A Molybdenum-Catalyzed Oxidative System Forming Oxazines (Hetero-Diels−Alder Adducts) from Primary Aromatic Amines, Hydrogen Peroxide, and Conjugated Dienes

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The development of a new molybdenum-catalyzed procedure for the formation of oxazines—hetero-Diels−Alder adducts—from primary aromatic amines, hydrogen peroxide, and conjugated dienes is presented. The method is based on a molybdenum−peroxo complex, which in the presence of hydrogen peroxide as the terminal oxidant selectively catalyzes the oxidation of primary aromatic amines to the corresponding dienophilic nitroso compounds. The molybdenum−peroxo catalyst is under the present reaction conditions not reactive toward conjugated dienes and substituents attached to the aromatic nuclei of the primary aromatic amines. Several oxazines are synthesized following this new procedure using primary aromatic amines having either electron-withdrawing or electron-donating substituents and 1,3-cyclohexadiene as the standard diene. The scope of the new procedure is also demonstrated by the preparation of several oxazines using different alkyl- and phenyl-substituted conjugated dienes and 4-chloroaniline as precursor for the dienophile. Moderate diastereomeric excesses are found when the reaction is carried out with 1-(2-aminophenyl)-ethanol and 1,3-cyclohexadiene or (*E*)-1-phenyl-1,3-butadiene. The stereochemical and electronic factors governing the reaction course are briefly discussed.

Introduction

Control of chemical reactions by use of catalysts is an area with increasing importance. One of the challenges in this field is to apply metal complexes in an attempt to control the chemo-, regio-, and stereoselectivity, and in recent years numerous improvements have been achieved.

In the field of catalytic oxidations mediated by transition-metal complexes, several new organic reactions have been developed.[1] Among the early transition-metal complexes, molybdenum(VI) complexes occupy a central position because they are able to catalyze a variety of oxidation reactions such as aromatic carbon−hydrogen bonds to the corresponding alcohols,[2−6] alkenes to epoxides,[7−10] alcohols to carbonyl compounds,[11,12] sulfides to sulfoxides,[13,14] sulfoxides to sulfones,[15] and amines to a variety of oxidized products.[16−21]

The catalytic properties of the molybdenum(VI) complexes are closely associated with the ability of the metal to react with peroxides to form molybdenum−peroxo compounds **1** or molybdenum−peroxide complexes. The reaction between a molybdenum(VI) complex and H_2O_2 gives **1**, while the use of other organic peroxides may lead to **1** as well as molybdenum−peroxide complexes depending on the peroxide.[8,9]

1

The activity of molybdenum−peroxo complexes is in part controlled by the co-ligands, and it has been found that even "minor" modifications of the ligand occupancy can change the properties of the complex dramatically.[11,22,23]

The control of the reaction course is one of the major problems and challenges in the transition-metal-catalyzed oxidation of organic nitrogen compounds. We have recently developed a molybdenum-catalyzed method which selectively oxidizes primary aromatic amines to the corresponding nitroso compounds.[24] Many of the problems associated with the classical methods for preparation of nitroso compounds by oxidation of primary aromatic amines, such as overoxidation and formation of

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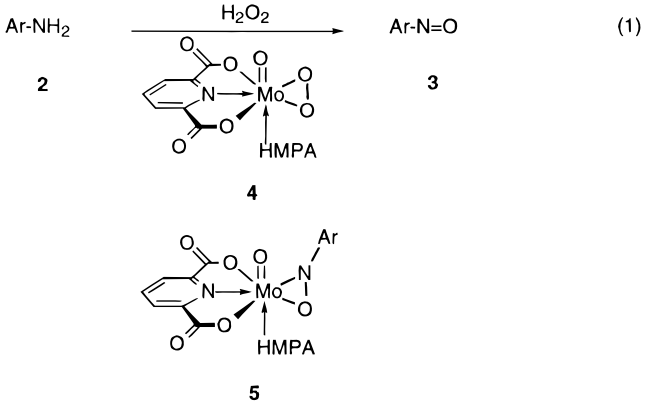
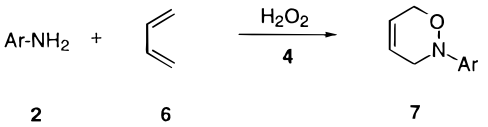
coupling byproducts, are suppressed by the molybdenum-catalyzed procedure.[24] The oxidation of primary aromatic amines **2** to the corresponding nitroso compounds **3** can either be performed as a catalytic reaction using oxoperoxo(2,6-pyridinedicarboxylato-*O*,*N*,*O*′)(hexamethylphosphortriamide)molybdenum(VI) (**4**) as the catalyst and H_2O_2 as the terminal oxidant (eq 1) or as a stoichiometric reaction which utilizes the molybdenaoxaziridine **5**.[24] The latter procedure is based on the reaction of **2** with **4** giving **5**, which upon treatment with H_2O_2 gives the desired aromatic nitroso compound **3** and regenerates the molybdenum−peroxo complex **4**.



Nitroso compounds are synthetic useful reagents in organic chemistry.[25−33] One of the most useful reactions of nitroso compounds is the cycloaddition reaction with conjugated dienes which form oxazines, hetero-Diels−Alder (HDA) adducts. These HDA adducts can be transformed by different procedures to a variety of products,[25,29] such as mitomycin and other compounds with pharmaceutical interest.[34−36]

One of the major general problems associated with the formation of oxazines from HDA reactions is the synthesis of the nitroso functionality. This work presents a new approach for the preparation of oxazines **7** from primary aromatic amines **2**, H_2O_2, and conjugated dienes **6** in the presence of the molybdenum−peroxo catalyst **4**, eq 2. The new procedure for oxazine formation has several advantages as compared with the classical methods since the isolation, purification, and handling of mutagene[37] nitroso compounds are avoided. Moreover, a wide range of substituted primary aromatic amines are commercially available, allowing the synthesis of several oxazines which previously have only been prepared with great difficulty or not at all.[27]

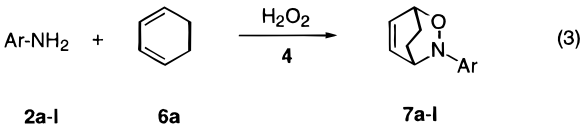


The pivotal element of the new method presented in eq 2 is the catalytic properties of **4**, which in the presence of H_2O_2 transforms primary aromatic amines to the corresponding nitroso compounds (eq 1). The success of this method derives from the chemoselectivity of the oxidation reaction, leaving the conjugated dienes and substituents bound to the aromatic nuclei of the primary aromatic amines unaffected.

The development and results of the catalytic reaction outlined in eq 2 will be presented in the following. Furthermore, the scope of the reaction by the reaction of different primary aromatic amines, including compounds having chiral substituents, with various dienes will be presented.

Results and Discussion

The formation of the HDA adducts, 3-aryl-2-oxa-3-azabicyclo[2.2.2]oct-5-enes **7a**−**l**, has been examined using a series of aromatic amines (**2a**−**l**), H_2O_2, and 1,3-cyclohexadiene (**6a**) in the presence of a catalytic amount of the molybdenum−peroxo complex **4**, eq 3. Several of the HDA adducts are, according to the best of our knowledge, described here for the first time. The results for these reactions are presented in Table 1 (for further details, see Experimental Section).



a: Ar = C_6H_5
b: Ar = 4-C_6H_4-OMe
c: Ar = 4-C_6H_4-Me
d: Ar = 4-C_6H_4-Cl
e: Ar = 4-C_6H_4-C(O)NH_2
f: Ar = 4-C_6H_4-C(O)OEt
g: Ar = 4-C_6H_4-C(O)Me
h: Ar = 4-C_6H_4-CF_3
i: Ar = 4-C_6H_4-CN
j: Ar = 4-C_6H_4-NO_2
k: Ar = 1-Naphthyl
l: Ar = 2-Naphthyl

It appears from the results in Table 1 that the reaction outlined in eq 3 in most cases leads to a smooth formation of the HDA adducts, 3-aryl-2-oxa-3-azabicyclo[2.2.2]oct-5-enes **7a**−**i**,**k**,**l**. The selectivity of the molybdenum−peroxo catalyst **4** is notable, leaving oxidizable substituents attached to the aromatic nuclei of the primary aromatic amines untouched. Furthermore, 1,3-cyclohexadiene (**6a**) and other conjugated dienes (*vide infra*) are neither oxidized to the corresponding epoxide or other oxidized products nor polymerized when treated with **4** and H_2O_2. In relation to the latter, it should be noted that polymerization of conjugated dienes in the presence of transition-metal catalysts and peroxides has been observed.[38] Both primary aromatic amines having electron-donating substituents **2b**,**c**,**k**,**l** (Table 1, entries 2,

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Table 1. Results for the Formation of the HDA Adducts, 3-Aryl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 7a−l, from Primary Aromatic Amines 2a−l, 1,3-Cyclohexadiene (6a) in the Presence of the Molybdenum−Peroxo Catalyst 4, and H_2O_2 as Oxidant

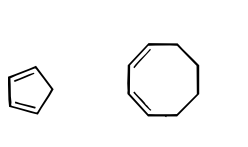
entry	Ar−NH_2	HDA adduct	yield (%)[a]
1	**2a**	**7a**	55
2	**2b**	**7b**	60
3	**2c**	**7c**	81
4	**2d**	**7d**	77
5	**2e**	**7e**	43
6	**2f**	**7f**	60
7	**2g**	**7g**	45
8	**2h**	**7h**	66
9	**2i**	**7i**	41
10	**2j**	**7j**	7
11	**2k**	**7k**	40
12	**2l**	**7l**	52

[a] Yields are based on ^{1}H NMR spectroscopy (see text).

3, 11, and 12) and those having electron-withdrawing substituents **2d**−**i** (entries 4−9) can be used to prepare the HDA adducts. The yield of the HDA adduct is generally good, with the exception of **7j** where 4-nitroaniline (**2j)** is the dienophile precursor (entry 10). This can be ascribed to a slow oxidation of **2j** (*vide infra*). All, but one (**7b**), of the HDA adducts in Table 1 were purified by TLC. In most cases the isolated yield of the product was 10−20% lower than the yield determined by NMR spectroscopy of the crude product. The decrease in yield of the HDA adduct by workup is probably due a chromatographic, photoinduced, or thermal transformation which previously has been observed for analogues HDA adducts.[39−44]

The formation of the HDA adduct is most likely to be a two-step process: (i) the initial step being the oxidation of the primary aromatic amine to the corresponding nitroso compound followed by (ii) a cycloaddition reaction of the aromatic nitroso dienophile with the diene. The last step can take place either with or without interaction of the molybdenum complex. Control experiments have shown[45] that the molybdenaoxaziridine complex **5** is not reactive toward 1,3-cyclohexadiene (**6a**) under the standard reaction conditions; thus **5** may be excluded as an intermediate in the HDA cycloaddition reaction. The kinetics of steps i and ii have different electronic demands. A kinetics investigation of the reaction between different 4-substituted primary aromatic amines and the molybdenum−peroxo complex **4** producing the molybdenaoxaziridines **5** gave a Hammett ρ value of −2.3, showing that 4-substituted primary aromatic amines having electron-donating substituents are the most reactive.[24] However, step ii proceeds faster for aromatic nitroso compound having electron-withdrawing substituents as compared to those with electron-donating substituents.[46] Thus, two counteracting electronic effects determine the overall reaction rate of this new method for the formation of HDA adducts. The results presented in Table 1 show that the two effects in most cases are appropriately balanced, because reasonable good yields of the HDA adducts, 3-aryl-2-oxa-3-azabicyclo[2.2.2]oct-5-enes **7a**−**i**,**j**,**k** are found using 4-substituted primary aromatic amines having either electron-donating or electron-withdrawing substituents. An example of a reaction where the overall reaction rate exclusively is determined by the first step is given in Table 1, entry 10, where the formation of 1-nitro-4-nitrosobenzene (**3j**) is very slow, giving a low yield of the HDA adduct **7j**. It is noteworthy that no attempts were made to optimize the reaction conditions.

The synthetic aspects of the new method outlined in eq 2 are clearly demonstrated by the results presented in Table 1, as according to the best of our knowledge, the only previous reported HDA adducts are **7a**[47−51] and **7d**.[52] Further investigation of the the synthetic aspects were undertaken using different conjugated dienes **6b**−**h,** 4-chloroaniline (**2d**) as a standard primary aromatic amine, H_2O_2, and the molybdenum−peroxo catalyst **4**. This standard amine was choosen because it gave high yield in the catalyzed reaction with 1,3-cyclohexadiene (Table 1) and because the isolated yield (69%) of **7d** was comparable to the yield of **7d** in the crude material determined by NMR spectroscopy (77%). Both cyclic dienes (**6b**,**c)** and the noncyclic alkyl- (**6d**−**f**) and phenyl-substituted dienes (**6g**,**h**) were examined.



6b **6c**

	R^1	R^2	R^3	R^4	R^5	R^6
6d:	H	H	Me	Me	H	H
6e:	Me	Me	H	Me	H	H
6f:	Et	H	H	H	H	H
6g:	Ph	H	H	H	H	H
6h	Ph	H	H	H	Ph	H

The use of cyclopentadiene (**6b**) produced 3-(4-chlorophenyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (**7m**) in 38% yield on the basis of NMR spectroscopy of the crude material. Unfortunately, **7m** could not be isolated by chromatographic methods due to the retro-HDA reaction.[39,53,54] In relation to this it should be noted that the equilibrium constant for the cycloaddition reaction of **6b** with nitrosobenzene (**3a**) leading to the corresponding HDA adduct is 13.23 M^{-1}.[53] The reacion which used (*Z*,*Z*)-1,3-cyclooctadiene (**6c)** as diene was found to proceed very slowly, and the HDA adduct could not be detected. A very slow rate of HDA adduct formation from **6c** and **3d** has also been described by others.[55]

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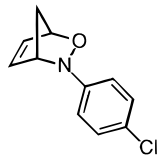
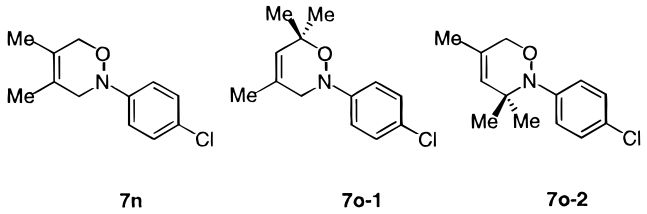
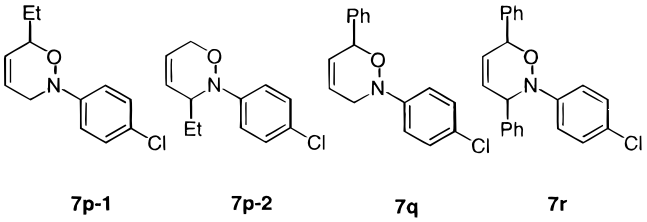


7m

The reaction of the noncyclic dienes **6d**−**h** and 4-chloroaniline (**2d**) under the present oxidative conditions produces substituted 2-(4-chlorophenyl)-3,6-dihydro-2*H*-[1,2]oxazines **7n**−**r** in fair to good yields. Of these adducts only **7n**[56] and **7q**[42,46,57] have been described previously. The reaction with 2,3-dimethyl-1,3-butadiene (**6d)** gave a 95% yield of 2-(4-chlorophenyl)-4,5-dimethyl-2*H*-[1,2]oxazine (**7n**) on the basis of NMR spectroscopy, while the isolated yield of **7n** was only 51%. It should be noted that no attempts were made to optimize this or the following reactions nor the isolation procedures. The two new compounds 2-(4-chlorophenyl)-4,6,6-trimethyl-3,6-2*H*-[1,2]oxazine (**7o-1**) and 2-(4-chlorophenyl)-3,3,5-trimethyl-3,6-2*H*-[1,2]oxazine (**7o-2**) were formed in 49% total yield in a ratio of 79:11 (NMR) from reaction with 2,4-dimethyl-1,3-pentadiene (**6e**). In the case of 1,3-hexadiene (**6f**), two new adducts, 2-(4-chlorophenyl)-3-ethyl-3,6-dihydro-2*H*-[1,2]oxazine (**7p-1**) and 2-(4-chlorophenyl)-6-ethyl-3,6-dihydro-2*H*-[1,2]oxazine (**7p-2**), were formed in 56% and 26% yields, respectively. Unsuccessful attempts were made to separate **7p-1** and **7p-2** by chromatography. However, NMR spectroscopy allowed a satisfactory characterization of the products. The phenyl-substituted noncyclic conjugated dienes (*E*)-1-phenyl-1,3-butadiene (**6g**) and (*E*,*E*)-1,4-diphenyl-1,3-butadiene (**6h**) reacted smoothly under the standard oxidation conditions. The reaction with **6g** gave exclusively 2-(4-chlorophenyl)-6-phenyl-3,6-2*H*-[1,2]oxazine (**7q)** in 78% yield, and the analogous use of **6h** afforded the HDA adduct 2-(4-chlorophenyl)-3,6-diphenyl-3,6-2*H*-[1,2]-oxazine (**7r**) in 72% isolated yield.



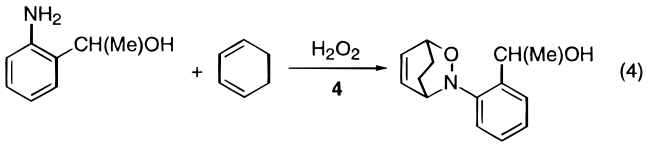
7n **7o-1** **7o-2**



7p-1 **7p-2** **7q** **7r**

The regioselectivity of the cycloaddition reaction of aromatic nitroso compounds to asymmetrically substituted dienes has gained much attention.[42,58−64] It has previously been described that the cycloaddition reaction of 1-chloro-4-nitrosobenzene (**3d**) with 1-phenyl-1,3-butadiene (**6g**) only produced one regioisomer (**7q**)[47,58,59] and that the cycloaddition reaction of **3d** with 1,3-pentadiene (**6i)** gave a 58:42 ratio of 2-(4-chlorophenyl)-3-methyl-3,6-dihydro-2*H*-[1,2]oxazine and 2-(4-chlorophenyl)-6-methyl-3,6-dihydro-2*H*-[1,2]oxazine.[58] Our finding of a 56:26 ratio of **7p-1** and **7p-2** shows that the directing effect of the ethyl substituent in **6f** is stronger than the methyl substituent in **6i**. A ratio of 79:11 of **7o-1** and **7o-2** shows in a similar manner that the directing effect of the three methyl substituents in **6e** is notably stronger than the directing effect of the single methyl substituent in **6i**. The increased regioselectivety in the latter example can be accounted for by the pericyclic selection rules[65] assuming that the directing effects of the three methyl substituents are additive.

In an attempt to perform diastereoselective reactions, 1-(2-aminophenyl)ethanol (**2m**) was prepared, both as a racemic mixture and as enantiomeric enriched compounds (*R*)-**2m** and (*S*)-**2m** (the experimental details are given in Experimental Section). The diastereoselectivities of the reaction of **2m** and either 1,3-cyclohexadiene (**6a**) (eq 4) or (*E*)-1-phenyl-1,3-butadiene (**6g**) using the oxidative conditions have been examined. In the reaction with **6a** two isomers of 1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s**) were formed in a 4:3 ratio. The two HDA adducts could be isolated by chromatography. Under similar reaction conditions, the reaction of **2m** and **6g** gives two isomers of 1-[2-(6-phenyl-3,6-dihydro[1,2]oxazin-2-yl)phenyl]ethanol (**7t**) in a 5:3 ratio. These HDA adducts were separated by preperative HPLC.



(4)

2m **6a** **7s**

Eight stereoisomers of both 1-[2-(2-oxa-3-azabicyclo-[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s**) and 1-[2-(6-phenyl-3,6-dihydro[1,2]oxazin-2-yl)phenyl]ethanol (**7t)** can be produced in the two reactions if the nitrogen atoms are regarded as chiral centers and if isomers arising from restricted rotation around the nitrogen−aryl bond and different ring conformations are excluded. With regard to the inversion of the nitrogen atom in the present systems, it should be noted that the inversion barrier of the nitrogen atom of 3-methyl-2-oxa-3-azabicyclo[2.2.2]-octane, an *N*-methyl-substituted saturated analogue of **7s**, has been determined to be 14.9 kcal/mol and the coalescence temperatures, T_c, were equal to 22 and 55 °C.[66] Moreover, the inversion barriers of two *N*-alkyl-substituted analogues of **7t** have been found to be in the order of 11 kcal/mol with a $T_c \approx 0$ °C.[67] Unfortunately we have not been able to find thermodynamic data for

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Table 2. Selected NMR Data for 3-(4-Chlorophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7d) and the Major and Minor Fractions of 1-[2-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol, 7s-1 and 7s-2, Respectively

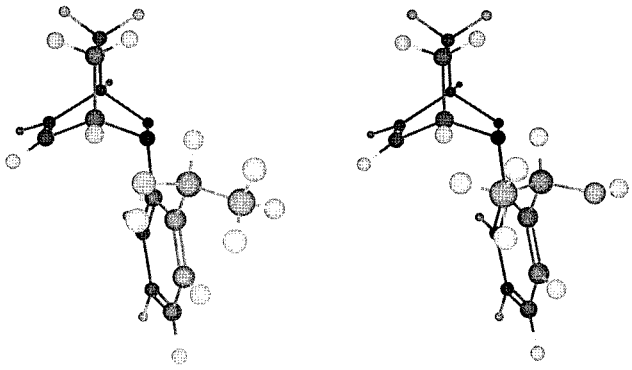
	7d	7s-1	7s-2
$H^{4''}$	4.38	4.19	4.00
$H^{5''}$	6.13	6.24	6.17
$H^{6''}$	6.58	6.77	6.79
OH		3.80	4.61
$\mathbf{C}H_3$		25.1	21.8
$C^{4''}$	56.4	57.1	56.4
$C^{5''}$	129.6	129.4	128.9
$C^{6''}$	131.4	133.1	133.2

N-aryloxazine compounds. The NMR spectra of both isomers of **7s** show no unexpected line broadening of the signals at ambient temperature, which indicate either a single preferred conformation with no nitrogen inversion at room temperature or a fast inversion of the nitrogen center.

The conformations of the two isomeric pairs of 1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol **7s** have been determined from an NMR analysis in combination with semiemperical theoretical calculations (AM1[68] and PM3[69]). A comparison of the chemical shift values of the two isomers of **7s-1** and **7s-2**, the major and minor isomer, respectively, with those of 3-(4-chlorophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**7d**), presented in Table 2 show only minor, but still significant differences. Therefore it must be expected that the spacial arrangement of the aryl and the bicyclic fragment are very similar in the three adducts, **7d**, **7s-1**, and **7s-2**.

It has previously been found that dihydroxylation of **7d** afforded only a single product. This result can be explained by an *endo* conformation of **7d**, whereby the appropriate side of the double bond is shielded.[52] A search in the Cambridge Structural Database gave six structures containing a 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl unit,[70] but unfortunately none of these structures has an aryl substituent attached to the 3-aza position. Five of the six structures have an *endo* orientation of the 3-aza substituent relative to the double bond.[71−74] The last structure showed a planar geometry at the 3-aza position[75] and must be regarded as a special case. Semiempirical AM1[68] structural optimizations of the *exo* conformations of **7s** position the $H^{3'}$ proton very close (≈2.2 Å) to the $H^{7''exo}$ proton which easily should be confirmed by NOE experiments, but the NOE experiments could not verify an *exo* conformation (for assignments/numbering of the atoms see Experimental Section). On the basis of the NMR spectroscopic data and the structural data available, it is most likely that both **7s-1** and **7s-2** are *endo* isomers.

The NOEDIF spectra of the two isomeric pairs of 1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol **7s-1** and **7s-2**, respectively, proved to be rather similar. A positive NOE of the integral of the $H^{4''}$ signal was found upon irradiation of the methin proton in both **7s-1** and **7s-2**. The NOEDIF results show that both isomers have an *anti* conformation of the N−O bond relative to the ethanol group on the benzene ring, which excludes the possibility that the two adducts are two stable rotamers of a single adduct.



(*SRS*)-**7s** (*RRS*)-**7s**

Figure 1. Optimized structures of (1*S*,1″*R*,4″*S*)-1-[2-(2-oxa-3azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol ((*SRS*)-**7s**) (left) and (1*R*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-phenyl]ethanol **((***RRS***)-7s)** (right).

Geometrical optimization of the two isomers, (1*S*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-phenyl]ethanol ((*SRS*)-**7s**) and (1*R*,1″*R*4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol ((*RRS*)-**7s**) using either AM1[68] or PM3[69] gave the two conformers shown in Figure 1 as the most stable. It appears from Figure 1 that the two calculated *endo* conformations of (*SRS*)-**7s** and (*RRS*)-**7s** are very similar, the major difference being the configuration of the C^1-carbon atom. The calculated *syn* orientation of the methine proton relative to the other 2′-substituent in both cases is in good agreement with other experimental results found for analogous compounds.[76,77] Similar theoretical calculations of the *endo* conformation of 3-(4-chlorophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**7d**) show that the N−O bond is located in the plane of the aromatic ring in the most stable conformation. Steric repulsion between the $H^{4''}$ bridgehead hydrogen atom and the ethanol fragment in both (*SRS*)-**7s** and (*RRS*)-**7s** forces the N−O bond out of the plane of the aromatic ring, which is reflected in the low-field shifts of the alkene nuclei in the 6″ position of (*SRS*)-**7s** and (*RRS*)-**7s** relative to **7d**, as seen from Table 2.

The different configurations of the C^1-carbon atoms in (1*S*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-phenyl]ethanol ((*SRS*)-**7s**) and (1*R*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol ((*RRS*)-**7s**) outlined in Figure 1 affect the ^{13}C chemical shift values of the methyl carbon atoms and may be used to determine the conformation of the two isolated isomers of **7s**. The methyl substituent and the bicyclic fragment in (*SRS*)-**7s** are located at opposite sides of the aromatic ring, and the methyl ^{13}C chemical shift value is found in the range of other 2′-substituted 1-phenyl-1-ethanols (CF_3 25.4 ppm, H 25.1 ppm, CH_3 24.6 ppm, Br 23.5 ppm, OCH_3

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23.0 ppm).[78,79] The methyl substituent and the bicyclic fragment in (*RRS*)-**7s** are located on the same side of the aromatic ring, with a distance between the C^1 and $C^{4''}$ nulcei calculated to be ≈3.7 Å. A consequence of this steric arrangement in (*RRS*)-**7s** is a 3.3 ppm high-field shift of the methyl ^{13}C chemical shift value (Table 2). Similar high-field shifts are well-known for substituted cyclohexanes, where methyl substitution in the axial γ-position places two carbon atoms ≈3.0 Å apart and causes a 6.4 ppm high-field shift, also known as the γ-effect.[80] Similar arguments can be used to explain the different chemical shift values of the alcohol proton (Table 2).

We have also, on the basis of the observed differences in the NMR spectra, examined other conformations of 1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s-1**) and 1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s-2)** than those presented in Figure 1, but they have all been discharged. It could, for example, be argued that the low-field locations of the alcohol protons, 3.8 ppm and 4.6 ppm in **7s-1** and **7s-2**, respectively, relative to other 2′-substituted 1-phenyl-1-ethanols (H 2.45 ppm, Br 2.45 ppm, CF_3 2.50 ppm, OCH_3 2.8 ppm)[78] indicate conformations involving hydrogen bonds, but then one of the isomers should have an *exo* conformation which we previously have excluded. It was also checked if the aromatic ring current could induce the observed differences in the NMR spectra. But a maximum difference of 0.27 ppm on the O−H protons was found using the approximative formula (eq 5)[80] for the influence of the aromatic ring current, which does not offer a satisfactory explanation of the observed difference.

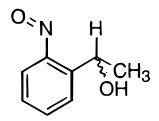
$$\Delta\delta\ (\text{ppm}) = \frac{\mu(1 - \cos^2\theta)}{r^3} \qquad (5)$$

On the basis of the arguments presented above, it can be concluded that the major product in the reaction of 1,3-cyclohexadiene (**6a)** and 1-(2-aminophenyl)ethanol (**2m**) under the oxidative conditions is a racemic mixture of (1*S*,1″*R*,4″*S*)- and (1*R*,1″*S*,4″*R*)-1-[2-(2-oxa-3-azabicyclo-[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s-1**) and that the minor product is a racemic mixture of (1*S*,1″*S*,4″*R*)- and (1*R*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-phenyl]ethanol (**7s-2**).

The two conformers of 1-[2-(6-phenyl-3,6-dihydro[1,2]-oxazine-2-yl)phenyl]ethanol (**7t**) did not exhibit a similar difference between the methyl substituents, and no attempts were made to assign the absolute conformation of these two products.

The use of enatiomeric enriched (*S*)-**2m** (90% ee) in eq 4 gives the same diastereoselectivity as observed for the reaction with racemic **2m**.

In order to obtain further information about the present reaction, the dienophile 1-(2′-nitrosophenyl)-ethanol (**8**) was prepared from catalytic oxidation of **2m** and then reacted with (*E*)-1-phenyl-1,3-butadiene (**6g**). The results showed that the diastereomeric excess in this reaction was similar to the one found above.



8

From comparison of the NMR spectroscopic data of **8** with those of other 2-substituted nitrosobenzenes[81] it is evident, that the N═O double bond is oriented *anti* to the ethanol group. It is most likely (*vide supra*) that the methine proton is located in the aromatic plane *syn* to the nitroso substituent. Assuming that the cycloaddition reaction between **8** and 1,3-cyclohexadiene (**6a**) leads directly to the two isolated adducts, it can be concluded that the cycloaddition reaction to the nitroso face shielded by the alcohol group and leading to (1*S*,1″*R*,4″*S*)- and (1*R*,1″*S*,4″*R*)-1-[2-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-phenyl]ethanol (**7s-1**) is less hindered than the methyl-shielded face of the nitroso functionality which leads to (1*S*,1″*S*,4″*R*)- and (1*R*,1″*R*,4″*S*)-1-[2-(2-oxa-3-azabicyclo-[2.2.2]oct-5-en-3-yl)phenyl]ethanol (**7s-2**).

Conclusion

A new molybdenum-catalyzed procedure for the formation of oxazines−hetero-Diels−Alder adducts—from primary aromatic amines, H_2O_2, and conjugated dienes has been developed. The catalyst—a molybdenum−peroxo complex—is chemoselective and catalyzes the oxidation of the primary aromatic amine to the corresponding dienophilic nitroso compound, leaving the conjugated diene and substituents attached to the aromatic nuclei of the primary aromatic amine untouched. A variety of different oxazines are synthezised in reasonable yield by this procedure using primary aromatic amines having either electron-withdrawing or electron-donating substituents and various dienes. Moderate diastereomeric excesses are found when the reaction is carried out with 1-(2-aminophenyl)ethanol and 1,3-cyclohexadiene or (*E*)-1-phenyl-1,3-butadiene. The mechanism for the molybdenum-catalyzed procedure for the formation of oxazines is probably first the oxidation of the primary aromatic amine to the corresponding nitroso compound followed by an off-metal cycloaddition reaction of the aromatic nitroso dienophile with the diene.

Experimental Section

Apparatus. NMR spectra were recorded on a Varian Gemini 300 in $CDCl_3$. $SiMe_4$ was used as the internal standard in ^1H spectra, and $CDCl_3$ (77.0 ppm) was used as reference in ^{13}C spectra. Enatiomeric excesses were determined using a l = 30 m, i.d. = 0.25 mm Chirasil-DEX CB column from Chrompack or with a l = 250 mm, i.d. = 4.6 mm Chiralcel OD HPLC column from Diacel.

Chemicals. The primary aromatic amines **2a**−**l** and the conjugated dienes **6a**,**c**−**f**,**h**, (−)-DIP-Cl = [(−)-*B*-chlorodiisopinocampheylborane], 2′-nitroacetophenone, and 2′-aminoacetophenone are commercially available and were used without further purification. Cyclopentadiene (**6b**) was prepared from cracking of the dimer[82] and (*E*)-1-phenyl-1,3-butadiene (**6g**) was prepared according to the literature.[83] The catalyst oxoperoxo(2,6-pyridinedicarboxylato-*O*,*N*,*O*)(hexamethylphos-

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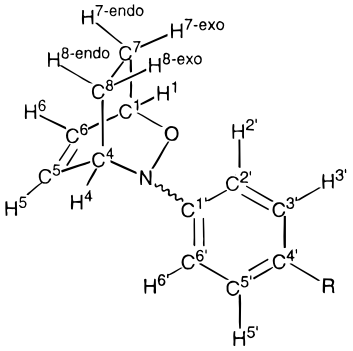
phortriamide)molybdenum(VI) (**4**) was prepared according to the literature.[24]

General Procedure for the Formation of Oxazines 7a−t. The primary aromatic amine (1.0 mmol), the conjugated diene (1.0 mmol), the catalyst oxoperoxo(2,6-pyridinedicarboxylato-*O*,*N*,*O*)(hexamethylphosphortriamide)molybdenum(VI) (**4**), and H_2O_2 (2.2 mmol) were mixed with 10 mL of petroleum ether (bp < 50 °C) at rt. The mixture was stirred for 18 h and filtered through a plug of HYFLO and the solvent removed. A ^{1}H NMR spectrum was recorded on the crude product. The product was purified using silica preparative TLC or flash chromatography. For some of the reactions Et_2O was used as solvent because of the low solubility of the primary aromatic amine and/or the HDA product in petroleum ether.

^{1}H and ^{13}C NMR Spectra. Several coupling patterns are described below as multiplets, but it may be noted that similar multiplets in analogous compounds have been analyzed and are fully understood.[84−87] The chemical shifts of **7a** were assigned using several NMR experiments, and the numbering of the atoms are given below. The aromatic protons were assigned from the coupling pattern in a normal ^{1}H NMR experiment. The H$^{4''}$ proton was assigned from a NOEDIF experiment with saturation of the H$^{2'}$-signal. The assignment of the remaining bicyclic protons was obtained from a COSY experiment. It was not possible from these spectra to make an *exo*/*endo* assignment, but Kresze *et al.* have examined bicyclic adducts very similar to **7a**−**l** and assigned *exo* protons to the chemical shift at ∼2.25 ppm and *endo* protons to be 1.60 ppm.[88] The proton-substituted carbon nuclei was assigned from the proton assignments and HETCOR experiments. The chemical shift value for C$^{1'}$ was finally identified from a normal ^{13}C spectrum. Chemical shifts values of the adducts **7b**−**l** were assigned in agreement with the assigned **7a** and tabulated substituent effect values.[89] Substituent effect values of substitution of 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl on benzene could be calculated from the data below as follows: ^{1}H, $Z_2 = -0.33 \pm 0.08$, $Z_3 = -0.09 \pm 0.05$, $Z_4 = -0.34$; ^{13}C, $Z_1 = 23.8 \pm 0.6$, $Z_2 = -11.9 \pm 0.9$, $Z_3 = 0.2 \pm 0.7$, $Z_4 = -7.1 \pm 1.1$. An asterisk indicates a quaternary carbon. The chemical shift values of the adducts **7m**−**t** were assigned by an analogous procedure.



3-Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7a). ^{1}H NMR δ: 1.35−1.39 (m, 1H, H^{7-endo}), 1.53−1.60 (m, 1H, H^{8-endo}), 2.2−2.3 (m, 2H, H^{7-exo}, H^{8-exo}), 4.40−4.43 (m, 1H, H^4), 4.67−4.70 (m, 1H, H^1), 6.10−6.15 (m, 1H, H^5), 6.53−6.59 (m, 1H, H^6), 6.92 (t, J = 8.8 Hz, 1H, H$^{4'}$), 6.99 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.20 (t, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 21.3 (C^8), 24.0 (C^7), 56.5 (C^4), 69.1 (C^1), 117.4 (C$^{2'/6'}$), 122.0 (C$^{4'}$), 128.3 (C$^{3'/5'}$), 129.9 (C^5), 131.6 (C^6), 152.3 (C$^{1'}$).

3-(4-Methoxyphenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7b). ^{1}H NMR δ: 1.30−1.39 (m, 1H, H^7), 1.51−1.60 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 3.74 (s, 3H, O**C**H$_3$), 4.24−4.29 (m, 1H, H^4), 4.65−4.69 (m, 1H, H^1), 6.09−6.14 (m, 1H, H^5), 6.57−6.62 (m, 1H, H^6), 6.77 (d, J = 9.3 Hz, 2H, H$^{3'/5'}$), 6.95 (d, J = 9.3 Hz, 2H, H$^{2'/6'}$). ^{13}C NMR δ: 21.5 (C^8), 23.8 (C^7), 55.3 (O**C**H$_3$), 57.1 (C^4), 68.9 (C^1), 113.5 (C$^{3'/5'}$), 119.1 (C$^{2'/6'}$), 129.7 (C^5), 131.7 (C^6), 145.6 (C$^{1'}$), 155.1 (C$^{4'}$).

3-(4-Tolyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7c). ^{1}H NMR δ: 1.31−1.40 (m, 1H, H^7), 1.53−1.62 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 2.26 (s, 3H, **C**H$_3$), 4.35−4.39 (m, 1H, H^4), 4.67−4.70 (m, 1H, H^1), 6.11−6.16 (m, 1H, H^5), 6.55−6.61 (m, 1H, H^6), 6.91 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.02 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 20.5 (**C**H$_3$), 21.3 (C^8), 23.9 (C^7), 56.5 (C^4), 68.9 (C^1), 117.4 (C$^{2'/6'}$), 128.8 (C$^{3'/5'}$), 129.9 (C^5), 131.3 (C$^{4'}$), 131.5 (C^6), 149.8 (C$^{1'}$).

3-(4-Chlorophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7d). ^{1}H NMR δ: 1.32−1.41 (m, 1H, H^7), 1.54−1.63 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.36−4.40 (m, 1H, H^4), 4.69−4.72 (m, 1H, H^1), 6.10−6.15 (m, 1H, H^5), 6.55−6.60 (m, 1H, H^6), 6.94 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.17 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 21.1 (C^8), 23.7 (C^7), 56.4 (C^4), 69.1 (C^1), 118.6 (C$^{2'/6'}$), 126.6 (C$^{4'}$), 128.1 (C$^{3'/5'}$), 129.6 (C^5), 131.4 (C^6), 150.9 (C$^{1'}$).

4-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)benzamide (7e). ^{1}H NMR δ: 1.35−1.43 (m, 1H, H^7), 1.58−1.65 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.55−4.58 (m, 1H, H^4), 4.74−4.77 (m, 1H, H^1), 5.6 (br, 1H, C(O)NH**H**), 5.9 (br, 1H, C(O)N**H**H), 6.16−6.22 (m, 1H, H^5), 6.54−6.59 (m, 1H, H^6), 7.04 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.68 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 21.1 (C^8), 23.9 (C^7), 55.8 (C^4), 69.6 (C^1), 116.5 (C$^{2/6}$), 126.1 (C$^{4'}$), 128.1 (C$^{3'/5'}$), 130.1 (C^5), 131.6 (C^6), 155.7 (C$^{1'}$), 168.9 (**C**=O).

Ethyl 4-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)benzoate (7f). ^{1}H NMR δ: 1.35 (t, J = 7.1 Hz, 3H, **C**H$_3$), 1.34−1.43 (m, 1H, H^7), 1.53−1.60 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.32 (q, J = 7.1 Hz, 2H, **C**H$_2$), 4.54−4.58 (m, 1H, H^4), 4.71−4.77 (m, 1H, H^1), 6.14−6.19 (m, 1H, H^5), 6.50−6.55 (m, 1H, H^6), 7.01 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.90 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 14.3 (**C**H$_3$), 20.9 (C^8), 23.8 (C^7), 55.5 (C^4), 60.4 (**C**H$_2$), 69.5 (C^1), 115.9 (C$^{2'/6'}$), 123.2 (C$^{4'}$), 130.0 (C^5), 130.2 (C$^{3'/5'}$), 131.4 (C^6), 156.3 (C$^{1'}$), 166.3 (**C**=O).

1-[4-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]-ethanone (7g). ^{1}H NMR δ: 1.40−1.45 (m, 1H, H^7), 1.58−1.65 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 2.53 (s, 3H, C**H**$_3$), 4.59−4.62 (m, 1H, H^4), 4.75−4.78 (m, 1H, H^1), 6.20−6.25 (m, 1H, H^5), 6.54−6.60 (m, 1H, H^6), 7.03 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.85 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 21.0 (C^8), 23.9 (C^7), 26.3 (**C**H$_3$), 55.5 (C^4), 69.8 (C^1), 116.0 (C$^{2'/6'}$), 129.4 (C$^{3'/5'}$), 130.2 (C^5), 130.6 (C^4), 131.6 (C^6), 156.5 (C$^{1'}$), 196.9 (**C**=O).

3-(4-(Trifluoromethyl)phenyl)-2-oxa-3-azabicyclo[2.2.2]-oct-5-ene (7h). ^{1}H NMR δ: 1.34−1.45 (m, 1H, H^7), 1.56−1.65 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.50−4.55 (m, 1H, H^4), 4.73−4.76 (m, 1H, H^1), 6.14−6.19 (m, 1H, H^5), 6.54−6.59 (m, 1H, H^6), 7.06 (d, J = 8.5 Hz, 2H, H$^{2'/6'}$), 7.45 (d, J = 8.5 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 21.1 (C^8), 23.9 (C^7), 56.0 (C^4), 69.5 (C^1), 116.7 (C$^{2'/6'}$), 123.4 (q, J_{C-F} = 32.3 Hz, C$^{4'}$), 124.5 (q, J_{C-F} = 271 Hz, **C**F$_3$), 125.7 (q, J_{C-F} = 4.0 Hz, C$^{3'/5'}$), 129.9 (C^5), 131.6 (C^6), 155.3 (C$^{1'}$).

4-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)benzonitrile (7i). ^{1}H NMR δ: 1.35−1.47 (m, 1H, H^7), 1.57−1.73 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.55−4.60 (m, 1H, H^4), 4.75−4.78 (m, 1H, H^1), 6.18−6.24 (m, 1H, H^5), 6.53−6.58 (m, 1H, H^6), 7.04 (d, J = 8.8 Hz, 2H, H$^{2'/6'}$), 7.48 (d, J = 8.8 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 20.8 (C^8), 23.7 (C^7), 55.3 (C^4), 69.8 (C^1), 103.7 (C$^{4'}$), 116.6 (C$^{2'/6'}$), 119.5 (**C**N), 130.0 (C^5), 131.5 (C^6), 132.6 (C$^{3'/5'}$), 155.9 (C$^{1'}$).

3-(4-Nitrophenyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7j). ^{1}H NMR δ: 1.39−1.47 (m, 1H, H^7), 1.58−1.68 (m, 1H, H^8), 2.2−2.3 (m, 2H, H^7, H^8), 4.65−4.67 (m, 1H, H^4), 4.80−4.82 (m, 1H, H^1), 6.24−6.30 (m, 1H, H^5), 6.55−6.60 (m, 1H, H^6), 7.04 (d, J = 9.1 Hz, 2H, H$^{2'/6'}$), 8.11 (d, J = 9.1 Hz, 2H, H$^{3'/5'}$). ^{13}C NMR δ: 20.9 (C^8), 23.7 (C^7), 55.3 (C^4), 70.2 (C^1), 115.6 (C$^{2'/6'}$), 124.9

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($C^{3'/5'}$), 130.2 (C^5), 131.7 (C^6) 157.5 ($C^{1'}$). $C^{4'}$ not detected but expected at 141.3 ppm.

3-(1-Naphthyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7k). ^{1}H NMR δ: 1.46−1.52 (m, 1H, H^7), 1.52−164 (m, 1H, H^8), 2.33−2.42 (m, 1H, H^7), 2.48−2.57 (m, 1H, H^8), 4.35−4.38 (m, 1H, H^4), 4.79−4.82 (m, 1H, H^1), 5.93−5.99 (m, 1H, H^5), 6.73−6.78 (m, 1H, H^6), 7.18 (m, 1H, $H^{2'}$), 7.32 (m,1H, $H^{3'}$), 7.47 (m, 2H, $H^{6'}$, $H^{7'}$), 7.53 (m, 1H, $H^{4'}$), 7.81 (m, 1H, $H^{5'/8'}$), 8.17 (d, J = 7.2 Hz, 1H, $H^{5'/8'}$). The aromatic chemical shift values were assigned according to estimated values using the calculated substituent effect of the 2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl substituent. ^{13}C NMR δ: 22.1, 23.8, 56.7, 69.4, 116.6, 123.0, 123.8, 125.2, 125.3, 125.5, 126.4*, 128.2, 129.2, 131.9, 134.0*, 146.8*.

3-(2-Naphthyl)-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7l). ^{1}H NMR δ: 1.43−1.44 (m, 1H), 1.58−1.66 (m, 1H), 2.24−2.38 (m, 1H), 4.53−4.57 (m, 1H), 4.77−4.81 (m, 1H), 6.07−6.12 (m, 1H), 6.57−6.62 (m, 1H), 7.19 (m, 1H, $H^{3'}$), 7.31 (m, 1H, $H^{6/7}$), 7.37 (m, 1H, H^1), 7.40 (m, 1H, $H^{6/7}$), 7.7 (m, 3H, H^4 H^5 H^8), see comment for **7k**. ^{13}C NMR δ: 21.4, 24.0, 56.4, 69.4, 113.5, 118.3, 124.0, 126.1, 127.2, 127.4, 128.1, 129.7, 131.5, 133.9*, 149.7*.

3-(4-Chlorophenyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (7m). ^{1}H NMR δ: 1.8 (d, J = 8 Hz, 1H), 2.1 (d, J = 8 Hz, 1H), 4.9 (s, 1H), 5.1 (s, 1H), 5.9 (d, J = 6 Hz, 1H), 6.4 (d, J = 6 Hz, 1H), 6.9 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 2H).

2-(4-Chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (7n). ^{1}H NMR δ: 1.63 (s, 3H, C^5CH_3), 1.72 (s, 3H, C^4CH_3), 3.62 (s, 1H, C^3CH_2), 4.31 (s, 1H, C^6CH_2), 7.05 (d, J = 9.0 Hz, 2H, $H^{2'/6'}$), 7.25 (d, J = 9.0 Hz, 2H, $H^{3'/5'}$). ^{13}C NMR δ: 13.6 (C^5CH_3), 15.9 (C^4CH_3), 56.1 (C^3), 72.0 (C^6), 56.1 (C^3), 117.0 ($C^{2'/6'}$), 122.0, 124.9, 127.1 ($C^{4'}$), 128.7 ($C^{3'/5'}$), 149.0 ($C^{1'}$).

2-(4-Chlorophenyl)-4,6,6-trimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (7o-1). ^{1}H NMR δ: 1.35 (s, 6H, C^6CH_3), 1.78 (s, 3H, C^4CH_3), 3.57 (s, 2H, H^3), 5.51 (s, 1H, H^5), 7.02 (d, J = 8.8 Hz, 2H, $H^{2'/6'}$), 7.24 (d, J = 8.8 Hz, 2H, $H^{3'/5'}$). ^{13}C NMR δ: 20.1 (C^3CH_3), 26.1 (C^6CH_3), 53.8 (C^3), 77.1 (C^6), 116.4 ($C^{2'/6'}$), 126.1 (C^4), 128.3 ($C^{4'}$), 128.6 ($C^{3'/5'}$), 128.9 (C^5), 149.1 ($C^{1'}$).

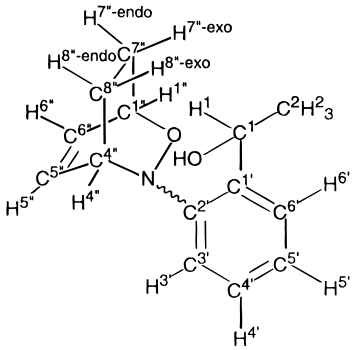
2-(4-Chlorophenyl)-3,3,5-trimethyl-3,6-dihydro-2*H*-[1,2]-oxazine (7o-2). ^{1}H NMR δ: 1.09 (s, 6H, C^3CH_3), 1.69 (s, 3H, C^5CH_3), 4.27 (s, 2H, H^6), 5.39 (s, 1H, H^4), 7.18 (d, J = 8.8 Hz, 2H, $H^{2'/6'}$), 7.27 (d, J = 8.8 Hz, 2H, $H^{3'/5'}$). ^{13}C NMR δ: 17.8 (C^3CH_3), 23.7 (C^5CH_3), 59.5 (C^3), 71.91 (C^6), 124.9 ($C^{2'/6'}$), 127.8 ($C^{3'/5'}$), 129.7 (C^4), 130.3 ($C^{4'}$), 130.8 (C^5), 145.9 ($C^{1'}$).

2-(4-Chlorophenyl)-6-ethyl-3,6-dihydro-2*H*-[1,2]oxazine (7p-1). ^{1}H NMR δ: 1.06 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.63 (m, 2H, CH_2CH_3), 3.69 (d, J = 16 Hz, 1H, H^3), 3.83 (d, J = 16 Hz, 1H, H^3), 4.48 (s, 1H, H^6), 5.89 (m, 1H, $H^{4(/5)}$), 5.92 (m, 1H, $H^{(4/)5}$), 7.03 (d, J=9 Hz, 2H, $H^{2'/6'}$), 7.24 (d, J=9 Hz, 2H, $H^{3'/5'}$). ^{13}C NMR δ: 10.0 (CH_3), 26.5 (CH_2CH_3), 51.6 (C^3), 79.1 (C^6), 116.6 ($C^{2'/6'}$), 122.6 ($C^{(4/)5}$), 126.4 ($C^{4'}$), 128.7 ($C^{3'/5'}$), 129.8 ($C^{4(/5)}$), 149.3 ($C^{1'}$).

2-(4-Chlorophenyl)-3-ethyl-3,6-dihydro-2*H*-[1,2]oxazine (7p-2). ^{1}H NMR δ: 0.93 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.68 (m, 2H, CH_2CH_3), 3.86 (s, 1H, H^3), 4.28 (d, 1H, H^6), 4.50 (d, 1H, H^6), 5.93 (m, 1H, $H^{4(/5)}$), 6.04 (m, 1H, $H^{(4/)5}$), 6.98 (d, J = 9 Hz, 2H, $H^{2'/6'}$), 7.24 (d, J = 9 Hz, 2H, $H^{3'/5'}$). ^{13}C NMR δ: 10.5 (CH_3), 23.4 (CH_2CH_3), 60.1 (C^3), 67.5 (C^6), 117.6 ($C^{2'/6'}$), 125.3 ($C^{4(/5)}$), 126.9 ($C^{(4/)5}$), 126.7 ($C^{4'}$), 128.8 ($C^{3'/5'}$), 147.2 ($C^{1'}$).

2-(4-Chlorophenyl)-6-phenyl-3,6-dihydro-2*H*-[1,2]oxazine (7q). ^{1}H NMR δ: 3.83 (m, 1H, H^3), 3.91 (m, 1H, H^3), 5.59 (s, 1H, H^6), 6.07 (m, 1H, $H^{(4)/5}$), 6.11 (m, 1H, $H^{4(/5)}$), 7.01 (d, 7.2H, $H^{2'/6'}$), 7.21 (d, 7.2H, $H^{3'/5'}$), 7.3−7.4 (m, 3H, $H^{3'/5''}$ $H^{4''}$), 7.43 (d, J = 7.7 Hz, 2H, $H^{2'/6''}$). ^{13}C NMR δ: 51.4 (C^3), 79.9 (C^6), 117.0 ($C^{2'/6'}$), 123.5 ($C^{4(/5)}$), 127.0 ($C^{4'}$), 128.1 ($C^{2'/6''}$), 128.5 ($C^{3'/5''}$ $C^{4''}$), 128.6 ($C^{3'/5'}$), 128.9 ($C^{(4/)5}$), 138.6 ($C^{1''}$), 148.9 ($C^{1'}$).

2-(4-Chlorophenyl)-3,6-diphenyl-3,6-dihydro-2*H*-[1,2]-oxazine (7r). ^{1}H NMR δ: 5.10 (s, 1H, H^3), 5.63 (s, 1H, H^6), 6.14 (m, 1H, $H^{4/5}$), 6.18 (m, 1H, $H^{4/5}$), 6.88 (d, J = 9.1 Hz, 2H, $H^{2'/6'}$), 7.08 (d, J = 9.1 Hz, 2H, $H^{3'/5'}$), 7.15−7.28 (m, 3H, H^{Ar}), 7.32−7.48 (m, 5H, H^{Ar}), 7.51 (d, J = 8 Hz, 2H, H^{Ar}). ^{13}C NMR δ: 63.5 (C^3), 79.5 (C^6), 118.0 ($C^{2'/6'}$), 126.5 (($C^{4'}$)), 127.6, 127.9, 128.0 ($C^{4/5}$), 128.1 ($C^{4/5}$), 128.2, 128.4 ($C^{3'/5'}$), 128.6, 128.8, 137.7*, 138.3*, 127.1 ($H^{1'}$).



1-[2-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]-ethanol (7s-1). ^{1}H NMR δ: 1.4−1.6 (m, 2H, $H^{7''-endo}$, $H^{8''-endo}$), 1.55 (d, J = 6.6 Hz, 3H, H^2), 2.2−2.4 (m, 2H, $H^{7''-exo}$, $H^{8''-exo}$), 3.80 (br, 1H, O**H**), 4.19 (m, 1H, $H^{4''}$), 4.70 (m, 1H, $H^{1''}$), 5.24 (q, J=6.6 Hz, 1H, H^1), 6.24 (m, 1H, $H^{5''}$), 6.77 (m, 1H, $H^{6''}$), 7.10 (m, 1H, H^5), 7.15 (m, 1H, H^4), 7.22 (m, 1H, $H^{3'}$), 7.28 (m, 1H, $H^{6'}$). ^{13}C NMR δ: 22.5 ($C^{8''}$), 23.4 ($C^{7''}$), 25.1 (C^2), 57.1 ($C^{4''}$), 67.3 (C^1), 69.3 ($C^{1''}$), 122.7 ($C^{3'}$), 125.2 ($C^{5'}$), 126.0 ($C^{6'}$), 127.0 ($C^{4'}$), 129.4 ($C^{5''}$), 133.1 ($C^{6''}$), 137.3 ($C^{1'}$), 148.1 ($C^{2'}$).

1-[2-(2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)phenyl]-ethanol (7s-2). ^{1}H NMR δ: 1.4−1.6 (m, 2H, $H^{7''-endo}$, $H^{8''-endo}$), 1.57 (d, J = 6.6 Hz, 3H, H^2), 2.2−2.4 (m, 2H, $H^{7''-exo}$, $H^{8''-exo}$), 4.00 (m, 1H, $H^{4''}$), 4.58 (s, 1H, O**H**), 4.73 (m, 1H, $H^{1''}$), 5.26 (q, J=6.6 Hz, 1H, H^1), 6.17 (m, 1H, $H^{5''}$), 6.79 (m, 1H, $H^{6''}$), 7.10 (m, 1H, H^5), 7.14 (m, 1H, $H^{4'}$), 7.17 (m, 1H, $H^{3'}$), 7.29 (m, 1H, $H^{6'}$). ^{13}C NMR δ: 21.8 (C^2), 22.8 ($C^{8''}$), 23.3 ($C^{7''}$), 56.4 ($C^{4''}$), 65.2 (C^1), 69.4 ($C^{1''}$), 122.4 ($C^{3'}$), 125.2 ($C^{5'}$), 125.6 ($C^{6'}$), 127.1 ($C^{4'}$), 128.9 ($C^{5''}$), 133.2 ($C^{6''}$), 137.1 ($C^{1'}$), 148.2 ($C^{2'}$).

1-[2-(6-Phenyl-3,6-dihydro-[1,2]oxazine-2-yl)phenyl]-ethanol (7t-1). ^{1}H NMR δ: 1.41 (d, J = 6.6 Hz, 3H, H^2), 3.67−3.74 (m, 1H, $H^{3''}$), 3.8 (br, 1H, OH), 3.94−4.02 (m, 1H, $H^{3''}$), 5.17 (q, J = 6.6 Hz, 1H, H^1), 5.65−5.67 (m, 1H, $H^{6''}$), 6.05−6.09 (m, 1H, $H^{4''/5''}$), 6.16−6.21 (m, 1H, $H^{4''/5''}$), 7.2−7.5 (m, 4H, H^{aromat}). ^{13}C NMR δ: 23.5, 53.2, 66.8, 88.3, 120.9, 124.6, 126.2, 127.0, 127.9, 128.4, 128.5, 128.6, 138.6*, 140.7*, 146.7*. Separated by preparative HPLC using a 250 mm, i.d. = 16 mm LiChrosorb CN column, 10 mL/min, t_R = 19 min.

1-[2-(6-Phenyl-3,6-dihydro[1,2]oxazin-2-yl)phenyl]ethanol (7t-2). ^{1}H NMR δ: 1.51 (d, J = 6.6 Hz, 3H, H^2), 3.62−3.69 (m, 1H, $H^{3''}$), 3.95 (br, 1H, OH), 3.99−4.05 (m, 1H, $H^{3''}$), 5.14 (q, J = 6.6 Hz, 1H, C^1), 5.72 (s br, 1H, $H^{6''}$), 6.03−6.07 (m, 1H, $H^{4''/5''}$), 6.15−6.20 (m, 1H, $H^{4''/5''}$), 7.2−7.5 (m, 4H, H^{aromat}). ^{13}C NMR δ: 23.4, 52.9, 66.9, 80.5, 121.1, 124.5, 126.5, 127.1, 128.0, 128.4, 128.5, 128.7, 138.2, 140.6, 146.8. Separated by preparative HPLC using a 250 mm, i.d. = 16 mm LiChrosorb CN column, 10 mL/min, t_R = 16 min.

(*R/S*)-1-(2′-Aminophenyl)ethanol (2n) was prepared by standard reduction of 2′-aminoacetophenone with $NaBH_4$ in MeOH. ^{1}H NMR δ: 1.50 (d, J = 6.6 Hz, 3H), 3.66 (br, 3H), 4.80 (q, J = 6.6 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 6.70 (t, J = 7.1 Hz, 1H), 7.02 (d, J = 6.6 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H). ^{13}C NMR δ: 21.5, 69.5, 116.7, 118.2, 126.5, 128.4*, 128.5, 144.9*. ^{1}H NMR data have been reported.[90]

(*S*)-1-(2′-Aminophenyl)ethanol ((*S*)-2n) was prepared by asymmetric reduction of 2′-nitroacetophenone with (−)-DIP-Cl at −40 °C according to a reported method.[91] The ee of (*S*)-1-(2′-nitrophenyl)ethanol was determined from GC to be >99% which was higher than a previously reported value at −25 °C.[92] Catalytic reduction using Raney nickel/H_2 gave (*S*)-**2n** with the ee reduced to 90%. The ee was determined by HPLC after acylation of (*S*)-**2n** with benzoyl chloride in the presence of Et_3N yielding *N*-[2-(1-hydroxyethyl)phenyl]benzamide.[93,94] The two enantiomers of the amide separate nicely within 10 min.

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(*R*)-1-(2′-Aminophenyl)ethanol ((*R*)-2n) was prepared by asymmetric reduction of 2′-aminoacetophenone with (−)-DIP-Cl as described above. NMR data were identical to those of the racemic compound. The ee was determined as described for (*S*)-**2n**.

1-(2′-Nitrosophenyl)ethanol (8) was prepared according to a literature procedure for analogous compounds.[24] Chemical shifts were assigned from HETCOR and homonuclear decoupling of aromatic signals and by comparison with data for other *ortho*-substituted nitrosobenzenes.[81] ^{1}H NMR δ: 1.82 (d, J = 6.6 Hz, 3H, H^2), 2.9 (br, 1H, OH), 6.23 (dd, J = 8.2, 1.6 Hz, 1H, H$^{3'}$), 6.63 (q, J = 6.6 Hz, 1H), 7.25 (m, 1H, H$^{4'}$), 7.74 (m, Hz, 1H, H$^{5'}$), 7.92 (d, J = 6.6 Hz, 1H, H^6). ^{13}C NMR δ: 27.0 (C^2), 67.1 (C^1), 105.9 (C$^{3'}$), 126.9 (C$^{4'}$), 127.6 (C$^{6'}$), 136.9 (C$^{5'}$), 148.3 (C$^{1'}$), 162.9 (C$^{2'}$).

Theoretical Calculations. Geometries were optimized using either PM3[69] or AM1[68] in the MOPAC program.

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Supporting Information Available: ^{1}H, ^{13}C, NOEDIF, HETCOR, and COSY NMR spectra (86 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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