Organocatalysts Promote Enantioselective 1,3-Dipolar Cycloadditions of Nitrones with 1-Cycloalkene-1-carboxaldehydes

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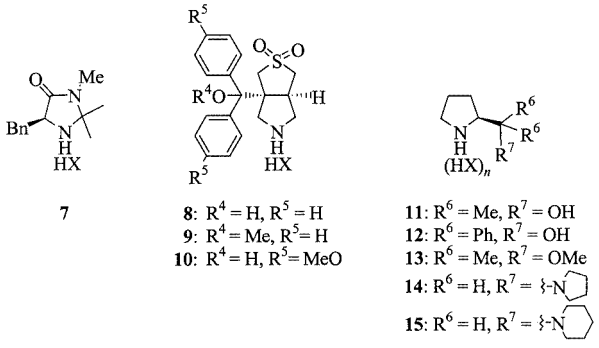
In the presence of enantiopure organocatalysts, 1-cycloalkene-1-carboxaldehydes and various nitrones furnished fused isoxazolidines. Thus, some chiral pyrrolidinium salts catalyzed the formation of such cycloadducts in high diastereo- and enantioselectivity (up to 92% *ee*). The predominant diastereomer, the *exo* one, was mostly obtained in excellent diastereoselectivity (> 99:1 *dr*). Furthermore, after recrystallization of one of the cycloadducts, this was obtained enantiomerically pure (> 99% *ee*). The absolute configuration of one of the cycloadducts was determined.

Introduction

Chiral nonracemic isoxazolidines are important building blocks for the construction of biologically active compounds.[1] One of the most efficient approaches for the preparation of such isoxazolidines is the enantioselective 1,3-dipolar cycloaddition of nitrones with olefins, catalyzed by various chiral metal-containing complexes.[2−4] Since the early 1970s when proline was found to catalyze intramolecular aldol reactions,[5] a range of other metal-free organic compounds have been applied as catalysts in a variety of organic reactions.[6] One example is the highly enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α,β-unsaturated aldehydes catalyzed by chiral imidazolidinone salts.[7] The catalytic effect of these salts has been described as being due to a reversible reaction between the catalyst and the starting aldehyde leading to an activation of the α,β-unsaturated aldehyde by iminium ion formation.[7] The LUMO energy of the alkene moiety of this intermediate is lower than that of the aldehyde. Therefore, interaction of this with the unaffected HOMO of the nitrone is facilitated, leading to an increased reaction rate.[7]

In the reaction of α,β-unsaturated aldehydes with nitrones, imidazolidinone salts such as **7** (Figure 1) have been found to be excellent catalysts.[7] However, to the best of our knowledge, there are only two examples in the literature of enantioselective catalyzed 1,3-dipolar cycloadditions of nitrones with 1-cycloalkene-1-carboxaldehydes, one of which employ chiral Lewis acids as catalysts,[8] and one preliminary communication by us in which organocatalysts are employed.[9]



7

8: R^4 = H, R^5 = H
9: R^4 = Me, R^5 = H
10: R^4 = H, R^5 = MeO

11: R^6 = Me, R^7 = OH
12: R^6 = Ph, R^7 = OH
13: R^6 = Me, R^7 = OMe
14: R^6 = H, R^7 = ⌇-N
15: R^6 = H, R^7 = ⌇-N

Figure 1. Organocatalysts for use in 1,3-dipolar cycloadditions of nitrones **2a**−**g** with either aldehyde **1A** or **1B**

Here we report in full, our studies on the catalytic performance of some chiral pyrrolidinium salts in the 1,3-dipolar cycloaddition reaction of the 1-cycloalkene-1-carboxaldehydes **1A** and **1B** with various nitrones **2a**−**g** resulting in highly enantio- and diastereoselective formation of fused bicyclic isoxazolidines (Scheme 1).

Results and Discussion

In the absence of a catalyst and at ambient temperature in either DMF or CH_3NO_2, no reaction occurred between aldehyde **1A** and nitrone **2a** (Scheme 1).

However, when catalyst **7**[7] (HX = HCl; Figure 1) was added, reaction took place. After $NaBH_4$ reduction of the bicyclic diastereomeric aldehyde products, the major reduced cycloadduct **3a** and the minor one **4a** were obtained. As described in our preliminary communication,[9] the imidazolidinone salt **7** was, however, not an efficient catalyst

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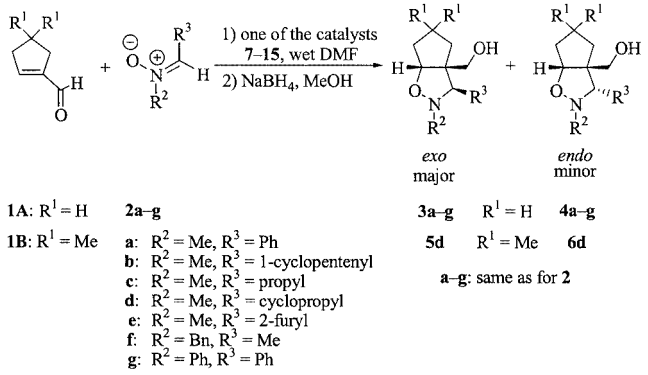


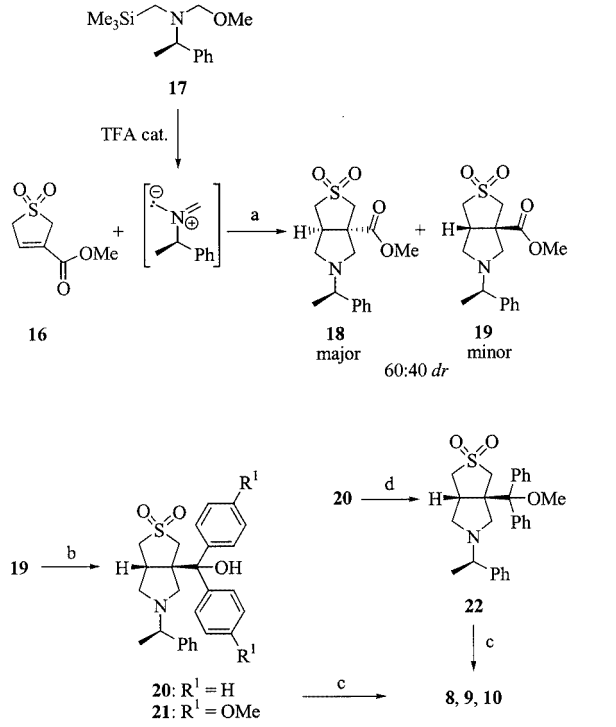
Scheme 1. The organocatalyzed reaction of either aldehyde **1A** or **1B** with various nitrones **2a**−**g**

in this reaction. Thus, **3a** was obtained as an approximately racemic mixture in a low yield.

Although compound **7** is a documented efficient catalyst for enantioselective 1,3-dipolar cycloaddition reactions of nitrones with acyclic dipolarophiles,[7] this catalyst was obviously not very efficient in reactions involving cyclic dipolarophiles. Therefore, we wanted to investigate the catalytic performance of some other chiral ammonium salts. First we wanted to test if increased rigidity and bulk in the catalyst would lead to higher enantioselectivity.

We recently described some 1,3-dipolar cycloaddition reactions of chiral azomethine ylides with chiral dipolarophiles containing a cyclic α,β-unsaturated alkenoic moiety attached to camphorsultam.[10] Using this approach, a facile method was established for the preparation of enantiopure highly functionalized bicyclic pyrrolidines. Such pyrrolidines should be very rigid and further transformation of the functional groups should lead to compounds containing bulky groups. Exploiting our recent results, we decided to prepare the rigid azabicyclo[3.3.0]octanes **8**−**10** (Scheme 2 and Figure 1) and to evaluate their potential as catalysts in the reaction depicted in Scheme 1. In the 1,3-dipolar cycloaddition reactions of chiral azomethine ylides with chiral cyclic dipolarophiles, the chirality of the azomethine ylide is more important than that of the dipolarophile for obtaining high diastereoselectivity.[10] Thus, methyl 2,5-dihydrothiophenecarboxylate (**16** with S instead of SO_2; Scheme 2) reacts with the ylide derived from *ent*-**17** to give a mixture of the major and the minor diastereomer *ent*-**18** and *ent*-**19** (both with S instead of SO_2; 64:36 *dr*), respectively.[10] After separation of the diastereomers, the major one can be transformed to the potential catalysts **8**−**10** through a few steps by oxidation of the sulfur moiety. However, in order to eliminate this oxidation step, we have chosen to use the methyl sulfolenecarboxylate **16** as the starting dipolarophile.

Thus, the chiral azomethine ylide produced from the (*R*)-phenylethylamine derivative **17** and the methyl sulfolenecarboxylate **16** reacted to give the diastereomeric cycloadducts **18** and **19** (60:40 *dr*), which were separated by chromatography. Although, the major diastereomer **18** could be transformed into compounds *ent*-**8**−**10**, the minor one, **19**, was



Scheme 2. Preparation of the potential organocatalysts **8**−**10**; reagents and conditions: a) CH_2Cl_2, trifluoroacetic acid (cat.), 0 → 20 °C, 94%; b) (i) PhMgBr or *p*-$MeOC_6H_4MgBr$, THF, (ii) water, 62%; c) (i) 1-chloroethyl chloroformate, 1,8-bis(dimethylamino)-naphthalene, $ClCH_2CH_2Cl$, reflux, (ii) MeOH, reflux, 65−96% overall yield; d) (i) NaH, MeI, THF, (ii) water, 88%

chosen for further reactions. The reason for this was, that preliminary cycloaddition reactions of nitrone **2a** with aldehyde **1A** catalyzed by **8** and its enantiomer *ent*-**8** showed that the former provided a mixture of enantiomeric products with suitable retention times (the minor enantiomer eluting prior to the major one) in the GC method used for the analysis of the enantiomeric purity. Therefore, the minor diastereomer **19** was treated with the appropriate Grignard reagent to furnish either compound **20** or **21**. Etherification of **20** furnished the methyl ether **22**. Initial attempts to remove the phenylethyl groups of **20**−**22** through hydrogenation (H_2 in the presence of Pd/C) were unsuccessful. Therefore, removal of the phenylethyl groups of these was accomplished using a dealkylation reagent.[11] Thus, treatment of compounds **20**−**22** with 1-chloroethyl chloroformate, gave the desired ammonium salts **8**−**10**.

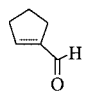
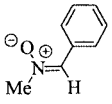
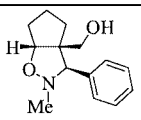
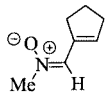
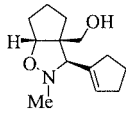
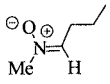
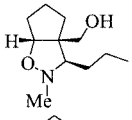
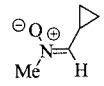
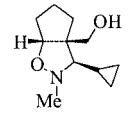
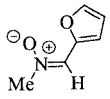
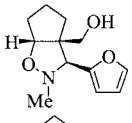
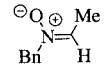
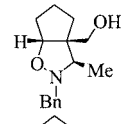
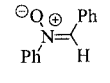
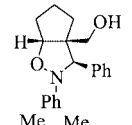
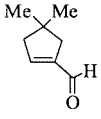
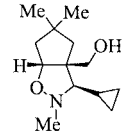
With the compounds **8**−**10** in hand, we explored their ability to catalyze the diastereo- and enantioselective addition of nitrone **2a** to cyclopent-1-enecarboxaldehyde **1A** (Scheme 1).[9] Although all these three catalysts gave a good selectivity, compound **10** was the most efficient one. In the presence of this catalyst, the reaction of nitrone **2a** with aldehyde **1A** furnished the reduced cycloadduct **3a** in a reasonable yield in up to 76% *ee* along with the separable diastereomer **4a**.[9] In terms of enantioselectivity, the solvent of choice appeared to be wet DMF. The sulfone moiety present in catalysts **8**−**10** had a major influence on the en-

antioselectivity. Thus, exchange of this moiety with a sulfur atom or a methylene group resulted in catalysts showing reduced enantioselectivity.

Although the catalysts studied so far yielded products in both fair yields and selectivity, we decided to try to search for ways to further improve the enantioselectivity in the reactions depicted in Scheme 1.

Proline and other enantiopure synthetic derivatives of this amino acid are known to activate the α-position of aliphatic aldehydes[12] and ketones[13] in Michael reactions with nitroolefins. Such organocatalysts also facilitate the Michael reactions of nitroalkanes with α,β-unsaturated cyclic[14] and acyclic ketones,[15] the reactions of α,β-unsaturated aldehydes with dienes in asymmetric Diels–Alder re-

Table 1. 1,3-Dipolar cycloaddition of aldehyde **1A** or **1B** (100 mol %) with various nitrones **2a–g** (100 mol %) in wet DMF catalyzed by **15** (·2HCl salt; 10 mol %)

Entry[a]	Aldehyde	Nitrone	Temp.	Time	*exo* product	Yield[b]	*dr exo/endo*[c]	*ee exo*[d]
1[e]	 **1A**	 **2a**	+10 °C	72 h	 **3a**	49 %	97:3	92 %
2[e,f]	**1A**	**2a**	+10 °C	120 h	**3a**	63 %	89:11	83 %
3[e,f]	**1A**	**2a**	–25 °C	120 h	**3a**	17 %	28:72	91 %
4	**1A**	 **2b**	+10 °C	120 h	 **3b**	68 %	98:2	76 % (> 99 %)[g]
5[h]	**1A**	**2b**	+10 °C	120 h	**3b**	63 %	99:1	84 % (> 99 %)[g]
6	**1A**	**2b**	–10 °C	120 h	**3b**	50 %	97:3	90 % (> 99 %)[g]
7	**1A**	 **2c**	–25 °C	144 h	 **3c**	76 %	> 99:1	57 %
8	**1A**	 **2d**	+20 °C	24 h	 **3d**	58 %	> 99:1	41 %
9	**1A**	**2d**	–20 °C	24 h	**3d**	48 %	> 99:1	41 %
10	**1A**	 **2e**	+20 °C	144 h	 **3e**	51 %	98.2	53 %
11	**1A**	 **2f**	–20 °C	96 h	 **3f**	56 %	> 99:1	70 %[i]
12	**1A**	 **2g**	+5 °C	72 h	 **3g**	–	56:44	–
13	 **1B**	**2d**	+20 °C	24 h	 **5d**	19 %	> 99:1	48 %
14	**1B**	**2d**	+20 °C	120 h	**5d**	38 %	> 99:1	37 %

[a] The nitrone (3.7 mmol) and the catalyst (0.37 mmol) were added to a solution of the aldehyde (3.7 mmol) in DMF (15 mL) and water (86 μL); after the specified time and when a satisfactory conversion had been obtained, water and EtOAc were added; extraction with EtOAc, drying (Na_2SO_4), filtration, and concentration gave a residue, which was subjected to chromatography (silica gel, EtOAc/cyclohexane as eluent); All fractions containing the desired products were collected and subjected to $NaBH_4$ reduction in MeOH; after a standard workup, the reduced diastereomeric *exo*/*endo*-cycloadducts were separated (silica gel, EtOAc/cyclohexane as eluent); no regioisomers could be detected in any instance [b] Combined overall yield of the *exo*/*endo* diastereomers. [c] Determined by GC analyses. [d] Determined by GC analyses on a chiral β-dex 325 column of the corresponding trifluoroacetate of **3a–3e** and **5d**. [e] 10:1:8 ratio of aldehyde/catalyst/nitrone. [f] No water added. [g] One recrystallization from EtOAc/heptane furnished **3b** in > 99% *ee*. [h] The nitrone, dissolved in DMF (10 mL), was slowly added (36 h) to a solution containing the aldehyde and the catalyst in DMF (5 mL) and water (86 μL). [i] Determined through ^1H NMR integration after esterification of **3f** using (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride (MTPA-Cl).

actions[16] and the newly discovered nucleophilic addition reactions of nitrones to ketones.[17] Hence, we turned our attention to the catalytic performance of some pyrrolidinium salts derived from proline.

When testing the prolinols **11**[18] and **12**[19] we found that they were inefficient as catalysts in the reaction of **1A** with nitrone **2a** (Scheme 1). However, the methyl ether **13**[20] did catalyze this reaction and after reduction of the formyl group of the corresponding cycloadduct, we obtained the isoxazolidine **3a** in high enantioselectivity (68% *ee*), albeit in a low yield.[9] A probable explanation for the lack of catalytic activity observed for the salts **11** and **12**, was that these became trapped as unreactive protonated cyclic N,O-acetals.[9] Probably due to their rigid structures, this side reaction did not seem to occur with catalysts **8**−**10**.

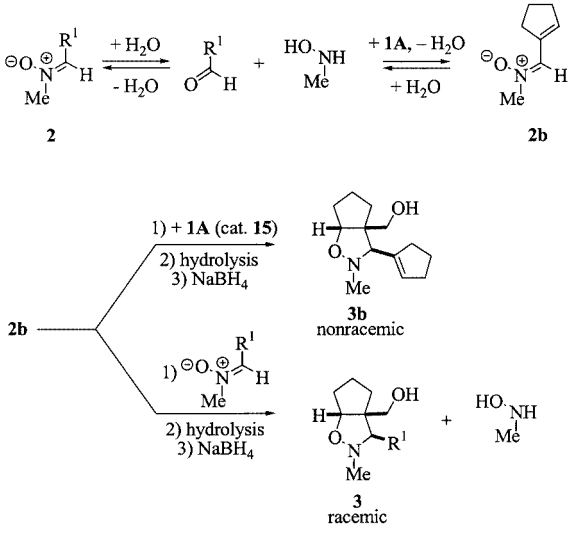
When we tested various mono- and diammonium salts of **14**[21] and **15**[21] (Figure 1) as catalysts in the reaction of aldehyde **1A** with nitrone **2a** (Scheme 1), we were pleased to find that the isoxazolidine **3a** was obtained in both a very high diastereoselectivity and enantioselectivity.[9] For example, in the presence of catalyst **15** (·2HCl salt), the major reduced cycloadduct **3a** was obtained in a reasonable yield in 97:3 *dr* and 92% *ee* (Table 1, Entry 1).[9] The best results were obtained when catalyst **15** (·2HCl salt) was used and therefore, further studies were performed using the latter. We wanted to investigate the effect of added water to the reaction mixture at both low and high temperatures. Hence, when the initial addition of water to the reaction mixture was excluded (Entry 2), both the enantioselectivity and diastereoselectivity decreased and under these dry conditions, the diastereoselectivity was to our surprise reversed in one reaction run at a low temperature (−25 °C; Entry 3). Having established that the organocatalyst **15** (·2HCl salt) (Figure 1) efficiently promoted the diastereo- and enantioselective addition of nitrone **2a** to cyclopentenecarboxaldehyde **1A**, we studied its catalytic efficiency in reactions involving other nitrones and aldehydes (Table 1, Entries 4−14). The nitrones were derived from both aliphatic and aromatic aldehydes. Although the diastereoselectivity remained high in the reactions of both aldehydes with nearly all of the nitrones, a considerable variation in enantioselectivity was observed. Thus, whereas the reduced cycloadduct **3b** was obtained in a high enantioselectivity (90% *ee*; Entry 6), that of **3d** was low (41% *ee*; Entries 8 and 9).

When treating the aldehyde **1A** with the nitrone **2g**, we obtained the known[8] diastereomeric cycloadducts **3g** and **4g** as an inseparable mixture after reduction in low diastereoselectivity (Entry 12; yield and *ee* not determined).

The structure of the aldehyde was found to be important for achieving a successful reaction. Thus, the reaction of the sterically more demanding dimethylcyclopentenecarboxaldehyde **1B** with the nitrone **2a** gave only trace amount of the corresponding major cycloadduct, albeit in high enantioselectivity (70% *ee*). However, the aldehyde **1B** did react with nitrone **2d** to give a low yield of the reduced cycloadduct **5d** in high diastereoselectivity and moderate enantioselectivity (Entry 13).

The reactions described so far have been performed on a small scale using 10−13 mol % of the catalyst. In order to demonstrate the synthetic utility of these reactions, the cyclopentenylnitrone **2b** and the aldehyde **1A** were chosen as reagent and substrate, respectively, in an experiment on a large scale using a low catalyst loading. Thus, when a stoichiometric amount of these were used on a 90 mmol scale in the presence of 5 mol % of catalyst **15** (·2HCl salt) while the reaction was allowed to go to completion at −8 °C, a diastereomeric mixture (94:6) of the reduced cycloadducts **3b** (85% *ee*) and **4b** in 80% overall yield after 11 d was obtained. One single recrystallization of the crude mixture from EtOAc/heptane improved the *ee* and *dr* of the major product **3b** to over 99% and > 99:1, respectively (56% overall yield). Thus, this result is similar to that obtained when the reaction was performed on a smaller scale using a higher catalyst loading (Table 1, Entry 6). However, the yield in the large-scale experiment was improved.

The significant difference in enantioselectivity observed, when the aldehyde **1A** reacts with various nitrones **2a**−**f**, is difficult to explain based only on steric factors. In some experiments we have noticed that a longer reaction time results in a lower enantioselectivity (compare Entries 13 and 14, Table 1). We have also found that if the concentration of the nitrone is kept at a minimum, we are able to improve the enantioselectivity (compare Entries 4 and 5, Table 1). These observations indicate that a competing reaction is taking place, which leads to racemic cycloadducts. Of course, this reaction can be the uncatalyzed reaction of the nitrones with the aldehydes. However, as mentioned above, at ambient temperature and in the absence of a catalyst, the aldehyde **1A** does not react with the nitrone **2a**. Moreover, the presence of a catalyst in the reaction of nitrone **2c** with the aldehyde **1A** at −25 °C (Entry 7, Table 1) is a prerequisite to obtain any conversion. Thus, another competing reaction is probably taking place.



Scheme 3. Proposed competing reactions furnishing either nonracemic **3b** as a by-product or one of the cycloadducts **3a**−**e** as a racemate

Such a competing reaction can involve nitrone **2b** acting as a spontaneously reacting dipolarophile (Scheme 3). The nitrone **2b** is indeed detected in many of the reactions involving the various nitrones **2** and aldehyde **1A** and is formed through hydrolysis of the original nitrone followed by condensation of the resulting hydroxylamine with aldehyde **1A** (Scheme 3). The nitrone **2b** can, of course, react with the aldehyde **1A** in the presence of catalyst **15** to give after reduction, nonracemic diastereomeric cycloadducts **3b** and **4b**. In fact, when performed at a low temperature (−10 °C), we do obtain the adduct **3b** in > 90% *ee* as a major by-product in the reaction of nitrone **2a** with aldehyde **1A**.[9]

Another possible competing reaction can occur if the π-bond of the cyclopentenyl moiety of nitrone **2b** is sufficiently activated for attack of the original nitrone. This will, after hydrolysis in situ and reduction with $NaBH_4$, result in a racemic cycloadduct **3** along with the corresponding hydroxylamine (Scheme 3). Thus, such a hypothetical competing reaction furnishing racemic cycloadducts can explain why longer reaction times and high concentrations of the original nitrones result in lower enantioselectivity.

To test the hypothesis of the nitrone **2b** acting as a spontaneously reacting dipolarophile, this nitrone was dissolved in dry DMF and stirred at ambient temperature. After five weeks, hydrolysis and reduction ($NaBH_4$) of the reaction mixture, furnished a considerably amount (ca. 30% yield) of the expected racemic product **3b**. Furthermore, when a diammonium salt (i.e. TMEDA·2HCl salt) not able to form a catalytically active iminium species was added, the reaction rate slightly increased. Thus, these observations strongly support that the competing reaction furnishing racemic cycloadducts (Scheme 3) is taking place. Although the main reason for the low *ee* values obtained in some of the reactions of the aldehydes **1A** and **1B** with the nitrones **2** is probably due to the catalyst used, the competing reaction furnishing racemic cycloadducts may also have a negative impact on the enantioselectivity.

In addition to the competing reaction furnishing racemic cycloadducts caused by the in situ production of the nitrone **2b**, its formation in the reactions depicted in Scheme 1 also leads to reduced yields. Thus, after workup and reduction, the major product is accompanied by the nonracemic by-product **3b** (Scheme 3). Reducing the amount of water added to the reaction mixture will lead to a decrease of the rate of formation of the unwanted nitrone **2b** from the original nitrone and thus the two competing reactions depicted in Scheme 3 will be suppressed. However, because the presence of water is a prerequisite for obtaining high diastereoas well as enantioselectivity (Table 1, Entries 2 and 3) another method, which will suppress the formation of **2b** is desirable. We have attempted to solve this problem by the addition of a large excess of the aldehyde corresponding to the original nitrone, in order to trap any hydroxylamine liberated. However, when we use butanal as an additive (10 equiv.) in the reaction of the corresponding nitrone **2c** with aldehyde **1A**, the yield of **3c** drops dramatically, while leaving the enantioselectivity unaffected.

Assignments of relative and absolute configurations of the major cycloadducts obtained from the reactions described above (Scheme 1, Table 1) were based on NMR spectroscopic data and chemical transformations.

The relative configuration of the major diastereomer **3a** and the minor one **4a** was determined through 1D NOE experiments (Figure 2). Thus, the minor diastereomer **4a** displayed a 2% NOE between the two methine protons shown. This NOE was absent in the major diastereomer **3a**. However, a strong NOE was observed for this isomer between the phenyl protons and the CH_2OH protons. The assignment of relative configuration of the major and minor diastereomer was also supported by the strong shielding effect of the phenyl group resulting in an upfield shift of the CH_2OH signals (δ = 3.27−3.42 ppm) of the major diastereomer **3a** relative to those of the minor diastereomer **4a** (δ = 3.56−3.75 ppm).

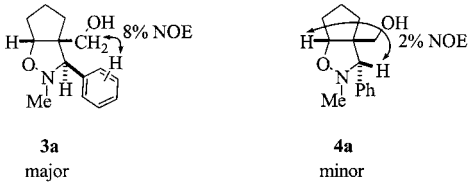
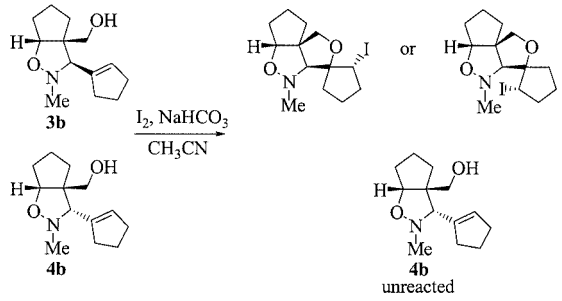


Figure 2. NOE observed in the major and minor diastereomer **3a** and **4a**, respectively

Assuming that all of the major cycloadducts **3** and **5** have the same relative configuration as that of **3a**, the R^3 substituents of those are in closer proximity to the hydroxymethyl moiety than they are in the minor cycloadducts **4** and **6** (Scheme 1). Thus, in the adduct **3b**, the alkene and the hydroxymethyl moieties will be located close enough for an iodoetherification reaction to take place. In contrast, such a reaction will not be possible for the minor diastereomer **4b**.

Indeed, when a diastereomeric mixture of **3b** and **4b** was subjected to I_2 in the presence of a base ($NaHCO_3$) in CH_3CN, only the major diastereomer **3b** undergoes iodoetherification (Scheme 4). Based on the results from the GC-MS and NMR analyses performed, a single tetracyclic adduct is formed (position of the iodine atom not determined).



Scheme 4. Iodoetherification of a mixture of the reduced major cycloadduct **3b** and the minor one **4b**

The ^1H NMR spectroscopic data of the known compound **4g**[8] allowed us to assign the same relative configu-

ration for the major cycloadduct **3g** obtained from the reaction of the aldehyde **1A** with the nitrone **2g**. Albeit the diastereoselectivity was low in this case (see Entry 12, Table 1), we were thus able to establish that this reaction also proceeded with *exo* selectivity.

The general *exo* selectivity observed in this work is opposite to that obtained when chiral Lewis acid catalysts are used in the reaction of aldehyde **1A** with *C*,*N*-diaryl nitrones.[8]

The *exo* selectivity can originate either from an *exo* attack of the (*Z*) forms of the nitrones **2a**−**g** or from an *endo* attack of the (*E*) forms of those (Figure 3).

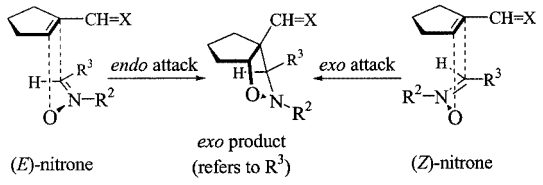
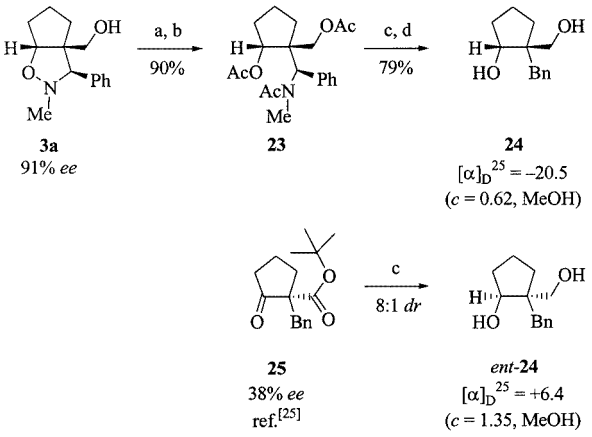


Figure 3. Origin of diastereoselectivity in the reactions of the nitrones **2a**−**g** with the reactive intermediate from cyclopentenecarboxaldehyde **1A** and catalyst **15**; the definition of *exo* and *endo* attack is related to the α,β-unsaturated system

Some aliphatic aldonitrones have previously been assigned the (*Z*) configuration, and acyclic nitrones in general exist almost exclusively in their (*Z*) forms with a large barrier of interconversion into the (*E*) form.[22] However, this barrier varies depending on the reaction conditions used. It has for example been demonstrated that traces of benzoic acid markedly reduce the barrier to isomerization.[23] Thus, a more reactive (*E*) isomer of the nitrone can be present due to such an isomerization. However, because it has been reported that some aldonitrones react in their (*Z*) forms with α,β-unsaturated aldehydes under similar conditions to those used in this work,[7] it is reasonable to believe that the major attack of the nitrones **2a**−**g** to aldehydes **1A** and **1B** proceeds in an *exo* mode with the nitrones adopting the (*Z*) configuration (Figure 3).

The absolute configuration of one of the major reduced cycloadducts, **3a**, could after transformation to the diol **24** be assigned by comparision of the sign of optical rotation of the latter with that of an independently prepared sample (Scheme 5).

We first tried to prepare the diol **24** directly from the reduced cycloadduct **3a** by hydrogenation in one single step. However, only N−O cleavage was observed. As demonstrated by others, similar difficulties were encountered in attempts to simultaneously reduce both N−O and N−Bn bonds of isoxazolidines.[24] Therefore, an alternative approach was chosen. Hydrogenolysis of the N−O bond of **3a** (91% *ee*) was followed by acetylation to give compound **23**. Reduction of the ester groups and the *N*-Ac moiety of **23** using $LiAlH_4$ gave an amino diol which, after catalytic hydrogenation, furnished the desired diol **24** {$[\alpha]_D^{25} = -20.5$ (c = 0.62, MeOH)}. An authentic sample of 38% *ee* of compound **25**[25] with known absolute configuration was reduced using $LiAlH_4$ to give *ent*-**24** {$[\alpha]_D^{25} = +6.4$ (c = 1.35, MeOH)} as the major product.



Scheme 5. Preparation of diol **24** and the enantiomer *ent*-**24** from compound **3a** and **25**, respectively; reagents and conditions: a) $Pd(OH)_2$, HCl, MeOH, H_2; b) AcCl, pyridine, CH_2Cl_2; c) (i) $LiAlH_4$, THF, (ii) water; d) Pd/C, H_2, MeOH

Thus, on the basis of the reasoning given above, the major reduced cycloadduct obtained from aldehyde **1A** and the nitrone **2a** is the stereoisomer **3a**. Although not certain, it is reasonable to assume that all the major cycloadducts obtained from the reactions of the nitrones **2b**−**g** with either the aldehyde **1A** or **1B** have related configurations.

The sense of enantioselectivity observed in these reactions may be due to steric factors in the reactive iminium ion intermediate. Considering only these factors, the sense of π-facial selectivity observed, when the nitrones **2a**−**g** reacted with aldehyde **1A** in the presence of catalyst **15** (·2HCl salt), can be explained through the models depicted in Figure 4. Thus, either (*Z*)- or (*E*)-iminium ion formation from the catalyst and the aldehyde can occur. The π-moiety from the aldehyde can adopt either an *s*-*cis* or an *s*-*trans* conformation. This results in the four possible intermediates **A**−**D** (Figure 4). Out of these, **A** and **D** are unlikely to be the major reactive ones, because in order to explain the pathway leading to the major enantiomers of the cycloadducts, attack of the nitrones have to occur from the sterically hindered side of the π-bond. However, attack on either the intermediate **B** or **C** by the nitrones from the sterically least hindered side will yield the major enantiomers obtained in this work.

Out of the two isomers **B** and **C**, the latter has one of the π-faces efficiently shielded by the piperidinium ring and should therefore best explain the observed enantioselectivity. In isomer **B**, due to the long distance between the piperidinium moiety of the catalyst and the reacting π-bond of the aldehyde moiety, such an efficient shielding cannot be obtained and thus attack of the nitrones are expected to occur with low enantioselectivity. Using a simple molecular modeling program (CS Chem3D Pro™ 4.0), we have calculated the relative energies of simplified models of the intermediates **B** and **C** in which the piperidinium moiety has been replaced by a trimethylammonium one. The variation

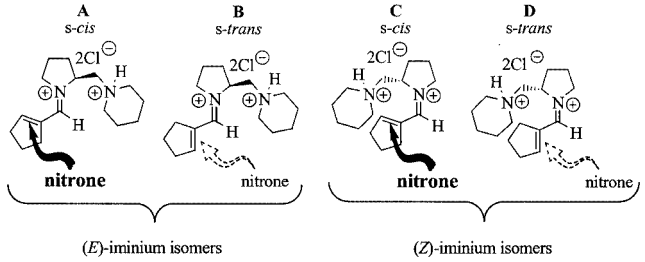


Figure 4. Potential reactive iminium ion intermediates **A**−D from catalyst **15** and aldehyde **1A**; as described by the arrows, α-Si,β-Re attack on the α,β-unsaturated iminium ion derivative gives the major enantiomer of the product obtained; filled arrows indicate attack from the front, and the unfilled ones attack from the back

in energies for the low-energy conformations of these intermediates all lie within 1 kcal/mol. According to the Hammet-Curtin principle, the reaction does not have to proceed via the most stable intermediate. Moreover, the charges in the dication intermediate as well as their counterions may also play a major role here in directing the approach of the incoming nitrone. Thus, although the dication intermediate **C** best seems to explain the observed enantioselectivity, intermediate **B** cannot be ruled out as the major reactive intermediate.

Conclusion

In summary, when catalyzed by various pyrrolidinium salts, nitrones undergo 1,3-dipolar cycloaddition reactions with 1-cycloalkene-1-carboxaldehydes, furnishing reasonable yields of fused *exo*-bicyclic isoxazolidines in both high diastereoselectivities and enantioselectivities. One of the cycloadducts could be obtained enantiomerically pure (> 99% *ee*) after recrystallization. The low loading of both the catalyst and the substrate aldehyde that can be employed for achieving a reasonable yield of the cycloadducts, should make this procedure useful for preparing enantiopure fused bicyclic isoxazolidines.

Experimental Section

General Remarks: All chemicals were used as received. THF (K, benzophenone), CH_2Cl_2, $ClCH_2CH_2Cl$ (both CaH_2) were distilled from the indicated drying agents. Diethyl ether, ethyl acetate (EtOAc) and cyclohexane were distilled prior to use. The ^1H and ^{13}C NMR spectra were recorded with a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) instrument. Preparative liquid chromatography was performed on straight phase silica gel 60 (Merck, 230−400 mesh). GC analyses were carried out using either a capillary column EC-5, 30 m, 0.32 mm i.d., d_f = 0.25 μm, carrier gas N_2 or a chiral capillary column β-Dex 325, 30 m, 0.25 mm i.d., d_f = 0.25 μm, carrier gas He. The elemental analyses (C, H, N) were performed by Mikro Kemi AB, 75228 Uppsala, Sweden. Boiling points are uncorrected and given as air bath temperatures (bath temp./mbar) in a bulb-to-bulb (Büchi GKR-51) apparatus. Optical rotations were measured with a Perkin−Elmer 241 MC polarimeter in a 1-dm cell. Mass spectra were recorded with a Saturn 2000 instrument, coupled to a Varian 3800 GC instrument. The nitrones **2a**−**g** were used without further purification and were generated from the corresponding hydroxylamine and aldehyde.[26] Aldehydes **1A**[27] and **1B**[28] and catalysts **7**,[16] **11**,[18] **12**,[19] **13**,[20] **14**[21] and **15**[21] were prepared according to literature procedures.

Methyl (3a*R*,6a*S*)-5-[(1*R*)-1-Phenylethyl]tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-3a(3*H*)-carboxylate 2,2-Dioxide (18) and Methyl (3a*S*,6a*R*)-5-[(1*R*)-1-Phenylethyl]tetrahydro-1*H*-thieno[3,4-*c*]-pyrrole-3a(3*H*)-carboxylate 2,2-Dioxide (19): To a solution of methyl 2,5-dihydrothiophene-3-carboxylate 1,1-dioxide (**16**)[29] (6.73 g, 38.2 mmol) in TFA/CH_2Cl_2 (5 mM; 50 mL) at 0 °C, *N*-[(*R*)-1-phenylethyl]-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine (**17**)[30] (10.0 g, 39.8 mmol) was added slowly (0.5 h). The reaction mixture was warmed to room temperature and after 0.5 h, $NaHCO_3$ (aq. satd.; 100 mL) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the pooled organic phases were dried ($MgSO_4$) and concentrated. ^1H NMR analysis of the crude product indicated a diastereomeric ratio of 60:40 (**18/19**). The residue was subjected to column chromatography [SiO_2; EtOAc/cyclohexane (10 → 60%)] to yield **18** (6.59 g, 53%), a mixture of the diastereomers **18** and **19** (0.70 g, 6%), and **19** (4.29 g, 35%). According to their NMR spectra, both diastereomers, which were obtained as highly viscous oils, were diastereomerically pure. **18 (Major):** $[\alpha]_D^{25}$ = +43.1 (*c* = 1.33, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.37 (d, *J* = 6.6 Hz, 3 H), 2.39 (d, *J* = 9.7 Hz, 1 H), 2.64 (d, *J* = 9.3 Hz, 1 H), 2.66 (d, *J* = 9.3 Hz, 1 H), 2.95−3.11 (m, 3 H), 3.28−3.53 (m, 3 H), 3.74 (s, 3 H), 3.74−3.82 (m, 1 H), 7.22−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9, 40.9, 53.1, 54.0, 54.8, 55.9, 57.3, 62.9, 63.3, 126.7, 127.4, 128.6, 144.3, 172.9 ppm. MS (EI): *m*/*z* (%) = 324 (8) $[M + H]^+$, 308 (100), 292 (3), 245 (9), 218 (7) 105 (25). $C_{16}H_{21}NO_4S$ (323.41): calcd. C 59.4, H 6.5, N 4.3; found C 59.3, H 6.7, N 4.2. **19 (Minor):** $[\alpha]_D^{25}$ = +8.5 (*c* = 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.35 (d, *J* = 6.6 Hz, 3 H), 2.48−2.60 (m, 2 H), 2.61 (d, *J* = 9.4 Hz, 1 H), 2.90 (dd, *J* = 8.6, 13.1 Hz, 1 H,), 3.09 (d, *J* = 9.4 Hz, 1 H), 3.15−3.42 (m, 4 H), 3.79 (s, 3 H), 3.89 (dd, *J* = 2.6, 13.8 Hz, 1 H), 7.21−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8, 40.8, 53.2, 54.1, 54.4, 56.2, 57.9, 62.2, 63.2, 126.7, 127.4, 128.6, 144.3, 173.0 ppm. MS (EI): *m*/*z* (%) = 324 (11) $[M + H]^+$, 308 (100), 292 (2), 245 (10), 218 (2), 105 (19). $C_{16}H_{21}NO_4S$ (323.41): calcd. C 59.4, H 6.5, N 4.3; found C 59.7, H 6.6, N 4.4.

[(3a*S*,6a*R*)-2,2-Dioxido-5-[(1*R*)-1-phenylethyl]tetrahydro-1*H*-thieno-[3,4-*c*]pyrrol-3a(3*H*)-yl]bis(4-methoxyphenyl)methanol (21): To a solution of the minor diastereomer **19** (2.30 g, 7.1 mmol) from above in THF (75 mL), *p*-$MeOC_6H_4MgBr$ (0.5 M in diethyl ether; 57 mL, 28 mmol) was added over a period of 2 h. After an additional 5 h, water (200 mL) and EtOAc (200 mL) were added. The aqueous phase was extracted with EtOAc (2 × 100 mL) and the pooled organic phases were dried (Na_2SO_4) and concentrated to give a residue, which was subjected to column chromatography [SiO_2; EtOAC/cyclohexane (5 → 100%)] followed by recrystallization from EtOAc/heptane. This afforded compound **21** (2.23 g, 62%) as colorless crystals in > 98% purity (GC). M.p. 205−206 °C. $[\alpha]_D^{25}$ = +10.6 (*c* = 0.42, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.40 (d, *J* = 6.1 Hz, 3 H), 2.45−3.10 (m, 6 H), 3.25−3.35 (m, 1 H), 3.53−3.80 (m, 3 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 6.68 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.94 (s, OH), 7.08−7.39 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 38.4, 52.7, 55.0, 55.1, 55.2, 56.3, 57.0, 61.6, 63.5, 82.5, 113.0, 113.4, 126.6, 127.4, 128.4, 128.5, 128.7, 135.4, 137.9, 143.3, 158.2, 158.6 ppm. MS (EI): *m*/*z* (%) = 508 (4) $[M + H]^+$, 492 (26), 264 (10), 243 (37), 201 (67), 135 (100), 105 (65). $C_{29}H_{33}NO_5S$ (507.64): calcd. C 68.6, H 6.6, N 2.8; found C 68.3, H 6.5, N 2.7.

[(3a*S*,6a*R*)-2,2-Dioxido-5-[(1*R*)-1-phenylethyl]tetrahydro-1*H*-thieno-[3,4-*c*]pyrrol-3a(3*H*)-yl]diphenylmethanol (20): The title compound was prepared from compound **19** and phenylmagnesium bromide according to the same procedure as that for the preparation of **21** with the following exception. The crude product was chromatographed with diethyl ether/cyclohexane as eluent. No further purification was necessary. Yield 62%, colorless crystals, > 99% purity (GC), m.p. 201−202 °C. $[\alpha]_D^{25}$ = +37.3 (*c* = 0.94, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.40 (d, *J* = 6.4 Hz, 3 H), 2.45−3.11 (m, 6 H), 3.25−3.35 (m, 1 H), 3.60−3.75 (m, 3 H), 7.11−7.46 (m, 16 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 38.4, 52.8, 54.7, 56.2, 57.0, 61.6, 63.5, 82.9, 126.5, 127.0, 127.3, 127.4, 127.5, 127.8, 128.2, 128.5, 143.0, 143.2, 145.5 ppm. MS (EI): *m*/*z* (%) = 448 (24) $[M + H]^+$, 432 (65), 264 (55), 184 (20), 105 (100). $C_{27}H_{29}NO_3S$ (447.59): calcd. C 72.5, H 6.5, N 3.1; found C 72.8, H 6.6, N 3.2.

(3a*S*,6a*R*)-3a-[(Methoxy)diphenylmethyl]-5-[(1*R*)-1-phenylethyl]-hexahydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-Dioxide (22): To a cold (0 °C) solution of compound **20** (1.43 g, 3.2 mmol) in THF (50 mL) was added NaH (400 mg, 16.7 mmol), followed by the addition of MeI (1.5 g, 10.6 mmol). After standing overnight, water (50 mL) and EtOAc (50 mL) were added, followed by extraction of the aqueous phase with EtOAc (2 × 50 mL). The pooled organic phases were dried (Na_2SO_4), concentrated and the residue was purified by flash chromatography [SiO_2; EtOAc/cyclohexane (0 → 40%)] to afford **22** (1.30 g, 88%) as colorless crystals in purity > 99% (GC). M.p. 75−77 °C. $[\alpha]_D^{25}$ = +34.7 (*c* = 0.38, $CHCl_3$). ^1H NMR (C_6D_6): δ = 1.15 (d, *J* = 6.5 Hz, 3 H), 2.31−2.68 (m, 5 H), 2.80 (s, 3 H), 2.98−3.35 (m, 4 H), 3.75−3.82 (m, 1 H), 7.00−7.25 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.3, 42.4, 53.2, 54.1, 55.6, 58.8, 62.8, 64.3, 64.8, 90.0, 126.8, 127.6, 127.9, 128.0, 128.1, 128.2, 130.3, 130.5, 138.9, 139.2, 145.0 ppm. MS (EI): *m*/*z* (%) = 462 (4) $[M + H]^+$, 446 (35), 431 (50), 264 (15), 197 (57), 105 (100). $C_{28}H_{31}NO_3S$ (461.62): calcd. C 72.8, H 6.8, N 3.0; found C 72.9, H 6.9, N 3.0.

2-[(3a*S*,6a*R*)-2,2-Dioxidotetrahydro-1*H*-thieno[3,4-*c*]pyrrol-3a(3*H*)-yl]bis-(4-methoxyphenyl)methanol Hydrochloride (10): 1-Chloroethyl chloroformate (2.5 g, 17 mmol) was added to a solution of **21** (2.23 g, 4.39 mmol) and 1,8-bis(dimethylamino)naphthalene (1.88 g, 8.8 mmol) in $ClCH_2CH_2Cl$ (40 mL). After 0.5 h at room temperature, the reaction mixture was refluxed for 8 h. After cooling, water (10 mL) and EtOAc (150 mL) were added, followed by the addition of HCl (aq. 2 M; 50 mL). The organic phase was extracted with HCl (aq. 2 M; 50 mL), $NaHCO_3$ (aq. satd.; 50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography [SiO_2; EtOAc/cyclohexane (5 → 80%)]. The resulting carbamate intermediate was dissolved in MeOH (5 mL) and refluxed for 0.5 h. Concentration afforded **10** (1.55 g, 80%) in > 99% purity (GC; free base). Recrystallization from 2-propanol/MeOH gave colorless needles of **10** (1.25 g, 65%). M.p. 188−190 °C (dec). $[\alpha]_D^{25}$ = −53.4 (*c* = 1.1, MeOH). ^1H NMR [$(CD_3)_2SO$]: δ = 1.78−1.98 (m, 1 H), 3.12−3.75 (m, 6 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.93−4.25 (m, 2 H), 6.58 (s, −OH), 6.84−6.96 (m, 4 H), 7.19−7.30 (m, 4 H), 8.80 (s, NH), 9.90 (s, NH) ppm. ^{13}C NMR (CD_3OD): δ = 41.1, 50.5, 51.8, 55.8 (2 C), 56.4, 57.1, 57.7, 84.0, 114.5, 114.8, 130.9 (2 C), 136.2, 137.4, 160.6, 160.8 ppm. MS (EI; free base): *m*/*z* (%) = 404 (23) $[M + H]^+$, 386 (12), 243 (14), 135 (100). $C_{21}H_{25}NO_5S{\cdot}HCl$ (439.95): calcd. C 57.3, H 6.0, N 3.2; found C 57.4, H 6.0, N 3.2.

(3a*S*,6a*R*)-3a-[(Methoxy)diphenylmethyl]hexahydro-1*H*-thieno-[3,4-*c*]pyrrole 2,2-Dioxide Hydrochloride (9): The title compound was prepared from **22** according to the same procedure as that described for the preparation of compound **10**. Yield 96%, colorless crystals, > 99% purity (GC; free base), m.p. 298−299 °C (dec). $[\alpha]_D^{25}$ = −29.7 (*c* = 0.67, MeOH). ^1H NMR [$(CD_3)_2SO$]: δ = 1.30−1.55 (m, 1 H), 3.03 (s, 3 H), 3.04−3.62 (m, 5 H), 3.68 (d, *J* = 12.3 Hz, 1 H), 4.12 (d, *J* = 14.9 Hz, 1 H), 4.15−4.31 (m, 1 H), 7.12−7.51 (m, 10 H), 8.70 (s, NH), 10.00 (s, NH) ppm. ^{13}C NMR [$(CD_3)_2SO$]: δ = 41.1, 47.4, 50.4, 52.6, 55.0, 56.4, 56.5, 89.5, 128.1, 128.2, 128.4, 128.7, 129.3, 131.2, 136.2, 137.9 ppm. MS (EI; free base): *m*/*z* (%) = 358 (100) $[M + H]^+$, 326 (8), 197 (82), 105 (68). $C_{20}H_{23}NO_3S{\cdot}HCl$ (393.93): calcd. C 61.0, H 6.1, N 3.6; found C 60.8, H 6.2, N 3.6.

[(3a*S*,6a*R*)-2,2-Dioxidotetrahydro-1*H*-thieno[3,4-*c*]pyrrol-3a(3*H*)-yl]diphenylmethanol Hydrochloride (8): The title compound was prepared from compound **20** according to the same procedure as that described for the preparation of compound **10**. Yield 65%, colorless crystals, > 99% purity (GC; free base). M.p. 292−293 °C (dec). $[\alpha]_D^{25}$ = −40.7 (*c* = 0.61, MeOH). ^1H NMR [$(CD_3)_2SO$]: δ = 1.51−1.97 (m, 1 H), 3.08−4.43 (m, 8 H), 6.75 (s, OH), 7.22−7.41 (m, 10 H), 9.20 (s, 2 H, NH_2) ppm. ^{13}C NMR [$(CD_3)_2SO$]: δ = 40.1, 48.5, 50.8, 54.5, 55.7, 56.9, 82.9, 127.5, 127.7, 127.8, 128.2 (2 C), 128.5, 143.2, 144.3 ppm. MS (EI; free base): *m*/*z* (%) = 344 (25) $[M + H]^+$, 325 (12), 183 (22), 160 (25), 105 (100). $C_{19}H_{21}NO_3S{\cdot}HCl$ (379.90): calcd. C 60.1, H 5.8, N 3.7; found C 60.3, H 5.9, N 3.8.

General Method for the 1,3-Dipolar Cycloaddition Reactions: The reactions were performed as described above (footnote [a], Table 1). When performed on a larger scale, a slightly modified procedure was used. To a cold (−8 °C) solution of nitrone **2b** (11.3 g, 90.3 mmol) in dimethylformamide (DMF; 150 mL) and water (0.75 mL), the aldehyde **1A** (8.68 g, 90.3 mmol) and the catalyst **15** (·2HCl salt; 1.08 g, 4.5 mmol) were added. The reaction mixture was stirred at −8 °C for 264 h, followed by the addition of water (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (5 × 50 mL) and the pooled organic phases were dried ($MgSO_4$) and concentrated. To the crude product mixture at 0 °C, MeOH (100 mL) and $NaBH_4$ (3.8 g, 100 mmol) were added. After stirring at ambient temperature for 30 min, the reaction was quenched by the addition of water (100 mL) and NH_4Cl (aq. satd.; 50 mL), followed by addition of EtOAc (100 mL). The aqueous phase was extracted with EtOAc (6 × 50 mL). The pooled organic phases were dried ($MgSO_4$) and concentrated. The resulting mixture of **3b** (94:6 *dr*, 85% *ee*; GC) and **4b** was placed on a short pad of silica gel and eluted with EtOAc/cyclohexane (20 → 100%). This furnished a diastereomeric mixture of **3b** and **4b** (16.1 g, 72.1 mmol; 80%) in 95% chemical purity (GC). One recrystallization from EtOAc/heptane furnished **3b** (11.2 g, 50.2 mmol; 56%) as colorless crystals in > 99% chemical purity and in > 99:1 *dr* and > 99% *ee*.

[(3*R*,3a*R*,6a*R*)-2-Methyl-3-phenylhexahydro-3a*H*-cyclopenta[*d*]-isoxazol-3a-yl]methanol (3a): 93% *ee*. M.p. 68−70 °C. $[\alpha]_D^{25}$ = −153 (*c* = 0.80, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.26−1.32 (m, OH), 1.46−1.65 (m, 2 H), 1.76−2.06 (m, 4 H), 2.57 (s, 3 H), 3.23 (s, 1 H), 3.31 (dd, *J* = 6.7, 11.2 Hz, 1 H), 3.39 (dd, *J* = 4.9, 11.2 Hz, 1 H), 4.30 (d, *J* = 5.1 Hz, 1 H), 7.28−7.38 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.0, 32.0, 33.6, 42.8, 64.0, 65.5, 81.2, 86.1, 127.3, 128.0, 128.8, 136.1 ppm. MS (EI): *m*/*z* (%) = 233 (57) $[M^+]$, 216 (2), 134 (100). $C_{14}H_{19}NO_2$ (233.31): calcd. C 72.1, H 8.2, N 6.0; found C 72.2, H 8.3, N 6.0.

[(3*S*,3a*R*,6a*R*)-2-Methyl-3-phenylhexahydro-3a*H*-cyclopenta[*d*]-isoxazol-3a-yl]methanol (4a): *ee* not determined. M.p. 68−71 °C. ^1H NMR ($CDCl_3$): δ = 0.90−1.02 (m, 1 H), 1.42−1.60 (m, 2 H), 1.75−2.01 (m, 4 H), 2.60 (s, 3 H), 3.60 (d, *J* = 10.9 Hz, 1 H), 3.63

(s, 1 H), 3.71 (d, J = 10.9 Hz, 1 H), 4.47−4.52 (m, 1 H), 7.25−7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 30.6, 35.1, 43.8, 64.1, 66.2, 77.7, 85.1, 127.4, 128.1, 128.3, 137.5 ppm. MS (EI): *m*/*z* (%) = 233 (63) [M^+], 216 (2), 134 (100). $C_{14}H_{19}NO_2$ (233.31): calcd. C 72.1, H 8.2, N 6.0; found C 72.3, H 8.1, N 5.9.

[(3*R*,3a*R*,6a*R*)-3-(Cyclopent-1-en-1-yl)-2-methylhexahydro-3a*H*-cyclopenta[*d*]isoxazol-3a-yl]methanol (3b): > 99% *ee*. M.p. 123−125 °C. $[\alpha]_D^{20}$ = −155 (*c* = 0.51, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ = 1.35−1.99 (m, 8 H), 2.23−2.48 (m, 5 H), 2.58 (s, 3 H), 2.74 (s, 1 H), 3.43 (dd, J = 6.1, 11.0 Hz, 1 H), 3.60 (dd, J = 3.5, 11.0 Hz, 1 H), 4.40 (d, J = 5.4 Hz, 1 H), 5.66−5.70 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.0, 24.0, 31.8, 32.4, 33.6, 34.8, 43.3, 63.1, 65.7, 78.1, 85.3, 127.6, 139.1 ppm. MS (EI): *m*/*z* (%) = 223 (40) [M^+], 125 (50), 68 (100). $C_{13}H_{21}NO_2$ (223.31): calcd. C 69.9, H 9.5, N 6.3; found C 69.8, H 9.6, N 6.2.

[(3*S*,3a*R*,6a*R*)-3-(Cyclopent-1-en-1-yl)-2-methylhexahydro-3a*H*-cyclopenta[*d*]isoxazol-3a-yl]methanol (4b): *ee* not determined. ^{1}H NMR ($CDCl_3$): δ = 1.23−1.93 (m, 9 H), 2.13−2.41 (m, 4 H), 2.60 (s, 3 H), 3.00 (s, 1 H), 3.60 (d, J = 10.8 Hz, 1 H), 3.69 (d, J = 10.8 Hz, 1 H), 4.37 (t, J = 4.6 Hz, 1 H), 5.60−5.66 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.3, 25.6, 30.7, 32.3, 34.7, 34.8, 44.3, 63.4, 67.0, 75.3, 85.2, 127.9, 139.7 ppm. MS (EI): *m*/*z* (%) = 223 (55) [M^+], 125 (42), 68 (100).

[(3*R*,3a*R*,6a*R*)-2-Methyl-3-propylhexahydro-3a*H*-cyclopenta[*d*]-isoxazol-3a-yl]methanol (3c): 57% *ee*. B.p. 120 °C/0.9 mbar. $[\alpha]_D^{25}$ = −58.3 (*c* = 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J = 7.0 Hz, 3 H), 1.22−1.91 (m, 10 H), 2.11−2.18 (m, 1 H), 2.59 (s, 3 H), 3.21 (s, OH), 3.45 (d, J = 10.6 Hz, 1 H), 3.85 (d, J = 10.6 Hz, 1 H), 4.43 (d, J = 5.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 20.4, 24.2, 28.7, 31.7, 33.1, 42.9, 61.7, 65.2, 76.0, 85.3 ppm. MS (EI): *m*/*z* (%) = 199 (14) [M^+], 156 (100), 102 (39). $C_{11}H_{21}NO_2$ (199.29): calcd. C 66.3, H 10.6, N 7.0; found C 66.2, H 10.7, N 6.9.

[(3*R*,3a*R*,6a*R*)-3-Cyclopropyl-2-methylhexahydro-3a*H*-cyclopenta[*d*]isoxazol-3a-yl]methanol (3d): 41% *ee*. M.p. 83−85 °C. $[\alpha]_D^{25}$ = −41.4 (*c* = 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.15−0.24 (m, 1 H), 0.29−0.38 (m, 1 H), 0.53−0.70 (m, 2 H), 0.86−1.00 (m, 1 H), 1.27−1.84 (m, 7 H), 2.67 (s, 3 H), 2.83 (s, OH), 3.60 (d, J = 10.5 Hz, 1 H), 3.96 (d, J = 10.5 Hz, 1 H), 4.40 (d, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −0.2, 3.9, 7.2, 23.9, 31.7, 33.5, 43.2, 62.5, 66.1, 81.7, 85.1 ppm. MS (EI): *m*/*z* (%) = 197 (33) [M^+], 156 (20), 100 (87), 84 (100). $C_{11}H_{19}NO_2$ (197.27): calcd. C 67.0, H 9.7, N 7.1; found C 67.0, H 9.6, N 7.1.

(3*S*,3a*R*,6a*R*)-3a-(Hydroxymethyl)-2-methylhexahydro-2*H*-cyclopenta[*d*]isoxazole-3-carbaldehyde (3e): 53% *ee*. M.p. 86−88 °C. $[\alpha]_D^{25}$ = −93.5 (*c* = 0.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.35−2.05 (m, 7 H), 2.60 (s, 3 H), 3.36 (s, 1 H), 3.47 (d, J = 11.4 Hz, 1 H), 3.52 (d, J = 11.4 Hz, 1 H), 4.49 (d, J = 5.4 Hz, 1 H), 6.37−6.43 (m, 2 H), 7.44−7.47 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.8, 31.8, 33.4, 43.2, 63.8, 65.6, 75.8, 85.8, 108.6, 110.6, 142.7, 149.6 ppm. MS (EI): *m*/*z* (%) = 223 (25) [M^+], 125 (100). $C_{12}H_{17}NO_3$ (223.27): calcd. C 64.6, H 7.7, N 6.3; found C 64.5, H 7.8, N 6.2.

[(3*R*,3a*R*,6a*R*)-2-Benzyl-3-methylhexahydro-3a*H*-cyclopenta[*d*]-isoxazol-3a-yl]methanol (3f): 70% *ee*. $[\alpha]_D^{25}$ = −93.7 (*c* = 0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.12−1.25 (m, 1 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.45−1.88 (m, 5 H), 2.50 (q, J = 6.7 Hz, 1 H), 3.00 (s, OH), 3.44 (d, J = 10.6 Hz, 1 H), 3.62 (d, J = 14.4 Hz, 1 H), 3.83 (d, J = 10.6 Hz, 1 H), 4.09 (d, J = 14.4 Hz, 1 H), 4.45 (d, J = 5.7 Hz, 1 H), 7.21−7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.3, 23.8, 32.0, 32.3, 59.1, 61.7, 65.6, 68.9, 84.9, 127.2, 128.2, 128.6, 137.0 ppm. MS (EI): *m*/*z* (%) = 247 (59) [M^+], 232 (37), 150 (31), 91 (100). $C_{15}H_{21}NO_2$ (247.33): calcd. C 72.8, H 8.6, N 5.7; found C 72.8, H 8.6, N 5.8.

[(3*R*,3a*R*,6a*R*)-3-Cyclopropyl-2,5,5-trimethylhexahydro-3a*H*-cyclopenta[*d*]isoxazol-3a-yl]methanol (5d): 48% *ee*. M.p. 41−42 °C. $[\alpha]_D^{25}$ = −55.0 (*c* = 0.96, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.16−0.34 (m, 2 H), 0.51−0.71 (m, 2 H), 0.80−0.95 (m, 1 H), 1.03 (s, 3 H), 1.15 (s, 3 H), 1.40 (d, J = 13.6 Hz, 1 H), 1.48 (d, J = 13.6 Hz, 1 H), 1.64 (dd, J = 4.5, 13.6 Hz, 1 H), 1.72 (d, J = 8.3 Hz, 1 H), 1.78 (dd, J = 6.3, 13.6 Hz, 1 H), 2.72 (s, 3 H), 3.52 (s, OH), 3.63 (d, J = 10.5 Hz, 1 H), 3.98 (d, J = 10.5 Hz, 1 H), 4.58 (dd, J = 4.5, 6.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = −0.4, 4.1, 7.0, 30.1, 30.5, 42.1, 43.5, 46.2, 47.7, 63.0, 66.8, 84.1, 86.1 ppm. MS (EI): *m*/*z* (%) = 225 (34) [M^+], 184 (10), 100 (100), 84 (82). $C_{13}H_{23}NO_2$ (225.33): calcd. C 69.3, H 10.3, N 6.2; found C 69.1, H 10.2, N 6.1.

[(1*R*,2*R*)-2-Acetoxy-1-{(*R*)-[acetyl(methyl)amino](phenyl)-methyl}cyclopentyl]methyl Acetate (23): Compound **3a** (434 mg, 1.86 mmol; 91% *ee*, > 98% *de*), 20% $Pd(OH)_2$/C (100 mg) and HCl (37% aq.; 0.3 mL) in MeOH (10 mL) were stirred under hydrogen at ambient pressure and room temperature overnight. The suspension was filtered, rinsed with MeOH, followed by concentration. To the resulting amino diol were added pyridine (1.5 g) and CH_2Cl_2 (25 mL), followed by dropwise addition of AcCl (1.5 g). After 1 h, HCl (2 M; 30 mL) and EtOAc (50 mL) were added. The organic phase was extracted with $NaHCO_3$ (aq. satd.; 30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography [SiO_2; EtOAc/cyclohexane (0 → 100%)] to give the title compound (612 mg, 1.69 mmol) as an oil in 98% purity (GC). $[\alpha]_D^{25}$ = −75.2 (*c* = 0.39, $CHCl_3$). ^{1}H NMR [$(CD_3)_2SO$; * denotes peaks arising from a minor rotamer]: δ = 1.35−2.18 (m, 7.8 H), 1.76 (s, 2.4 H), 1.93 (s, 2.4 H), 1.98 (s, 2.4 H), 2.93 (s, 3 H), 3.84 (d, J = 12.0 Hz, 1 H), 4.02* (d, J = 11.9 Hz, 0.2 H), 4.10 (d, J = 12.0 Hz, 0.8 H), 5.12−5.19 (m, 1 H), 5.25* (s, 0.2 H), 6.05 (s, 0.8 H), 7.21−7.50 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$; * denotes peaks arising from a minor rotamer]: δ = 20.8*, 20.9, 21.1, 21.2, 22.0*, 22.4, 30.9, 31.0*, 31.7, 34.1, 52.6*, 52.9, 57.4, 62.9*, 65.7, 67.0*, 79.1, 79.7*, 127.1, 127.6*, 128.2, 128.5*, 128.6*, 129.4, 138.8*, 139.2, 169.8*, 170.3*, 170.4, 170.8, 171.1, 171.4* ppm. MS (EI): *m*/*z* (%) = 361 (8) [M^+], 302 (10), 162 (70), 120 (100). $C_{20}H_{27}NO_5$ (361.43): calcd. C 66.5, H 7.5, N 3.9; found C 66.7, H 7.6, N 3.9.

(1*R*,2*R*)-2-Benzyl-2-(hydroxymethyl)cyclopentanol (24) by Reduction of 23: To a cold (0 °C) suspension of $LiAlH_4$ (0.48 g, 12.7 mmol) in dry THF (10 mL), compound **23** (460 mg, 1.27 mmol; 91% *ee*, > 98% *de*) was added, dissolved in dry THF (10 mL). The reaction mixture was then allowed to reach room temperature. After 0.5 h, water (0.53 mL) and NaOH (aq. 15%, 0.53 mL) were added, followed by the addition of water (1.6 mL). The resulting suspension was filtered, the solid rinsed with EtOAc and the filtrate concentrated. The resulting amino diol was dissolved in MeOH (5 mL). 10% Pd/C (100 mg) was added, followed by stirring under hydrogen at ambient pressure and room temperature overnight. Filtration, followed by concentration furnished the crude diol **24**. Flash chromatography [SiO_2; EtOAc/cyclohexane (0 → 100%)] gave the title compound as colorless crystals in > 99% purity (GC). M.p. 116−118 °C. $[\alpha]_D^{25}$ = −20.5 (*c* = 0.62, MeOH). ^{1}H NMR ($CDCl_3$): δ = 0.93−1.09 (m, 1 H), 1.50−2.16 (m, 5 H), 2.23−2.31 (m, OH), 2.51 (d, J = 13.4 Hz, 1 H), 2.60−2.65 (m, OH), 3.10 (d, J = 13.4 Hz, 1 H), 3.27 (dd, J = 3.0, 10.4 Hz, 1 H), 3.55 (dd, J = 5.1, 10.4 Hz, 1 H), 4.18 (dt, J = 3.3, 7.4 Hz, 1 H), 7.15−7.35 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 29.2, 31.6, 33.0, 49.6, 68.1, 80.1, 125.9, 128.0, 130.5, 139.0 ppm. MS (EI):

m/z (%) = 207 (5) $[M + H]^+$, 188 (22), 171 (100), 115 (22), 91 (27). $C_{13}H_{18}O_2$ (206.28): calcd. C 75.7, H 8.8; found C 75.7, H 8.8.

(1*S*,2*S*)-2-Benzyl-2-(hydroxymethyl)cyclopentanol (*ent*-24) by Reduction of Oxo Ester 25: To a suspension of $LiAlH_4$ (200 mg, 5.2 mmol) in dry THF (2 mL) at 0 °C was added **25**[25] (83 mg, 0.3 mmol; 38% *ee*), dissolved in dry THF (2 mL). The reaction mixture was then allowed to reach room temperature. After 12 h, water (10 mL) and HCl (2 M; 30 mL) were added, followed by dilution with EtOAc (30 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The pooled organic phases were dried (Na_2SO_4) and concentrated. GC-MS analysis indicated a diastereomeric ratio of 8:1 of the crude diol. The major and the minor diastereomer were separated by column chromatography [SiO_2; EtOAc/cyclohexane (0 → 100%)]. This furnished the title compound (34 mg; 55%) in > 98:2 diastereomeric ratio and in purity > 99% (GC). $[\alpha]_D^{25}$ = +6.4 (*c* = 1.35, MeOH). Other data are identical with those for the enantiomer **24** described above.

Supporting Information: Copies of the ^1H and ^{13}C NMR spectra for the cycloadducts **3a**–**f**, **4a**–**b** and **5d** (see also footnote on the first page of this article).

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