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Regio- and Stereochemical Studies on the Nitroso-Diels–Alder Reaction with 1,2-Disubstituted Dienes

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Abstract: The regioselectivity of the nitroso-Diels–Alder reaction between unsymmetrical acyclic dienes and Boc-nitroso (Boc = *tert*-butoxycarbonyl) reagent or the Wightman chiral chloronitroso reagents has been studied. With the Boc-nitroso reagent, the selectivity is a consequence of steric effects at the C1-position in the diene and electronic effects at the C2-position in the diene. The combination of an unprotected hydroxyethyl side chain at C1 and an electron-withdrawing group at C2 allows complete regioselectivity in favour of the proximal isomer. The same isomer was obtained exclusively with the chiral nitroso reagent with high enantioselectivities. A model based on steric effects is proposed.

Keywords: asymmetric synthesis · cycloadditions · enol phosphate · nitroso-Diels–Alder reaction · regioselective

Introduction

Heterocycloadditions have been recognized as valuable tools for heterocycle synthesis as well as for the selective functionalization of acyclic compounds.[1] Amongst these reactions, the nitroso-Diels–Alder reaction has been the subject of intense studies and has found many applications in the synthesis of various natural products.[2] Since the introduction of the first nitroso-Diels–Alder by Wichterle in 1947,[3] several nitroso reagents have been designed for the reaction, the most important ones being arylnitroso, chloronitroso and acylnitroso reagents, which possess different stabilities and reactivities. Recently, we have also introduced acetoxynitroso derivatives as stable and easy-to-handle chloronitroso surrogates[4] (Figure 1).

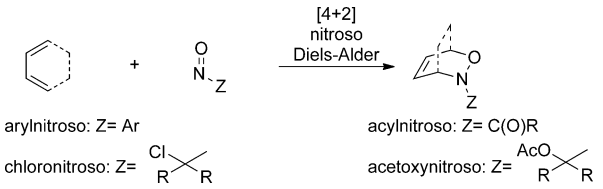

Figure 1. Nitroso-Diels–Alder reaction.

The asymmetric version of the nitroso-Diels–Alder reaction has also been the subject of intense scrutiny, leading to the design of several chiral reagents with high levels of stereoinduction,[5–7] and culminating in the achievement of the catalytic asymmetric nitroso-Diels–Alder reaction of 2-pyridylnitroso derivatives by using a chiral copper(I) complex[8] These recent results have played an important role in the renewed interest for this reaction and its synthetic applications.

As for many heterocycloadditions, the regioselectivity of the nitroso-Diels–Alder reaction is an important feature, which may limit its scope. Indeed, reactions with unsymmetrical dienes often result in low regioselectivity. Cycloaddition may lead to two regioisomers, the *proximal* isomer, in which the main substituent is close to the oxygen atom in the dihydrooxazine cycloadduct, and the *distal* isomer, in which the main substituent is close to the nitrogen atom in the cycloadduct. Figure 2 shows the regiochemical outcome for 1- and 2-substituted dienes.

The regioselectivity of the reaction has been studied by several groups and is believed to be a consequence of both steric and electronic effects. Nitroso reagents are dichotomic dienophiles reacting either with the HOMO or LUMO orbitals, which makes the rationale quite difficult. Kresze and

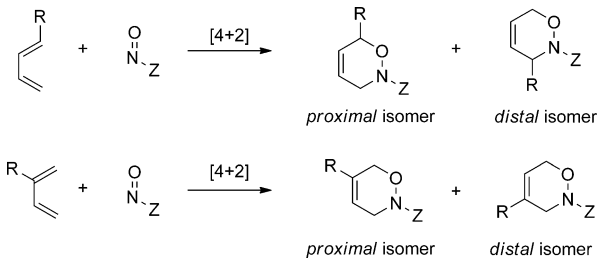

Figure 2. Regiochemical outcome of the nitroso-Diels–Alder reaction.

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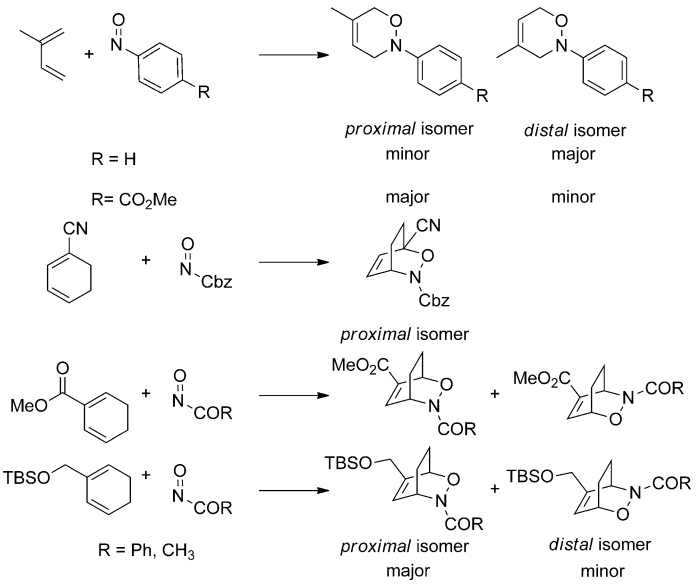
Wichterle have studied the cycloaddition between several arylnitroso derivatives and isoprene and have compared the stability of dipolar transition states: although phenylnitroso reagents give predominantly the *distal* isomer, reversal of regioselectivity is observed when an electron-withdrawing group is attached to the aromatic ring.[9,10] Likewise, the *proximal* isomer is predominantly obtained when a chloronitroso derivative is used with the same diene (Scheme 1). Steric effects are believed to be responsible for such a selectivity.[11]



Scheme 1. Literature examples of regiochemical studies for the nitroso-Diels–Alder reaction.

Acylnitroso reagents react with dienes bearing an electron-withdrawing group, such as a nitrile, to give the *proximal* isomer with high selectivity. Once again, steric effects were involved to explain this outcome.[12] The same selectivity was observed with 2-substituted dienes, the *proximal* isomer being obtained with electron-poor but also with weakly electron-rich dienes.[13] These examples illustrate the difficulty to rationalize the regioselectivity of the reaction on the basis of electronic and orbital effects (Scheme 1).

Houk and co-workers proposed a general rationale for the regioselectivity of the nitroso-Diels–Alder reaction between various nitroso derivatives and monosubstituted dienes.[14] This rationale was based on DFT calculations and was supported by experimental results. The regioselectivity depends on the nature of the nitroso derivative and on the nature and position of substituents onto the diene. The configuration of the diene may also play a role in the selectivity. As demonstrated by experimental results, acylnitroso derivatives often show better regioselectivity than their alkyl or aryl counterparts (Table 1).

As a part of an ongoing synthetic project within our laboratory, we faced the necessity to prepare in a regio- and stereoselective fashion the 5,6-disubstituted-3,4-dihydrooxazine

Table 1. Rationale for regioselectivity as proposed by Houk and co-workers.

Diene[a]	Alkyl and acylnitroso		Acylnitroso	
	major regioisomer	selectivity level	major regioisomer	selectivity level
EDG	*proximal*	medium	*proximal*	high
EWG	*proximal*	high	*proximal*	high
EDG	*proximal*	weak	*distal*	medium
EWG	*distal*	medium	*distal*	weak
EDG	*distal*	weak	–	–
EWG	*proximal*	high	–	–

[a] EDG = electron-donating group, EWG = electron-withdrawing group.

1, in which the substituent onto the double bond would be a ketone precursor (silyl enol ether, enol phosphate or bromide; Figure 3). The intermediate **1** would be obtained from a nitroso-Diels–Alder reaction between a 1,2-disubstituted diene **2** and a chiral nitroso reagent R*–N=O (acyl- or alkylnitroso).[15]

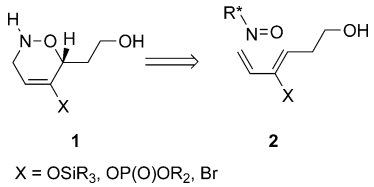


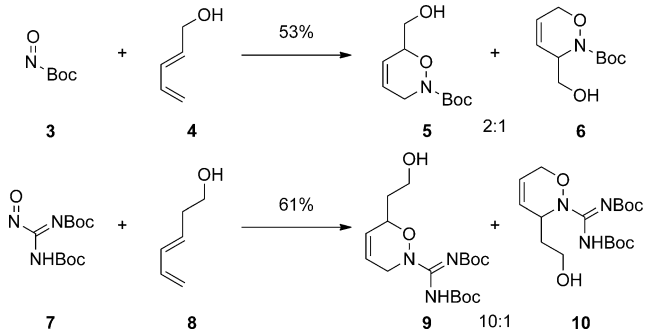
Figure 3. Retrosynthetic scheme for intermediate **1**.

According to Houk's rules, the substituent on the terminal carbon atom of the diene should favour the *proximal* isomer (which corresponds to cycloadduct **1**), whereas the internal substituent should lead to the undesired *distal* isomer. However, Houk's rules apply only to monosubstituted dienes and it is not sure whether the substituent effects are additive in disubstituted dienes. Moreover, the nature of the nitroso reagent can also influence the regioselectivity of the reaction. To the best of our knowledge, no systematic study concerning the regioselectivity of nitroso-Diels–Alder reactions with 1,2-disubstituted dienes has been reported in the literature.[16] In the present article, we wish to report our studies concerning the regioselectivity of such a reaction, as well as stereoselectivity studies with a chiral nitroso reagent.

Results and Discussion

Our studies began with the influence of the hydroxyl-containing side chain on the regioselectivity; unprotected dienic

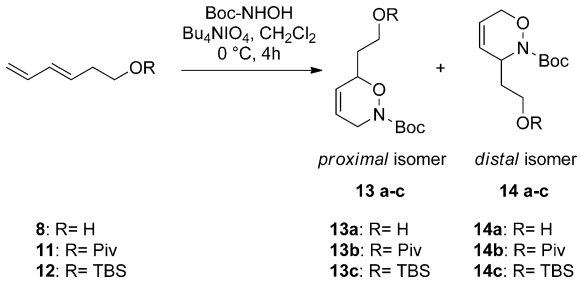
alcohols have already been used in the nitroso Diels–Alder, albeit with moderate selectivities: indeed, Bols and co-workers have reported that Boc-nitroso (Boc = *tert*-butoxycarbonyl) reagent **3** reacts with 2,4-pentadien-1-ol **4** to give a 2:1 ratio of regioisomers.[17] However, reaction between the bulkier nitrosoamidine **7** and 3,5-hexadien-1-ol **8** resulted in a good selectivity in favour of the *proximal* isomer[18] **10** (Scheme 2).



Scheme 2. Regioselectivity of nitroso-Diels–Alder reactions with dienic alcohols.

Apparently, the chain length of the diene substituent has a strong influence on the regioselectivity of the reaction. To verify this hypothesis, the alcohol **8** was prepared and protected as its pivaloate ester **11** or the known[19] silyl ether **12**. These three dienes were submitted to a nitroso-Diels–Alder reaction with Boc-nitroso reagent **3** according to standard procedures: in situ periodate oxidation of *N*-Boc hydroxylamine in the presence of the diene gave the transient nitroso reagent **3**, which reacted with the diene to give the corresponding cycloadduct as a mixture of *proximal* and *distal* isomers **13a–c**/**14a–c**, which could be easily assigned by using standard NMR spectroscopic techniques (Scheme 3, Table 2).

These results show the remarkable influence of the chain length on the regioselectivity: in comparison with Bols' results, one carbon homologation onto the diene resulted in a high selectivity in favour of the *proximal* isomer. This result, in agreement with Batey's observations, shows that the nature of the diene has more influence than the nature of the nitroso substituent. Hydroxyl group protection was



Scheme 3. Regioselectivity of nitroso-Diels–Alder reactions with 3,5-hexadien-1-ol derivatives.

Table 2. Regioselectivity of the nitroso-Diels–Alder reactions with 3,5-hexadien-1-ol derivatives.

Entry	Diene	R	Yield	Ratio **13**/**14**[a]	Major compound
1	**8**	H	74	10:1	**13a**
2	**11**	Piv	96	1:1.5	**14b**
3	**12**	TBS	90	1:2	**14c**

[a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude product.

deleterious to the regioselectivity, regardless of the electronic properties of the protecting groups: both pivaloic ester **11** and silyl ether **12** induced low regioselectivity in favour of the *distal* isomer.

The observed regioselectivities may be explained by taking account of the following features: the possibility of intermolecular hydrogen bonding between the oxygen atom of the nitroso function and the free hydroxyl group, as well as steric effects, as we have observed from molecular modelling of the transition states: it is known that the *N*-Boc nitroso reagent adopts a *s-trans* conformation in the Diels–Alder transition state; this conformation induces repulsive interactions between the *tert*-butyl group of the Boc substituent and the oxygen protecting group in the cycloaddition reactions with dienes **11** and **12**. This hypothesis could account for the observed regioselectivities (Figure 4).

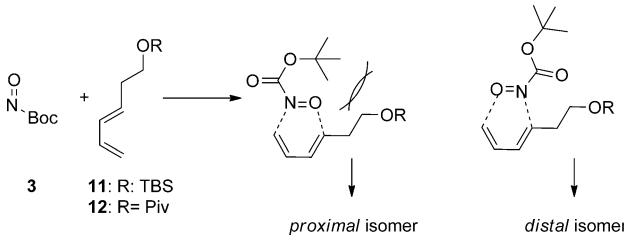
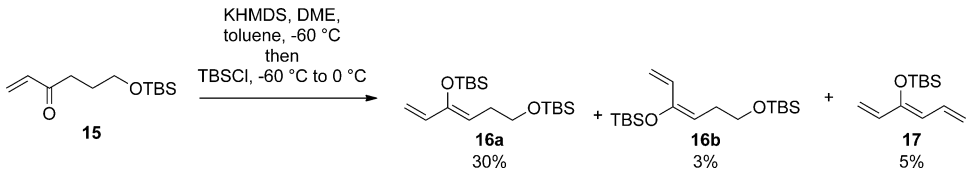


Figure 4. Steric effects in the cycloaddition reactions between Boc-nitroso reagent **3** and dienes **11** and **12**.

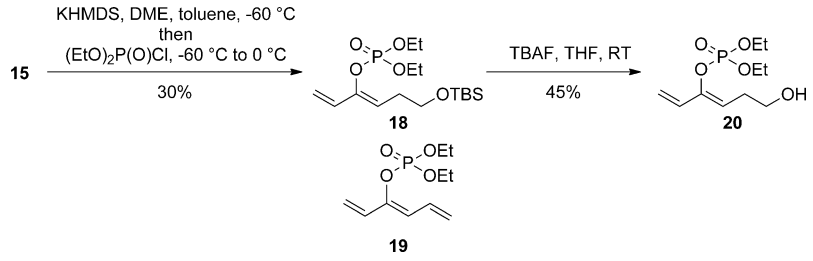
These preliminary results confirmed the importance of both the side-chain length and the hydroxyl protecting group, and showed the pathway for the design of 1,2-disubstituted dienes. Thus, the α,β-unsaturated ketone **15**[20] was selected as a precursor to the target dienes (Scheme 4). Enolization of **15** was troublesome, due to several side reactions, such as polymerization and elimination leading to the triene **17**.[21] Under optimized conditions (potassium hexamethyl disilazide (KHMDS), dimethoxyethane (DME)/toluene, −60 °C), a modest yield of the silyl enol ether **16a–b** could be obtained, in a 10:1 ratio of *Z*/*E* isomers[22] that could be separated by chromatography.

The same strategy was applied for the synthesis of the enol phosphate **20**, an electron-poor analogue to the silyl enol ether.[23,24] Deprotonation of ketone **15** and treatment of the corresponding enolate with diethylchlorophosphate gave **18** as a pure *Z* isomer. Here also prolonged reaction times or the use of excess reagents resulted in β-elimination



Scheme 4. Synthesis of dienic silyl enol ether **16**.

leading to the triene **19**. Desilylation of **18** gave the free alcohol **20** (Scheme 5).

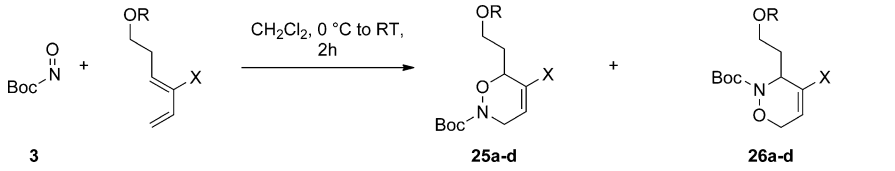


Scheme 5. Synthesis of the enol phosphates **18** and **20**. TBAF = tetrabutylammonium fluoride.

Finally, the vinyl bromide **24**, a potential substrate for nitroso-Diels–Alder cycloaddition, was prepared from 1,3-propanediol via the aldehyde **21**, which was homologated to the *gem*-dibromoalkene **22**.[25] It was crucial to perform the homologation in the presence of triethylamine[26] as classical conditions led to the corresponding tribromide. The key step was a stereoselective Negishi coupling[27] with vinylzinc bromide, leading to the (*Z*)-vinyl bromide, which was subsequently deprotected to give the alcohol **24** (Scheme 6).

With all the dienes in hand, their reactions with Boc-nitroso reagent were investigated. On the basis of previous experiences and Houk's rules, the presence of a substituent on the C_2-position should favour the *distal* isomer, whereas the influence of side chain on the C_1-position in the diene depends on chain length and the protecting group, with a hydroxyethyl substituent strongly favouring the formation of the *proximal* isomer. It would be interesting to see which substituent possesses most influence. Consequently, dienes **16a**, **18**, **20** and **24** were reacted with the Boc-nitroso under standard conditions (Scheme 7); results are presented in Table 3.

The observed selectivities emphasize the role of the electronic properties of the C_2 substituent: with the TBS-protected side chain (which disfavours the formation of the *proximal* isomer), an electron-donating group, such as OTBS, leads to the formation of the *distal* isomer with good selectivity; a reversal of regioselectivity is observed when an electron-withdrawing group, such as an enol phosphate or a bromine, is present (Table 3, entries 2–4). The conjugation of an electron-withrawing group and an unprotected hydroxylated side chain results in a dramatic enhancement of selectivity in favour of the *proximal* isomer



16a: R= TBS; X= OTBS
18: R= TBS; X= $OP(O)(OEt)_2$
20: R= H; X= $OP(O)(OEt)_2$
24: R= H; X= Br

25a: R= TBS; X= OTBS
25b: R= TBS; X= $OP(O)(OEt)_2$
25c: R= H; X= $OP(O)(OEt)_2$
25d: R= H; X= Br

26a: R= TBS; X= OTBS
26b: R= TBS; X= $OP(O)(OEt)_2$
26c: R= H; X= $OP(O)(OEt)_2$
26d: R= H; X= Br

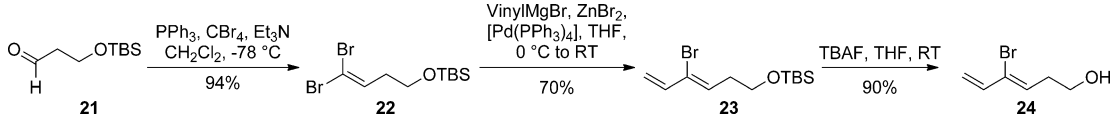
Scheme 7. Nitroso-Diels–Alder reactions between Boc-nitroso **3** and dienes **16a**, **18**, **20** and **24**.

Table 3. Regioselectivity of nitroso-Diels–Alder reactions between Boc-nitroso and 1,2-disubstituted dienes.

Entry	Diene	R	X	Yield	Major compound	Ratio **29**/**30**[a]
1	**16a**	TBS	OTBS	70	**26a**	1:7
2	**18**	TBS	$OP(O)(OEt)_2$	45	**25b**	2:1
3	**20**	H	$OP(O)(OEt)_2$	68	**25c**	10:1
4	**24**	H	Br	64	**25d**	>10:1

[a] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude product.

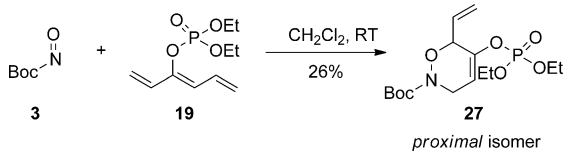
(entries 3 and 4). Thus, the optimal conditions for a regioselective nitroso-Diels–Alder reaction with a 1,2-disbustituted



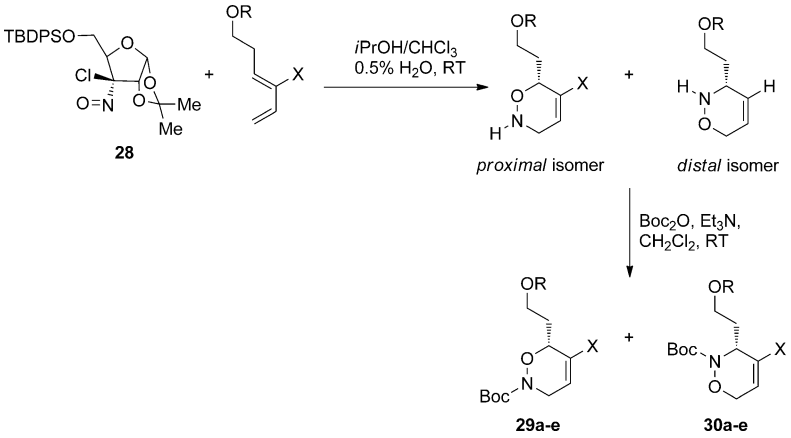
Scheme 6. Synthesis of the vinyl bromide **24**.

diene are: 1) A bulky substituent at C_1 and an electron-donating group at C_2 for the *distal* isomer and 2) a nonbulky substituent at C_1 and an electron-withdrawing group at C_2 for the *proximal* isomer.

The selectivities reported in Table 3 can be rationalized on the basis of steric and electronic effects. The possibility of hydrogen bonding between the free hydroxyl group (in dienes **20** and **24**) and the nitroso oxygen atom cannot be ruled out but is not always crucial for the regioselectivity. Actually, the triene **19**, which is a byproduct in the synthesis of enol phosphate **18** reacted with the Boc-nitroso reagent **3** with complete selectivity in favour of the *proximal* isomer **27** (Scheme 8); this experiment tends to prove that electronic or steric effects are at least as important as noncovalent bonding in the transition state.



Scheme 8. Nitroso-Diels–Alder reaction of trienic enol phosphate **19**.



Scheme 9. Cycloadditions with Wightman's reagent **28**.

Table 4. Regio- and stereoselectivity of cycloadditions with Wightman's chloronitroso derivative **28**.

Entry	Diene	R	X	Yield [%][a]	Ratio **29**/**30**[b]	Major compound	*ee* [%][c]
1	**8**	H	H	65	>99:1	**29a**	90
2	**11**	Piv	H	16[d]	>99:1	**29c**	72
3	**12**	TBS	H	65	>99:1	**29a**[e]	90
4	**16a**	TBS	OTBS	–[f]	–		–
5	**20**	H	$OP(O)(OEt)_2$	55	>99:1	**29d**	90
6	**24**	H	Br	40	>99/1	**29e**	81

[a] Overall yield for the cycloaddition, hydrolysis and protection. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] Determined by HPLC analysis on chiral column. [d] Degradation of the dienophile was observed. [e] In situ desilylation was observed. [f] Degradation of the diene was observed.

With all the previous reactions being performed with an acylnitroso reagent (Boc-nitroso), it would be interesting to check whether the rules for regioselectivity apply to other nitroso species, especially alkylnitroso derivatives. Moreover, it would be important to evaluate the possibility for enantioselective nitroso-Diels–Alder reactions between chiral nitroso reagents and 1,2-disubstituted dienes, as most of enantioselective nitroso-Diels–Alder reactions have been developed with simple symmetrical dienes, such as cyclopentadiene or cyclohexadiene. For all these reasons, we selected the Wightman chloronitroso **28** as a model reagent for this study. The Wightman reagent has been designed as a simple, easily available and highly efficient dienophile for enantioselective nitroso-Diels–Alder reactions with simple dienes, such as cyclopentadiene, cyclohexadiene, or cycloheptadiene (enantiomeric excess (*ee*) = > 96 %).[5a,b]

Chloronitroso derivative **28** was prepared according to the literature procedure and reacted with monosubstituted dienes **8**, **11**, **12** and the disubstituted dienes **16a**, **20** and **24** in $CHCl_3$/*i*PrOH/H_2O (Scheme 10). After hydrolysis of the reaction, the crude cycloadducts **29**/**30** were protected as their *N*-Boc derivatives for comparison with previously prepared cycloadducts (Scheme 9, Table 4).

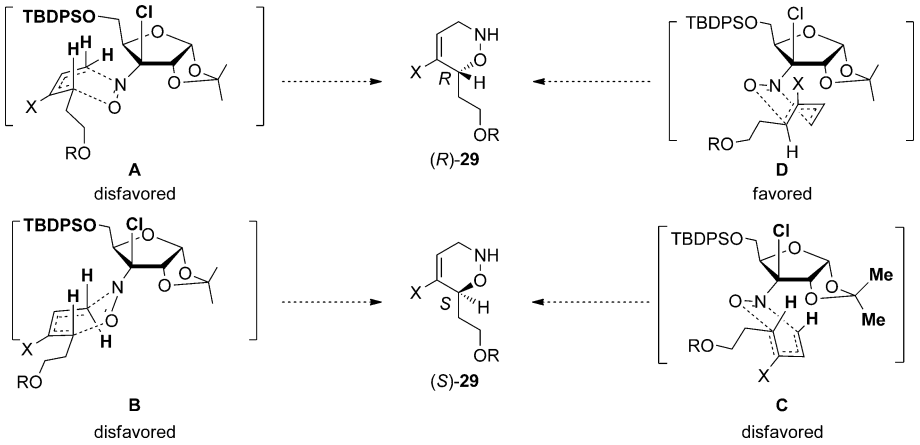
The cycloaddition reactions were performed at room temperature. As expected, chloronitroso reagent **28** was less reactive than the Boc-nitroso derivative **3**, which resulted in longer reaction times (18–36 h). The reaction sequence involving the release of hydrochloric acid prolonged reaction times and caused the cleavage of acid-sensitive functional groups. Thus, low yields were obtained with the poorly reactive pivaloyl ester **11**, due to the degradation of the carbohydrate backbone, probably by hydrolysis of the acetonide (Table 4, entry 2). This was also observed for the cycloaddition with the silyl enol ether **12**, for which partial desilylation occurred during cycloaddition (entry 3). Unfortunately, the silyl enol ether **16a** was unstable under the reaction conditions, giving no cycloadduct (entry 4). The other dienes (and their corresponding cycloadducts) were stable and reactive enough to provide appreciable yields of dihydrooxazines **29**/**30**.

NMR spectroscopic analysis of the crude reaction products showed that all the reactions proceeded with complete regioselectivity in favour of the *proximal* isomer **29**, no trace of the *distal* isomer being detected. Noteworthy is the selectivity for the cycloaddition with pivalate **11**, for which the cycloaddition with Boc-nitroso **3** was not regioselective. Moreover, all the cycloadditions were highly stereoselective, giving the cycloadducts with high enantiomeric excesses.

The stereoselectivity of the cycloadditions could be rationalized after analysis of the transition states. Therefore,

we examined qualitatively the steric interactions for each transition state by molecular modelling,[28] assuming a late transition state that would be close to the primary adduct. For a given regioisomer, four possible transition states **A**–**D** can be involved, leading to each of the enantiomers of the cycloadduct. Scheme 10 represents the four possible transition states leading to the *proximal* isomer **29**. Molecular modelling of the transition states revealed that transition-states **A** and **B** are disfavoured due to severe steric interactions between the $CH_2OTBDPS$ appendage and the terminal methylene of the diene. Moreover, steric interactions between the chlorine atom and the hydrogen atom located on the sp2 carbon atom (distance of 2.27 and 2.84 Å, respectively) disfavour the same transition-states **A** and **B**, whereas transition-state **C** is disfavoured by the equivalent interaction (distance of 2.33 Å) and another between the hydrogen and the acetonide oxygen atom (distance: 1.87 Å). Figure 5 shows the molecular modelling of transition states with diene **24**. Transition-state **D** should be the most favoured one; this transition state would lead to the *R* enantiomer (*R*)-**29**, which is consistent with previously reported results:[29]

The determination of the preferred facial approach in the cycloaddition may account for the regiochemical control: as shown in Figure 6 (using diene **8** as a representative example), assuming that the facial approach **D** is favoured, the transition-state leading to the *distal* isomer would be disfavoured by steric interaction between the side chain located on position-1 of the diene and the acetonide. This proposal for regioselectivity was already proposed for the cycloaddition between 1,3-disubstitued dienes and the Wightman reagent **28**.[16a]



Scheme 10. Putative transition states for the cycloaddition leading to the *proximal* isomer **29**.

According to this proposal, the regio- and stereoselectivity of cycloadditions with the Wightman reagent are governed by pure steric effects. It should be worth pointing out that protection of the hydroxyl group on the side chain should not significantly affect the regiochemistry of the reaction. Furthermore, the nature and electronic properties of the 2-substituent in the diene should also not affect the selectivity of the reaction.

To verify this hypothesis, cycloadditions between Wightman's reagent **28** and 1,4-disub-

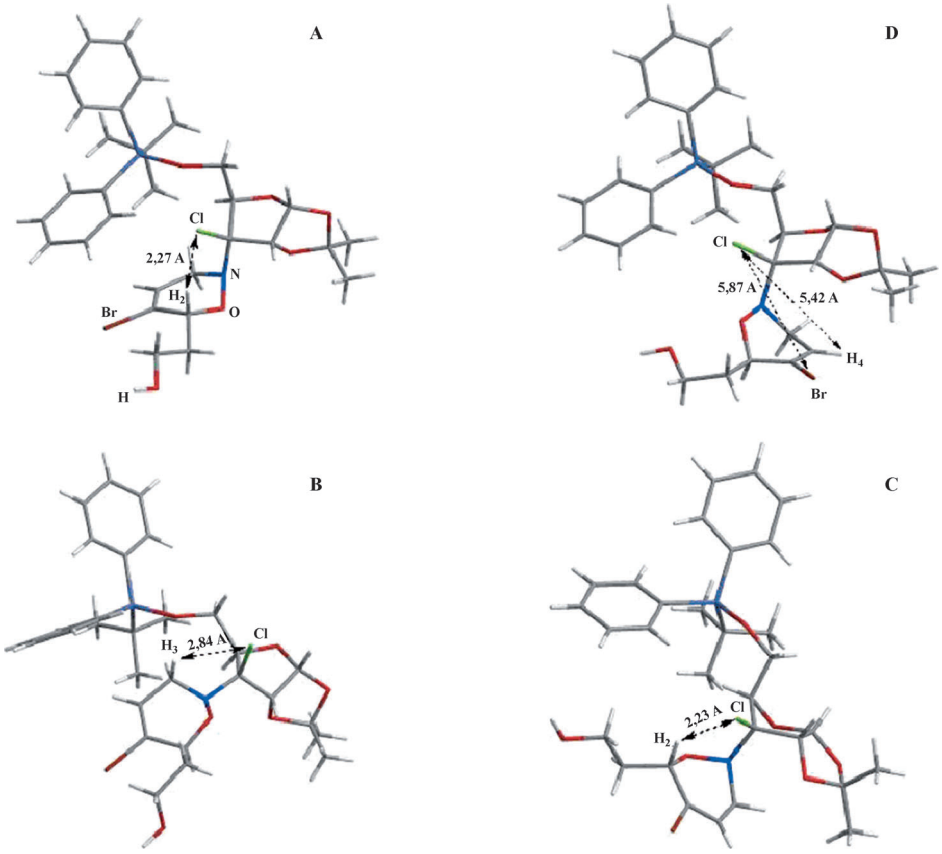


Figure 5. Molecular modelling of the putative transition states with diene **24** (X = Br, R = H).

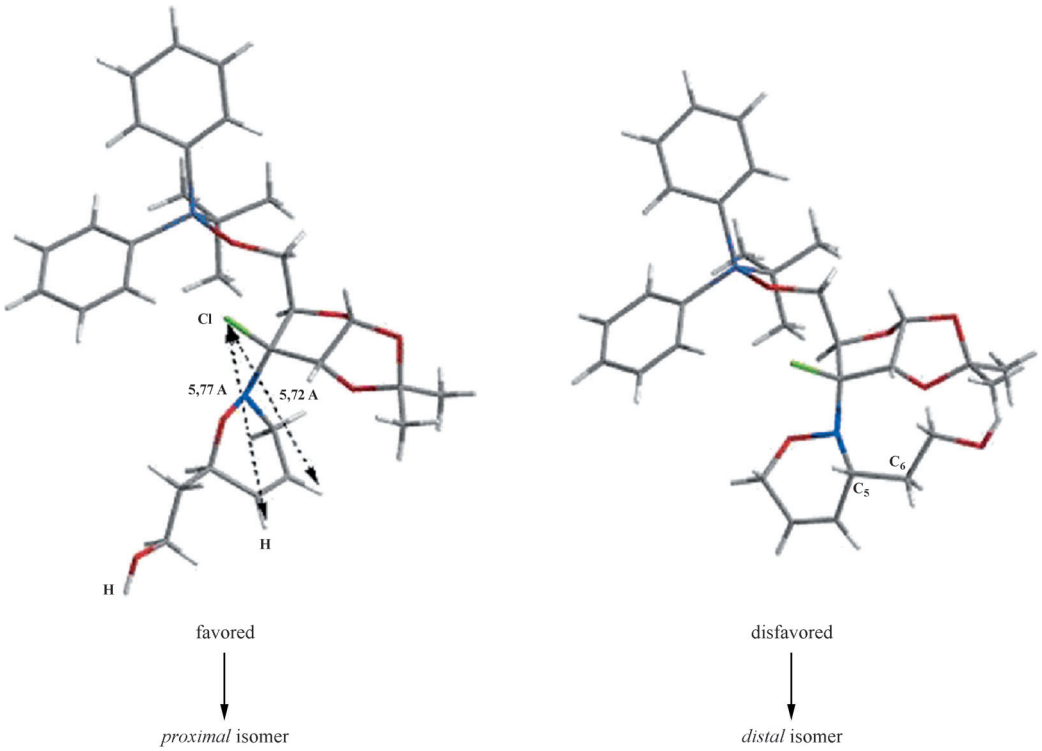
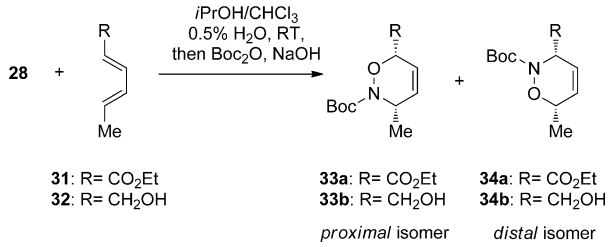


Figure 6. Transition states for both possible regioisomers in the cycloaddition reaction between Wightmann derivative **28** and diene **8**.

stituted dienes, such as ethyl sorbate **31**, and its reduction product **32** were undertaken (Scheme 11, Table 5):

Cycloadditions with ethyl sorbate **31** and its reduction product 2,4-hexadien-1-ol **32**[30] were slow and increased



Scheme 11. Cycloadditions of **28** with 1,4-disubstituted dienes.

Table 5. Regio- and stereoselectivity of the cycloadditions of **28** with 1,4-disubstituted dienes.

Entry	Diene	R	Yield [%]	Ratio **33**/**34**[a]	*ee* major[b]	*ee* minor [%][b]
1	**31**	CO_2Et	60	1.5:1	0	n.d.[c]
2	**32**	CH_2OH	70	4:1	42	72

[a] Determined by ^1H NMR spectroscopic analysis of the crude product. [b] Determined by HPLC analysis on a chiral column. [c] Not determined.

amounts of diene were required for appreciable conversion. Furthermore, regio- and enantioselectivity were significantly reduced relative to those obtained with 1,2-disubstituted dienes. Especially, the *proximal* isomer **33a** was found to be nearly racemic.[31] It is probable that the transition-state **D** (Scheme 11) is destabilized by steric interactions between the methyl substituent and the acetonide group. Therefore, other transition-states may be involved, resulting in the formation of the other enantiomer. Moreover, the low regioselectivities could be explained by the weak difference of steric hindrance between the methyl substituent or the R group with the acetonide (see Figure 5). This experience validates our hypothesis for the stereochemical induction in the Wightman reagent and shows the necessity for appropriate substitution patterns for a selective nitroso-Diels–Alder reaction.

Cycloaddition reactions between Wightman reagent **28** and both 1,2- and 1,4-disubstituted dienes reveals some insights about the role of each substituent in the chiral nitroso reagent: although the TBDPS substituent of the primary hydroxyl group of the xylose backbone, as well as the chlorine atom contributes to facial control, the acetonide group plays an important role in the regiochemical control with unsymmetrical dienes. The combination of all these features allows highly selective reactions (Figure 7).

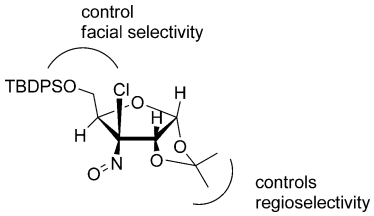


Figure 7. Elements for selectivity in the cycloaddition reactions with Wightman reagent **28**.

Conclusion

We have demonstrated the possibility of performing highly regioselective nitroso-Diels–Alder cycloadditions with 1,2-disubstituted dienes leading to the selective formation of the *proximal* isomer. However, the factors ruling the regioselectivity strongly depend on the nature of the nitroso reagent. With the Boc-nitroso dienophile, the selectivity of the reaction is a consequence of steric effects at the C_1-position of the diene, and electronic effects at the C_2-position. For the latter, we have highlighted the utility of enol phosphates as stable and electron-withdrawing analogues to silyl enol ethers in cycloaddition reactions. This work has also led to an analysis of the factors governing the regio- and stereoselectivity of asymmetric nitroso-Diels–Alder reactions with the chiral Wightman nitroso reagent, for which complete regio- and stereoselectivities were observed with 1,2-disubstituted dienes. For this cycloaddition, we have proposed a model based only on steric factors. These results should lead to a rational design of the diene substitution pattern for selective cycloadditions, and increase the synthetic scope of the nitroso-Diels–Alder reaction.

Experimental Section

General procedure for the nitroso-Diels–Alder reactions with the *N*-Boc nitroso reagent (3): A solution of *N*-Boc hydroxylamine (287 mg, 2.16 mmol) and the diene (1.43 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C with stirring and a solution of tetrabutylammonium periodate (455 mg, 1.05 mmol) in CH_2Cl_2 (3 mL) was added over 25 min. The reaction mixture was stirred for 3 h at 0 °C, and then allowed to warm to RT within 1 h. The reaction mixture was diluted with ether (20 mL) and washed with saturated sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ether (3×20 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography to give the pure cycloadduct.

(*RS*) *tert*-Butyl-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (13a): Prepared according to the general procedure with diene **8**. Flash chromatography over silica gel (AcOEt/heptane, 40:60) gave a 10:1 mixture of the *proximal* **13a** and *distal* **14a** cycloadducts as a light-yellow oil (243 mg, 74%).

Data for proximal *isomer* ***13a***: R_f=0.20 (AcOEt/heptane 40:60); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): δ=5.81–5.71 (m, 2H), 4.61 (br d, 1H, J=9.3 Hz), 4.05 (br d, 1H, J=~18 Hz), 3.93 (br d, 1H, J=18 Hz), 3.85–3.72 (m, 2H), 2.7 (br s; OH), 1.81 (m, 1H), 1.74 (m, 1H), 1.45 ppm (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$): δ=155.2 (N*C*OO), 128.4 (*HC*=), 122.7 (*HC*=), 82.1 (O*C*Me$_3$), 77.1 (*CH*ON), 60.0 (*CH*$_2$OH), 45.1 (*CH*$_2$NO), 35.7 (*CH*$_2$CH$_2$OH), 28.4 ppm ((*CH*$_3$)$_3$C); MS (ESI): m/z: 252 [M+Na$^+$], 196 [M+Na$^+$−Me$_2$C=CH$_2$], 152 (M+Na$^+$−Me$_2$C=−CO$_2$); HRMS (ESI-QTOF): m/z: calcd for $C_{11}H_{19}NO_4Na$: 252.1212 [M+Na$^+$]; found: 252.1213.

The minor *distal* cycloadduct **14a** could not be isolated as a pure compound and was partially characterized in mixtures with **13a** for a distinct resonance in ^{1}H NMR (360 MHz, $CDCl_3$; TMS): δ=4.55 (br d, 1H, C*H*N or C*H*$_2$ON; J=15.3 Hz).

(*RS*) *tert*-Butyl-6-(2-*tert*-butylcarbonyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (13b) and (*RS*) *tert*-butyl-3-(2-*tert*-butylcarbonyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (14b): Prepared according to the general procedure with diene **11**. Chromatography over silica gel (AcOEt/heptane 10:90) gave a first fraction that was a 1:1.2 mixture of the *proximal* **13b** and *distal* **14b** cycloadducts (146 mg, 90%), and then the pure *distal* cycloadduct **14b** (9 mg, 6%) as colourless oils (96% global yield of cycloadducts, **13b**/**14b** 1:1.5).

Data for distal *isomer* ***14b***: R_f=0.12 (AcOEt/heptane 10:90); ^{1}H NMR (360 MHz, C_6D_6; TMS): δ=5.45 (ddt, 1H, J=10.4, 4.5, 2.3 Hz), 5.27 (dt, 1H, J=10.4, 1.8 Hz), 4.58 (m, 1H), 4.41 (br d, 1H, J=15.9 Hz), 4.22 (m, 1H), 4.15 (m, 1H), 3.68 (ddd, 1H, J=15.9, 3.9, 1.6 Hz), 1.99 (m, 1H), 1.81 (m, 1H), 1.41 (s, 9H; *t*Bu), 1.20 ppm (s, 9H; *t*Bu); ^{13}C NMR (360 MHz, C_6D_6): 177.9 (*C*OO), 155.1 (N*C*OO), 126.9 (=*CH*), 124.9 (=*CH*), 81.2 (O*C*Me$_3$), 67.6 (*CH*$_2$O), 61.8 (*CH*$_2$OPiv), 52.1 (*CH*N), 39.2 (Me$_3$*C*), 32.8 (*CH*$_2$CH$_2$OPiv), 28.7 (C(*CH*$_3$)$_3$), 27.7 ppm (C(*CH*$_3$)$_3$); MS (ESI): m/z: 336 [M+Na$^+$], 280 [M+Na$^+$−Me$_2$C=], 236 [M+Na$^+$−Me$_2$C=−CO$_2$]; HRMS (ESI-QTOF): m/z: calcd for $C_{16}H_{27}NO_5Na$: 336.1787 [M+Na]$^+$; found: 336.1792.

The *proximal* racemic cycloadduct **13b** could not be isolated as a pure compound and was partially characterized in mixtures with **14b** by ^{1}H NMR spectroscopy. ^{1}H NMR (360 MHz, C_6D_6; TMS): δ=5.35–5.27 (m, 2H), 4.50–4.41 (m, 1H), 4.34–4.27 (m, 2H), 3.97 (br d, 1H, J=17.6 Hz), 3.81 (br d, 1H, J=17.6 Hz), 1.89–1.74 (m, 1H), 1.70–1.57 (m, 1H) 1.44 (s, 9H), 1.15 ppm (s, 9H).

(*RS*)-*tert*-Butyl-6-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (13c) and (*RS*)-*tert*-butyl-3-(2-*tert*butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (14c): Prepared according to the general procedure with diene **12**. Chromatography over silica gel (AcOEt/heptane 5:95) gave a 1:2 mixture of the *proximal* **13c** and *distal* **14c** cycloadducts as a colourless oil (376 mg, 90%).

Data for the proximal *isomer* ***13c***: R_f=0.51 (AcOEt/heptane 10:90); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): δ=5.82–5.75 (m, 2H), 4.59 (m, 1H), 4.06 (br d, 1H, J=~17 Hz), 3.96 (br d, 1H, J=~17 Hz), 3.82 (m, 1H), 3.74 (m, 1H), 1.86 (ddt, 1H, J=14.3, J=8.5, J=5.1 Hz), 1.70 (m, 1H), 1.47 (s, 9H), 0.87 (s, 9H), 0.042 (s, 3H; Si*Me*$_2$), 0.037 ppm (s, 3H; Si*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2 (N*C*OO), 128.8 (=*CH*), 122.6 (=*CH*), 81.4 (O*C*Me$_3$), 75.5 (*CH*−O), 59.6 (*CH*$_2$OTBS), 45.0 (*CH*$_2$N), 36.5 (*CH*$_2$CH$_2$OTBS), 28.6 (C(*CH*$_3$)$_3$), 28.1 (C(*CH*$_3$)$_3$), 18.5 (*C*Me$_3$), −5.1 ppm (Si*CH*$_3$); MS (ESI): m/z: 366 [M+Na$^+$], 310 [M+Na$^+$−Me$_2$C=], 266 [M+Na$^+$−Me$_2$C=−CO$_2$]; HRMS (ESI-QTOF) m/z: calcd: 366.2077 [M+Na$^+$], found: 366.2081.

Data for distal *isomer* ***14c***: R_f=0.45 (AcOEt/heptane 10:90); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): δ=5.87 (ddt, 1H, J=10.4, 4.2, 2.0 Hz), 5.79 (ddt, 1H, J=10.4, 3.7, 1.5 Hz), 4.59 (dq, 1H, J=15.7, 2.0 Hz), 4.48 (m, 1H), 4.11 (ddd, 1H, J=15.7, 3.7, 1.5 Hz), 3.74–3.62 (m, 2H), 1.94 (m, 1H), 1.81 (m, 1H), 1.47 (s, 9H), 0.87 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): 154.9 (N*C*OO), 127.3 (*HC*=), 123.8 (*HC*=), 81.5 (O*C*Me$_3$), 67.7 (*CH*$_2$O), 60.2 (*CH*$_2$OTBS), 52.1 (*CH*N), 36.3 (*CH*$_2$CH$_2$OTBS), 28.6 ((*CH*$_3$)$_3$C), 26.2 ((*CH*$_3$)$_3$C), 18.5 (*C*Me$_3$), −5.1 (Si*CH*$_3$), −5.2 ppm (Si*CH*$_3$); MS (ESI): m/z: 366 [M+Na$^+$], 310 [M+Na$^+$−Me$_2$C=], 266 [M+Na$^+$−Me$_2$C=−CO$_2$]; HRMS (ESI-QTOF): m/z: calcd for $C_{17}H_{33}NO_4SiNa$: 366.2077 [M+Na]$^+$; found: 366.2076.

(*RS*)-*tert*-Butyl-4-*tert*-butyldimethylsilyloxy-3-(2-*tert*butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (26a): A solution of Bu_4NIO_4 (112 mg, 0.26 mmol) in dichloromethane (3 mL) was added to a solution of BocNHOH (70 mg, 0.52 mmol) and diene **16a** (110 mg, 2 mmol) in dichloromethane (2 mL) over 25 min at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The mixture was then diluted with ether (20 mL) and treated with an aqueous saturated $Na_2S_2O_3$ solution (10 mL). After extraction with ether (3×20 mL), the organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford a brown oil that was purified by silica gel chromatography (AcOEt/heptane 5:95) to afford a mixture of the *proximal* **25a** and *distal* **26a** cycloadducts as a colourless oil (67 mg, 70%, **25**/**26** 1:7).

Data for the distal *isomer* ***26a***: Colourless oil. R_f=0.44 (AcOEt/heptane, 10:90): ^{1}H NMR (250 MHz, $CDCl_3$; TMS): δ=4.78 (dd, 1H, J=4.1, 1.0 ppm), 4.64 (d, 1H, J=14.5 ppm), 4.27 (br t, 1H, J=6.4 Hz), 4.12 (dd, 1H, J=14.3, 4.1 Hz), 3.67 (t, 2H, J=6.5 Hz), 1.97–1.86 (m, 2H), 1.47 (s, 9H), 0.91 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.02 ppm (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): 155.2 (=*C*−O), 150.0 (N*C*OO), 98.6 (*HC*=), 81.7 (quat, O*C*Me$_3$), 66.6 (*CH*$_2$ON), 60.0 (*CH*$_2$OTBS), 54.9 (*CH*N), 34.4 (*CH*$_2$CH$_2$OTBS), 28.5 ((*CH*$_3$)$_3$C), 26.2 ((*CH*$_3$)$_3$C), 25.8 ((*CH*$_3$)$_3$C), 18.5 (quat, *t*Bu), 18.2 (quat, *t*Bu), −4.2 (Si*CH*$_3$), −4.4 (Si*CH*$_3$),

−5.1 ppm (SiCH_3); MS (ESI): *m/z*: 496 [*M*+Na^+], 440 [M+Na^+−Me_2C=], 396 [M+Na^+−Me_2C=−CO_2]; HRMS (ESI-QTOF): *m/z*: calcd for $C_{23}H_{47}NO_5Si_2Na$: 496.2891 [*M*+Na]$^+$; found: 496.2882.

The minor *proximal* cycloadduct **25a** could not be isolated as a pure compound and was partially characterized in a mixture with **26a** for distinct resonances in ^{1}H NMR (250 MHz, $CDCl_3$; TMS): δ = 4.84 (td, 1H; C*H*N or CH_2ON, *J* = 3.3, *J* = 1.0 Hz).

(*RS*)-*tert*-Butyl-5-diethylphosphoryloxy-6-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (25b) and (*RS*)-*tert*-butyl-4-diethylphosphoryloxy-3-(2-*tert*-butyldimethylsilyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (26b): A solution of Bu_4NIO_4 (43 mg, 0.1 mmol) in dichloromethane (1 mL) was added to a solution of Boc-NHOH (25 mg, 0.2 mmol) and diene **18** (69 mg, 0.2 mmol) in dichloromethane (1 mL) over 25 min at 0 °C, and the reaction mixture was then stirred for 2 h at this temperature. The cooling bath was then removed to allow the mixture to warm up to RT. After further stirring for 30 mn, TLC analysis showed still some unreacted diene **18**. Hence, Boc-NHOH (21 mg, 0.16 mmol) and Bu_4NIO_4 (87 mg, 0.2 mmol) were added without any solvent to the reaction mixture at RT. After further stirring at RT for 2 h 30 min, the mixture was then diluted with ether (20 mL) and treated with an aqueous saturated sodium thiosulfate solution (10 mL). After extraction with ether (3×20 mL), the organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford a brown oil that was purified by silica gel chromatography over Merck 60 TLC plates (AcOEt/heptane 40:60, double elution) to afford the *proximal* cycloadduct **25b** (colourless oil, 29 mg, 30%) and the *distal* cycloadduct **26b** (colourless oil, 15 mg, 15%).

Data for the proximal *isomer* ***25b***: R_f = 0.63 (double elution, AcOEt/heptane 40:60); ^{1}H NMR (400 MHz, $CDCl_3$; TMS): δ = 5.66 (brt, 1H, *J* = 3.4 Hz), 4.50 (brd, 1H, *J* = 9.7 Hz), 4.14 (quint., 4H, *J* = 7.3 Hz), 4.11–4.00 (m, 2H), 3.90–3.84 (m, 1H), 3.78–3.73 (m, 1H), 1.99–1.82 (m, 2H), 1.47 (s, 9H), 1.33 (brt, 6H, *J* = 7.1 Hz), 0.86 (s, 9H), 0.039 (s, 3H), 0.033 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 154.9 (quat., =*C*<C->O), 146.9 (quat., N*C*OO), 105.2 (*HC*=), 81.9 (quat., O*C*Me_3), 75.3 (*CH*ON), 64.9 (O*CH*$_2$CH$_3$), 59.0 (*CH*$_2$OTBS), 43.9 (*CH*$_2$N), 33.6 (*CH*$_2$CH$_2$OTBS), 28.5 ((*CH*$_3$)$_3$C), 26.1 ((*CH*$_3$)$_3$C), 18.4 (quat., *t*Bu), 16.3 (CH$_2$*CH*$_3$), −5.1 ppm (Si*CH*$_3$).

Data for the distal *isomer* ***26b***: R_f = 0.57 (double elution, AcOEt/heptane 40:60); ^{1}H NMR (400 MHz, $CDCl_3$; TMS): δ = 5.64 (brd, 1H, *J* = 3.5 Hz), 4.66 (brd, 1H, *J* = 14.8 Hz), 4.49 (brt, 1H, *J* = 5.9 Hz), 4.21 (brdd, 1H, *J* = 15.0, 4.0 Hz), 4.16 (dquint., 4H, *J* = 7.4, 2.7 Hz), 3.69 (t, 2H, *J* = 6.4 Hz), 1.96 (q, 2H, *J* = 6.4 Hz), 1.47 (s, 9H), 1.34 (t, 6H, *J* = 7.2 Hz), 0.86 (s, 9H), 0.02 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 154.8 (quat., =*C*−O), 146.2 (quat., N*C*OO), 105.4 (*HC*=), 82.2 (quat., O*C*Me_3), 66.3 (*CH*$_2$ON), 64.9 (O*CH*$_2$CH$_3$), 59.6 (*CH*$_2$OTBS), 53.2 (*CH*N), 34.1 (*CH*$_2$CH$_2$OTBS), 28.5 ((*CH*$_3$)$_3$C), 26.1 ((*CH*$_3$)$_3$C), 18.5 (quat, *t*Bu), 16.3 (CH$_2$*CH*$_3$), −5.2 ppm (Si*CH*$_3$); MS (ESI): *m/z*: 518 [*M*+Na^+], 462 [*M*+Na^+−Me_2C=], 418 [*M*+Na^+−Me_2C=−CO_2]; HRMS (ESI-QTOF): *m/z*: calcd for $C_{21}H_{42}NO_8PSiNa$: 518.2315 [*M*+Na]$^+$; found: 518.2316.

(*RS*)-*tert*-Butyl-5-diethylphosphoryloxy-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (25c) and (*RS*)-*tert*-butyl-4-diethylphosphoryloxy-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (26c): A solution of Bu_4NIO_4 (24 mg, 0.55 mmol) in dichloromethane (1 mL) was added to a solution of Boc-NHOH (15 mg, 0.11 mmol) and diene **20** (28 mg, 0.11 mmol) in dichloromethane (0.5 mL) over 25 min at 0 °C. The reaction mixture was then stirred for 2 h at that temperature. The cooling bath was then removed to allow the mixture to warm up to RT. After further stirring for 1 h, TLC analysis still showed some unreacted diene **20**. Hence, Boc-NHOH (7 mg, 0.05 mmol) and Bu_4NIO_4 (6 mg, 0.014 mmol) were added without any solvent to the reaction mixture at RT. After further stirring at RT for 1 h, the mixture was then diluted with ether (10 mL) and treated with aqueous saturated sodium thiosulfate solution (5 mL). After extraction with ether (3×10 mL), the organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford a yellow oil that was purified by silica gel chromatography (AcOEt/heptane, 60:40) to afford a 10:1 mixture of the *proximal* cycloadduct **25c** and the *distal* cycloadduct **26c** as a light yellow oil (26 mg, 68%).

Data for proximal *isomer* ***25c***: R_f = 0.28 (AcOEt/heptane 70:30); ^{1}H NMR (400 MHz, $CDCl_3$; TMS): δ = 5.67 (m, 1H), 4.54 (brd, 1H, *J* = 9.8), 4.14 (quint., 4H, *J* = 7.3 Hz), 4.08 (m, 2H), 3.90–3.77 (m, 2H), 2.06–1.90 (m, 2H), 1.47 (s, 9H), 1.33 ppm (t, 6H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 155.0 (=*C*−O), 146.4 (N*C*OO), 105.3 (*HC*=), 82.8 (quat., O*C*Me_3), 77.7 (*CH*ON), 65.0 (O*CH*$_2$CH$_3$), 60.3 (*CH*$_2$OH), 44.2 (*CH*$_2$N), 32.7 (*CH*$_2$CH$_2$OH), 28.4 ((*CH*$_3$)$_3$C), 16.3 ppm (CH$_2$*CH*$_3$); MS (ES): *m/z*: 404 [*M*+Na^+], 348 [*M*+Na^+−Me_2C=], 304 [*M*+Na^+−Me_2C=−CO_2], 273; HRMS (ESI-QTOF): *m/z*: calcd for $C_{15}H_{28}NO_8PNa$ [*M*+Na]$^+$; 404.1450; found: 404.1460.

The minor *distal* cycloadduct **26c** could not be isolated as a pure compound and was partially characterized in mixtures with **25c** for distinct resonances in ^{1}H NMR (400 MHz, $CDCl_3$; TMS): δ = 4.59 (brd, 1H; C*H*N or CH_2ON, *J* = 15.4 Hz).

(*RS*)-*tert*-Butyl-5-bromo-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate (25d): A solution of Bu_4NIO_4 (202 mg, 0.47 mmol) in dichloromethane (2 mL) was added to a solution of Boc-NHOH (124 mg, 0.93 mmol) and diene **24** (112 mg, 0.62 mmol) in dichloromethane (1 mL) over 25 min at 0 °C. The reaction mixture was then stirred for 2 h at that temperature. The cooling bath was then removed to allow the mixture to warm up to RT. After further stirring for 2 h, TLC analysis still showed some unreacted diene **24**. Hence, after cooling at 0 °C, Boc-NHOH (130 mg, 0.97 mmol) and a solution of Bu_4NIO_4 (207 mg, 0.47 mmol) in dichloromethane (1 mL) were added over 20 min to the reaction mixture. After further stirring at 0 °C for 1 h 30 min, the cooling bath was removed and after 20 min at RT, the reaction mixture was then diluted with ether (20 mL) and treated with an aqueous saturated sodium thiosulfate solution (10 mL). After extraction with ether (3×20 mL), the organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford a brown oil that was purified by flash chromatography over silica gel (AcOEt/heptane 30:70) to give as the only product the *proximal* cycloadduct **25d** (colourless oil, 125 mg, 64% yield).

R_f = 0.36 (AcOEt/heptane 50:50); ^{1}H NMR (250 MHz, $CDCl_3$; TMS): δ = 6.13 (m, 1H), 4.57 (d, 1H, *J* = 10.5 Hz), 4.06 (m, 2H), 3.85 (m, 2H), 2.40 (brs; OH), 2.20 (m, 1H), 1.95 (m, 1H), 1.48 ppm (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$): 155.1 (quat., N*C*OO), 124.4 (*HC*=), 121.4 (*BrC*=), 82.9 (quat., O*C*Me_3), 81.5 (*CH*ON), 60.2 (*CH*$_2$OH), 47.6 (*CH*$_2$NO), 33.6 (*CH*$_2$CH$_2$OH), 28.4 ppm ((*CH*$_3$)$_3$C); MS (ESI): *m/z*: 332, 330 [*M*+Na^+], 276, 274 [*M*+Na^+−Me_2C=], 232, 230 [*M*+Na^+−Me_2C=−CO_2]; HRMS (ESI-QTOF): *m/z*: calcd for $C_{11}H_{18}{}^{79}BrNO_4Na$: 330.0317 [*M*+Na]$^+$; found: 330.0313; calcd for $C_{11}H_{18}{}^{81}Br\,NO_4Na$: 332.0296; found: 332.0296.

General procedure for asymmetric nitroso-Diels–Alder reactions with Wightman chloronitroso reagent 28: A solution of the diene (0.5 mmol) in chloroform (1 mL) was added dropwise to a solution of the chloronitroso reagent **28** (0.75 mmol) and water (0.2 mL) in *iso*-propanol (1 mL). The blue reaction mixture was stirred at room temperature for 20 h, and then diluted with CH_2Cl_2 (20 mL) and extracted with water (5×10 mL). The organic layer was discarded, and the combined aqueous layer concentrated in vacuo to give a brown solid that was triturated with cyclohexane. The crude dihydrooxazinium chloride was suspended in CH_2Cl_2, whereas triethylamine (0.7 mL, 5 mmol) and di-*tert*-butyldicarbonate (144 mg, 0.75 mmol) were successively added. After stirring overnight at room temperature, the mixture was diluted with ether (10 mL), washed with saturated ammonium chloride solution (5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography to give the pure *N*-Boc protected dihydrooxazine.

(6*R*)-2-*tert*-Butyloxycarbonyl-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine (29a): Cycloaddition was accomplished with diene **8**. Yield: 65% (74 mg); yellow oil; R_f = 0.20 (AcOEt/heptane 40:60); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): δ = 5.81 (m, 1H), 5.76 (m, 1H), 4.63 (brd, 1H, *J* = 9.4 Hz), 4.08 (m, 1H), 3.97 (m, 1H), 3.89–3.77 (m, 2H), 2.3 (brs; OH), 1.88 (m, 1H), 1.77 (m, 1H), 1.48 ppm (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$): 155.2 (N*C*OO), 128.4 (*HC*=), 122.7 (*HC*=), 82.1 (O*C*Me_3), 77.1 (*CH*ON), 60.0 (*CH*$_2$OH), 45.1 (*CH*$_2$NO), 35.7 (*CH*$_2$CH$_2$OH), 28.4 ppm ((*CH*$_3$)$_3$C); MS (ESI): 252 [*M*+Na^+], 196 [*M*+Na^+−Me_2C=], 174 [*M*+H^+−Me_2C=], 130 [*M*+H^+−Me_2C=−CO_2]; HRMS (ESI-QTOF): *m/z*: calcd for $C_{11}H_{19}NO_4Na$: 252.1212 [*M*+Na]$^+$; found: 252.1204;

$[\alpha]_D^{25} = -4.3$ ($c = 1.1$ in CH_2Cl_2); enantiomeric ratio (e.r.): (HPLC) = 19.9:1.

(6*R*)-2-*tert*-Butyloxycarbonyl-6-(2-*tert*-butylcarbonyloxyethyl)-3,6-dihydro-2*H*-1,2-oxazine (29c): Cycloaddition was accomplished with diene **11**. Yield: 16% (25 mg); yellow oil; $R_f = 0.14$ (AcOEt/heptane 10:90); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): $\delta = 5.83$ (br dq, 1H, $J = 10.2$, 1.8 Hz), 5.77 (br dq, 1H, $J = 10.2$, 1.8 Hz), 4.55 (m, 1H), 4.24 (dd, 2H, $J = 7.3$, 5.7 Hz), 4.07 (br dq, 1H, $J = 17.4$, 2 Hz), 3.98 (br dq, 1H, $J = 17.4$, 2 Hz), 2.01–1.82 (m, 2H), 1.48 (s, 9H), 1.18 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 178.6 (quat., OO*C*tBu), 155.1 (quat., N*C*OO), 127.9 (*HC*=), 123.4 (*HC*=), 81.7 (quat., O*C*Me$_3$), 75.1 (*CH*ON), 60.9 (CH_2OPiv), 44.9 (CH_2NO), 38.9 (OOC*C*Me$_3$), 32.5 (CH_2CH_2OPiv), 28.5 ((*C*H$_3$)$_3$C), 27.4 ppm ((*C*H$_3$)$_3$C); MS (ESI): *m*/*z*: 336 [*M*+Na$^+$], 280 [M+Na$^+$ −Me$_2$C=], 258 [*M*+H$^+$−Me$_2$C=]; HRMS (ESI-QTOF): *m*/*z*: calcd for $C_{16}H_{27}NO_5Na$: 336.1787 [*M*+Na]$^+$; found: 336.1772; $[\alpha]_D^{25} = +6.4$ ($c = 0.2$ in CH_2Cl_2); e.r. (HPLC): 6.2:1.

(6*R*)-2-*tert*-Butyloxycarbonyl-5-diethylphosphoryl-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine (29d): Compound **29d** was obtained from diene **20** by a slight modification of the cycloaddition protocol: A solution of the diene **20** (76 mg, 0.3 mmol) in chloroform (0.5 mL) was added dropwise at RT to a solution of the chloronitroso reagent **28** (207 mg, 0.43 mmol) and water (0.005 mL, 0.3 mol) in *iso*-propanol (0.5 mL),. The blue reaction mixture was stirred at room temperature for 24 h, and then diluted with CH_2Cl_2 (20 mL) and treated with an aqueous solution of phosphate buffer (10 mL). The aqueous phase was extracted with dichloromethane (3×20 mL). The whole organic solution was dried over Na_2SO_4 and concentrated under vacuum to afford a crude green/kaki oil that gave after chromatography (dichloromethane/MeOH 95:5) a colourless oil. Nitrogen protection was performed according to the general protocol. Yield: 55% (105 mg). Yellow oil; $R_f = 0.28$ (AcOEt/heptane 70:30); ^{1}H NMR (400 MHz, $CDCl_3$; TMS): $\delta = 5.68$ (m, 1H), 4.55 (br d, 1H, $J = 9.0$ Hz), 4.15 (quint., 4H, $J = 7.4$ Hz), 4.10 (m, 2H), 3.91–3.78 (m, 2H), 2.05–1.96 (m, 2H, OH), 1.48 (s, 9H), 1.34 Hz (dt, 6H, $J = 7.1$, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 155.0 (=*C*–O), 146.4 (N*C*OO), 105.3 (*HC*=), 82.8 (q, O*C*Me$_3$), 77.6 (*CH*ON), 65.0 (O*C*H$_2$CH$_3$), 60.3 (*C*H$_2$OH), 44.2 (*C*H$_2$N), 32.7 (*C*H$_2$CH$_2$OH), 28.4 ((*C*H$_3$)$_3$C), 16.3 ppm (CH$_2$*C*H$_3$); MS (ES): *m*/*z*: 404 [*M*+Na$^+$], 348 [M+Na$^+$−Me$_2$C=], 304 [M+Na$^+$−Me$_2$C=−CO$_2$], 273; HRMS (ESI-QTOF): *m*/*z*: calcd for $C_{15}H_{28}NO_8PNa$: 404.1450 [*M*+Na]$^+$; found: 404.1460; $[\alpha]_D^{25} = +11.7$ ($c = 0.6$ in CH_2Cl_2); e.r. (HPLC): 17.8:1.

(6*R*)-5-Bromo-2-*tert*-butyloxycarbonyl-6-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,2-oxazine (29e): Cycloaddition was accomplished with diene **24**. Yield: 40% (62 mg); colourless oil; $R_f = 0.36$ (AcOEt/heptane 50:50); ^{1}H NMR (360 MHz, $CDCl_3$; TMS): $\delta = 6.11$ (m, 1H), 4.56 (br d, 1H, $J = 10.1$ Hz), 4.04 (m, 2H), 3.83 (m, 2H), 2.70 (br s, 1H; OH), 2.17 (m, 1H), 1.93 (m, 1H), 1.46 ppm (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$): 155.1 (quat., N*C*OO), 124.4 (*HC*=), 121.4 (*BrC*=), 82.9 (quat, O*C*Me$_3$), 81.5 (*CH*ON), 60.2 (*C*H$_2$OH), 47.6 (*C*H$_2$NO), 33.6 (*C*H$_2$CH$_2$OH), 28.4 ppm ((*C*H$_3$)$_3$C); MS (ESI): *m*/*z*: 332, 330 [*M*+Na$^+$], 276, 274 [*M*+Na$^+$ −Me$_2$C=], 232, 230 [*M*+Na$^+$−Me$_2$C=−CO$_2$]; HRMS (ESI-QTOF): *m*/*z*: calcd for $C_{11}H_{18}{}^{79}BrNO_4Na$: 330.0317 [*M*+Na]$^+$; found: 330.0313; calcd for $C_{11}H_{18}{}^{81}BrNO_4Na$ 332.0296; found 332.0296; $[\alpha]_D^{27} = -16.2$ ($c = 0.36$ in CH_2Cl_2); e.r. (HPLC): 9.5:1.

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