta = 1.16$ (t, ^{3}J(H,H) = 7.2 Hz, 3H), 3.22 (dd, ^{3}J(H,H) = 5.8 Hz, ^{2}J(H,H) = 16.0 Hz, 1H), 3.37 (dd, ^{3}J(H,H) = 5.8 Hz, ^{2}J(H,H) = 16.0 Hz, 1H), 4.14 (m, ^{3}J(H,H) = 7.2 Hz, 2H), 4.79 (s, 2H), 6.08 (s, 1H), 6.77 (t, ^{3}J(H,H) = 5.8 Hz, 1H), 7.20 (m, 2H), 7.24–7.38 (m, 6H), 7.53 (m, 2H); ^{13}C NMR: $\delta = 14.19$, 38.07, 62.63, 69.23, 78.88, 125.37, 128.23, 128.67, 129.11, 129.16, 129.18, 132.72, 136.61, 141.36, 174.03; MS (TOF ES^{+}): *m*/*z*: 350 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{19}H_{21}NNaO_4$: 350.1368; found: 350.1375.

Benzyl-(3-allyloxycarbonyl-3-hydroxy-3-phenylpropylidene)amine *N*-oxide (3l): ^{1}H NMR: $\delta = 1.32$ (s, 3H), 2.22 (s, 3H), 3.25 (dd, ^{3}J(H,H) = 5.6 Hz, ^{2}J(H,H) = 16.0 Hz, 1H), 3.39 (dd, ^{3}J(H,H) = 5.6 Hz, ^{2}J(H,H) = 16.0 Hz, 1H), 4.59 (m, 2H), 4.81 (s, 2H), 5.15 (d, ^{3}J(H,H) = 10.4 Hz, 1H), 5.16 (d, ^{3}J(H,H) = 17.2 Hz, 1H), 5.78 (ddt, ^{3}J(H,H) = 6.0, 10.4, 17.2 Hz, 1H), 6.18 (s, 1H), 6.77 (t, ^{3}J(H,H) = 5.6 Hz, 1H), 7.20–7.23 (m, 2H), 7.26–7.39 (m, 6H), 7.53–7.56 (m, 2H); ^{13}C NMR: $\delta = 38.10$, 66.82, 69.24, 79.20, 119.03, 125.39, 128.30, 128.69, 129.14, 129.21, 129.22, 131.43, 132.62, 136.55, 141.26, 173.69; MS (TOF ES^{+}): *m*/*z*: 362 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{20}H_{21}NNaO_4$: 362.1368; found: 362,1366.

Benzyl-(3-hydroxy-4-oxo-3-methylpentylidene)amine *N*-oxide (3m): ^{1}H NMR: $\delta = 1.32$ (s, 3H), 2.22 (s, 3H), 2.76 (dd, ^{3}J(H,H) = 4.8 Hz, ^{2}J(H,H) = 15.2 Hz, 1H), 2.85 (dd, ^{3}J(H,H) = 6.0 Hz, ^{2}J(H,H) = 15.2 Hz, 1H), 4.84 (s, 2H), 6.29 (s, 1H), 6.84 (dd, ^{3}J(H,H) = 6.0, 4.8 Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR: $\delta = 24.11$, 26.35, 36.88, 69.28, 80.41, 129.26, 129.33, 129.41, 132.59, 137.26, 213.61; MS (TOF ES^{+}): *m*/*z*: 258 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{13}H_{17}NNaO_3$: 258.1106; found: 258.1103.

Benzyl-(3-hydroxy-4-oxo-3-phenylpentylidene)amine *N*-oxide (3n): ^{1}H NMR: $\delta = 2.07$ (s, 3H), 3.09 (dd, ^{3}J(H,H) = 6.0 Hz, ^{2}J(H,H) = 14.8 Hz, 1H), 3.21 (dd, ^{3}J(H,H) = 6.0 Hz, ^{2}J(H,H) = 14.8 Hz, 1H), 4.82 (s, 2H), 6.29 (s, 1H), 6.84 (t, ^{3}J(H,H) = 6.0 Hz, 1H), 7.21–7.38 (m, 8H), 7.47 (d, 2H), 7.66 (s, 1H); ^{13}C NMR: $\delta = 24.07$, 37.27, 68.98, 85.35, 125.30, 128.14, 128.81, 128.84, 129.25, 129.37, 132.39, 138.45, 141.20, 209.91; MS (TOF ES^{+}): *m*/*z*: 258 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{13}H_{17}NNaO_3$: 258.1106; found: 258.1103.

Benzyl-(3-benzoyl-3-hydroxybutylidene)amine *N*-oxide (3o): ^{1}H NMR: $\delta = 1.32$ (s, 3H), 2.22 (s, 3H), 2.76 (dd, ^{3}J(H,H) = 4.8 Hz, ^{2}J(H,H) = 15.2 Hz, 1H), 2.85 (dd, ^{3}J(H,H) = 6.0 Hz, ^{2}J(H,H) = 15.2 Hz, 1H), 4.84 (s, 2H), 6.29 (s, 1H), 6.84 (dd, ^{3}J(H,H) = 6.0, 4.8 Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR: $\delta = 28.36$, 38.76, 68.70, 82.65, 128.118, 129.00, 129.04, 129.07, 130.41, 132.21, 132.82, 134.08, 138.66, 203.29; MS (TOF ES^{+}): *m*/*z*: 258 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{13}H_{17}NNaO_3$: 258.1106; found: 258.1103.

Benzyl-(3-but-3-enyl-3-hydroxy-4-oxo-oct-7-enylidene)amine *N*-oxide (3p): ^{1}H NMR: $\delta = 1.68$ (ddd, ^{2}J(H,H) = 13.7, ^{3}J(H,H) = 11.3, 5.1 Hz, 1H), 1.78 (ddd, ^{2}J(H,H) = 13.7, ^{3}J(H,H) = 11.3, 4.7 Hz, 1H), 1.94 (m, 1H), 2.11 (m, 1H), 2.29 (s, 3H), 2.20 (dt, ^{3}J(H,H) = 6.7, 7.2 Hz, 2H), 2.69 (t, ^{3}J(H,H) = 7.2 Hz, 2H), 2.86 (dd, ^{2}J(H,H) = 15.0, ^{3}J(H,H) = 6.4 Hz, 3H), 2.80 (dd, ^{2}J(H,H) = 15.0, ^{3}J(H,H) = 5.3 Hz, 3H), 4.82 (d, ^{2}J(H,H) = 15 Hz, 1H), 4.86 (d, ^{2}J(H,H) = 15 Hz, 1H), 4.97 (m, 4H), 5.73 (ddt, ^{3}J(H,H) = 17.0, 10.15, 6.6 Hz, 2H), 6.21 (brs, 1H), 6.82 (t, ^{3}J(H,H) = 6.0 Hz, 1H); ^{13}C NMR: $\delta = 27.50$, 27.70, 35.97, 36.21, 38.91, 69.35, 82.86, 115.37, 115.55, 125.77, 129.28, 129.37, 132.58, 136.98, 137.31, 137.78, 215.18; MS (TOF ES^{+}): *m*/*z*: 338 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{19}H_{25}NNaO_3$: 338.1732; found: 338.1732.

Benzyl-(2-benzyloxy-3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxybutylidene)amine *N*-oxide (3q): First diastereomer: ^{1}H NMR: $\delta = 1.21$ (t, ^{3}J(H,H) = 7.2 Hz, 3H), 4.14 (dq, ^{3}J(H,H) = 7.2 Hz, ^{2}J(H,H) = 10.8 Hz, 1H), 4.32 (dq, ^{3}J(H,H) = 7.2 Hz, ^{2}J(H,H) = 10.8 Hz, 1H), 4.53 (s, 2H), 4.69 (s, 1H), 4.87 (d, ^{3}J(H,H) = 15 Hz, 1H), 4.91 (d, ^{3}J(H,H) = 15 Hz, 1H), 5.47 (d, ^{3}J(H,H) = 8.0 Hz, 1H), 6.89 (t, ^{3}J(H,H) = 8.0 Hz, 1H), 7.21–7.24 (m, 3H), 7.29–7.32 (m, 3H), 7.35–7.41 (m, 5H); ^{13}C NMR: $\delta = 14.04$, 64.23, 70.62, 71.36, 73.08, 79.96 (q, ^{2}J(C,F) = 28 Hz), 122.28 (q, ^{1}J(C,F) = 285 Hz), 128.19, 128.35, 128.67, 129.28, 129.52, 129.60, 132.32, 133.72, 137.17, 167.40; MS (TOF ES^{+}): *m*/*z*: 448 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{21}H_{22}F_3NNaO_5$: 448.1348; found: 448.1348.

Second diastereomer: ^{1}H NMR: $\delta = 1.20$ (t, ^{3}J(H,H) = 7.2 Hz, 3H), 4.14 (dq, ^{3}J(H,H) = 7.2, ^{2}J(H,H) = 10.4 Hz, 1H), 4.23 (dq, ^{3}J(H,H) = 7.2, ^{2}J(H,H) = 10.4 Hz, 1H), 4.53 (d, ^{3}J(H,H) = 12 Hz, 1H), 4.66 (d, ^{3}J(H,H) = 12 Hz, 1H), 4.76 (d, ^{3}J(H,H) = 13.6 Hz, 1H), 4.80 (d, ^{3}J(H,H) = 13.6 Hz, 1H), 5.43 (d, ^{3}J(H,H) = 6.8 Hz, 1H), 5.44 (s, 1H), 6.72 (t, ^{3}J(H,H) = 6.8 Hz, 1H), 7.25–7.33 (m, 7H), 7.36–7.40 (m, 3H); ^{13}C NMR: $\delta = 13.98$, 63.88, 70.04, 73.92, 74.11, 80.11 (q, ^{2}J(C,F) = 28 Hz), 123.01 (q, ^{1}J(C,F) = 285 Hz), 128.25, 128.43, 128.70, 129.29, 129.62, 129.72, 132.04, 135.35, 137.05, 166.95; MS (TOF ES^{+}): *m*/*z*: 448 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{21}H_{22}F_3NNaO_5$: 448.1348; found: 448.1352.

Benzyl-(2-(*tert*-butyloxycarbonylamino)-3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxybutylidene)amine *N*-oxide (3r): Mixture of diastereomers: ^{1}H NMR: $\delta = 1.14$ (t, ^{3}J(H,H) = 7.2 Hz, 3H), 1.27 (t, ^{3}J(H,H) = 7.2 Hz, 3H), 1.36 (s, 9H), 1.39 (s, 9H), 4.08 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 4.26 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 4.85 (s, 2H), 4.90 (s, 2H), 5.26 (dd, ^{3}J(H,H) = 4.4, 9.2 Hz, 1H), 5.92 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 6.12 (d, ^{3}J(H,H) = 8.8 Hz, 1H), 7.00 (d, ^{3}J(H,H) = 4.4 Hz, 1H), 7.31–7.37 (m, 2H), 7.40–7.42 (m, 3H), 7.75 (brs, 1H); ^{13}C NMR: $\delta = 14.02$, 28.26, 50.28, 63.43, 63.90, 69.69, 81.20, 122.91 (q, ^{1}J(C,F) = 286 Hz), 129.29, 129.51, 129.67, 131.53, 135.56, 155.60, 167.36; MS (TOF ES^{+}): *m*/*z*: 457 [*M*+Na]$^{+}$; HRMS: *m*/*z*: calcd for $C_{19}H_{25}F_3N_2NaO_6$: 457.1562; found: 457.1564.

Benzyl-(3,3-bis(ethoxycarbonyl)-2-methyl-3-hydroxypropylidene)amine *N*-oxide (3s): The enantiomeric excess was determined by HPLC with a Chiralpak AS column (hexane/*i*PrOH 80:20; flow rate 1.0 mL min^{-1}; $\tau_{major} = 13.8$ min; $\tau_{minor} = 18.5$ min); $[\alpha]_{D}^{RT} = -10.7$ ($c = 11.9$ g per 100 mL in $CHCl_3$); ^{1}H NMR: $\delta = 1.07$ (t, ^{3}J(H,H) = 7.2 Hz, 3H), 1.08 (d, ^{3}J(H,H) = 6.8 Hz, 3H), 1.18 (t, ^{3}J(H,H) = 7.2 Hz, 3H), 3.80 (dq, ^{3}J(H,H) = 6.8 Hz, 1H), 4.02 (m, 2H), 4.16 (m, 2H), 4.78 (s, 2H), 5.55 (brs, 1H), 6.84 (d, ^{3}J(H,H) = 6.8 Hz, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR: $\delta = 10.6$, 13.9, 14.1, 37.1, 62.5, 62.8, 69.4, 80.8, 128.9 (2C), 128.9, 129.1 (2C), 133.1, 139.4, 169.5, 169.6; MS (TOF ES$^+$): *m*/*z*: 360 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{17}H_{23}NNaO_6$: 360.1423; found: 360.1429.

Benzyl-(3,3-bis(ethoxycarbonyl)-2-ethyl-3-hydroxypropylidene)amine *N*-oxide (3t): The enantiomeric excess was determined by HPLC with a Chiralpak AS column (hexane/*i*PrOH 80:20; flow rate 1.0 mL min^{-1}; $\tau_{major} = 8.3$ min; $\tau_{minor} = 11.1$ min); $[\alpha]_D^{RT} = -17.7$ ($c = 12.5$ g per 100 mL in $CHCl_3$); ^{1}H NMR: $\delta = 0.80$ (t, ^3J(H,H) = 7.2 Hz, 3H), 1.06 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.18 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.47–1.56 (m, 1H), 1.63–1.72 (m, 1H), 3.66–3.71 (m, 1H), 3.91–4.05 (m, 2H), 4.11–4.19 (m, 2H), 4.79 (s, 2H), 6.24 (brs, 1H), 6.79 (d, ^3J(H,H) = 7.6 Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR: $\delta = 12.1$, 13.8, 14.0, 20.7, 43.7, 62.5, 62.6, 69.7, 81.5, 128.9 (2C), 129.0, 129.3 (2C), 133.0, 138.7, 169.5, 169.8; MS (TOF ES$^+$): *m*/*z*: 374 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{18}H_{25}NNaO_6$: 374.1580; found: 374.1584.

Benzyl-(3,3-bis(ethoxycarbonyl)-2-isopropyl-3-hydroxypropylidene)amine *N*-oxide (3u): The enantiomeric excess was determined by HPLC with a Chiralpak AS column (hexane/*i*PrOH 80:20; flow rate 1.0 mL min^{-1}; $\tau_{major} = 6.7$ min; $\tau_{minor} = 9.1$ min); $[\alpha]_D^{RT} = -9.8$ ($c = 10.5$ g per 100 mL in $CHCl_3$); ^{1}H NMR: $\delta = 0.84$ (d, ^3J(H,H) = 6.8 Hz, 3H), 0.89 (d, ^3J(H,H) = 6.4 Hz, 3H), 0.99 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.16 (t, ^3J(H,H) = 7.0 Hz, 3H), 1.96–2.06 (m, 1H), 3.77–3.83 (m, 2H), 3.88–3.94 (m, 1H), 3.97 (s, 1H), 4.10–4.20 (m, 2H), 4.77 (s, 2H), 6.83 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR: $\delta = 13.9$, 14.1, 20.2, 22.8, 29.6, 46.8, 62.7, 62.8, 70.0, 81.3, 128.9 (2C), 129.1, 129.5 (2C), 133.3, 137.8, 170.0, 170.1; MS (TOF ES$^+$): *m*/*z*: 388 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{19}H_{27}NNaO_6$: 388.1736; found: 388.1739.

***tert*-Butyl-(3,3-bis(ethoxycarbonyl)-2-methyl-3-hydroxypropylidene)-amine *N*-oxide (3v)**: The enantiomeric excess was determined by HPLC with a Chiralpak AS column (hexane/*i*PrOH 98:2; flow rate 1.0 mL min^{-1}; $\tau_{major} = 18.9$ min; $\tau_{minor} = 23.8$ min); ^{1}H NMR: $\delta = 1.06$ (d, ^3J(H,H) = 7.2 Hz, 3H), 1.15 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.18 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.36 (s, 9H), 3.74 (dq, ^3J(H,H) = 7.2 Hz, 1H), 4.06–4.14 (m, 2H), 4.17 (q, ^3J(H,H) = 7.2 Hz, 2H), 5.67 (brs, 1H), 6.86 (d, ^3J(H,H) = 6.8 Hz, 1H); ^{13}C NMR: $\delta = 10.7$, 14.2 (2C), 28.1, 37.3, 62.4, 62.7, 69.7, 81.5, 134.9, 169.7, 169.8; MS (TOF ES$^+$): *m*/*z*: 326 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{14}H_{25}NNaO_6$: 326.1580; found: 326.1579.

***tert*-Butyl-(3,3-bis(ethoxycarbonyl)-2-ethyl-3-hydroxypropylidene)amine *N*-oxide (3w)**: The enantiomeric excess was determined by HPLC with a Chiralpak AS column (hexane/*i*PrOH 95:5; flow rate 1.0 mL min^{-1}; $\tau_{major} = 7.6$ min; $\tau_{minor} = 10.4$ min); ^{1}H NMR: $\delta = 0.90$ (t, ^3J(H,H) = 7.2 Hz, 3H), 1.25 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.28 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.46 (s, 9H), 1.52–1.63 (m, 1H), 1.80–1.91 (m, 1H), 3.65–3.71 (m, 1H), 4.18 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.25 (q, ^3J(H,H) = 7.2 Hz, 2H), 6.54 (s, 1H), 6.92 (d, ^3J(H,H) = 7.2 Hz, 1H); ^{13}C NMR: $\delta = 12.5$, 14.2, 14.3, 20.3, 28.3 (3C), 44.3, 62.5, 62.6, 70.1, 82.6, 134.4, 169.9, 170.2; MS (TOF ES$^+$): *m*/*z*: 340 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{15}H_{27}NNaO_6$: 340.1736; found: 340.1749.

2-Benzyl-3-(2-ethoxycarbonyl-3,3,3-trifluoro-2-hydroxypropyl)isoxazolidine-5-carboxylic methyl ester (9): Nitrone **3a** (0.4 mmol) was dissolved in methyl acrylate (8 mL) and heated at reflux for 1 h. Excess methyl acrylate was evaporated in vacuo and the residue was purified by flash chromatography (Et_2O/pentane). The major diastereomer eluted first. Major diastereomer: ^{1}H NMR: $\delta = 1.18$ (t, ^3J(H,H) = 7.2 Hz, 3H), 1.82 (dd, ^3J(H,H) = 4.0 Hz, ^2J(H,H) = 14.0 Hz, 1H), 2.22 (dd, ^3J(H,H) = 12 Hz, ^2J(H,H) = 14.0 Hz, 1H), 2.26 (m, ^3J(H,H) = 8.8 Hz, ^2J(H,H) = 12.8 Hz, 1H), 2.75 (ddd, ^3J(H,H) = 7.2, 8.8 Hz, ^2J(H,H) = 12.8 Hz, 1H), 3.58 (d, ^2J(H,H) = 12.8 Hz, 1H), 3.70 (m, 1H), 3.71 (s, 3H), 3.99 (d, ^2J(H,H) = 12.8 Hz, 1H), 4.23 (qd, ^3J(H,H) = 7.2, ^2J(H,H) = 10.8 Hz, 1H), 4.06 (qd, ^3J(H,H) = 7.2, ^2J(H,H) = 10.8 Hz, 1H), 4.27 (s, 1H), 4.50 (dd, ^3J(H,H) = 8.8, 8.8 Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR: $\delta = 14.00$, 34.35, 37.21, 52.77, 60.16, 62.33, 63.78, 75.97 (q, ^2J(C,F) = 29 Hz), 123.87 (q, ^1J(C,F) = 285 Hz), 127.80, 128.38, 130.00, 130.18, 136.90, 169.66, 173.35; MS (TOF ES$^+$): *m*/*z*: 428 [*M*+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{18}H_{22}F_3NNaO_6$: 428.1297; found: 428.1299.

X-ray data: The crystal structure of *tert*-butyl-(3-ethoxycarbonyl-4,4,4-trifluoro-3-hydroxy-butylidene)amine *N*-oxide (**3b**; $C_{11}H_{18}F_3NO_4$) was solved by using data collected from a colorless needle on a SIEMENS SMART CCD diffractometer at 120 K. The unit cell is monoclinic, $P2_1/n$, $a = 5.6754(5)$, $b = 13.066(1)$, $c = 18.625(2)$ Å, $\beta = 97.476(2)°$, $V = 1369.4(2)$ Å^3, $Z = 4$. Direct methods were applied,[16] and the structure was refined by least squares methods to a final $R = 0.040$, $Rw = 0.045$, goodness-of-fit (GOF) = 1.23. The conformation is stabilized by a hydrogen bond from the hydroxyl group to the nitrone oxygen.

The crystal structure of 2-benzyl-3-(2-ethoxycarbonyl-3,3,3-trifluoro-2-hydroxy-propyl)isoxazlidine-5-carboxylic methyl ester (**9**; $C_{18}H_{21}F_3NO$) was solved by using data collected from a colorless needle on a SIEMENS SMART CCD diffractometer at 120 K. The unit cell is monoclinic, $P2_1/c$, $a = 14.956(4)$, $b = 8.638(2)$, $c = 14.427(4)$ Å, $\beta = 94.902(2)°$, $V = 1857(1)$ Å^3, $Z = 4$. Direct methods were applied,[16] and the structure was refined by least squares methods to a final $R = 0.048$, $Rw = 0.053$, GOF = 1.43. The molecules are held together as dimers around a center of symmetry by hydrogen bonds between the hydroxyl groups and the ester oxygen atoms O2.

CCDC-189358 and -189359 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

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