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PAPER

Electronic effects in 1,3-dipolar cycloaddition reactions of *N*-alkyl and *N*-benzyl nitrones with dipolarophiles†

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1,3-Dipolar cycloadditions afforded fast access to isoxazolidines bearing *N*-alkyl or *N*-benzyl substituents. The electronic properties of the substituents in the nitrones define the activity of the dipoles and modulate diastereoselectivity in the non-catalyzed reactions. Using a chiral one-point binding ruthenium Lewis acid catalyst, products were obtained in good yields and with excellent regio-, diastereo-, and enantioselectivity.

Introduction

2010 was a special year for the 1,3-dipolar cycloadditions (1,3-DCs). Along with 50 years of continuous evolution and expansion in the field, we celebrated the 90th anniversary of the father of this chemistry, Prof. Rolf Huisgen.[1] Cycloadditions have always attracted the interest of the scientific community through the apparent practical simplicity that hides a complex mechanism, the elegant end efficient access to cyclic compounds, and the versatility of both starting materials and products.[2] Recent developments in asymmetric catalysis have further emphasized the value of 1,3-DCs as fast and clean reactions towards functionalized, enantiopure N,O-heterocyclic compounds.[3]

We have previously reported efficient and selective homogeneous chiral catalysts for the Diels–Alder reactions of enals[4,5] and enones[6] with dienes, intramolecular Diels–Alder reactions,[7] as well as 1,4-additions of thiols to enones.[8] The catalysts that were developed are monocationic, one-point binding Cp-complexes of iron(II), and Cp- and indenyl-complexes of ruthenium(II) that bear electron-poor diphosphinite ligands to enhance the Lewis acidity and control the chiral environment around the metal.

Exploring the versatility of these chiral Lewis acid catalysts, we turned our attention to 1,3-DCs and provided the first examples of asymmetric metal-catalyzed reactions of nitrones[9] and nitrile oxides[10] with enals. This field has seen rapid development with efficient metal-based catalysts[11] and organocatalysts[12] being reported in the literature.

In this context, we studied in depth the reactions with diarylnitrones and showed that regioselectivity is a function of the substituents on the nitrone.[13] *N*-Alkyl and *N*-benzyl nitrones are less reactive dipoles when compared to diaryl- and cyclic nitrones.[14] However, modularity, ease of synthesis, and stability are the key characteristics of these dipoles and explain their widespread use in synthesis (Fig. 1).

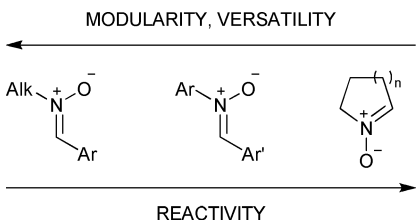

Fig. 1 Properties and reactivity of common nitrone classes.

Asymmetric catalytic 1,3-DCs have entered the field resolutely.[15,16] The seminal work of MacMillan and coworkers on using organocatalysts allowed for the use of simpler and more versatile monodentate dipolarophiles.[12a] Since then, several other organic[12] and metal-based catalysts[11g–o] have been found to successfully catalyze 1,3-DC reactions with *N*-"alkyl" nitrones.

In the present article, we extend our initial findings in the Ru-catalyzed 1,3-DC of *N*-alkyl and *N*-benzyl nitrones with enals[17] and investigate intriguing selectivity aspects observed for the non-catalyzed reactions with the same dipoles.

Results and discussion

Non-catalyzed reactions

Variation of the electronic properties of the nitrones. In order to assess reactivity, selectivity, and to obtain clear HPLC signals for the racemic isoxazolidine products, a series of *N*-Me, α-(4-substituted)-Ph nitrones **17a–n** were synthesized by condensation of *N*-Me hydroxylamine hydrochloride with the corresponding substituted benzaldehydes.[18] ^{1}H NMR analysis at r. t. showed only the *Z* isomer present in solution.

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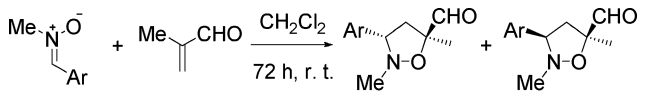
† Electronic supplementary information (ESI) available: General experimental information, data on solvent and temperature optimization, full experimental procedures and characterization data for all compounds. See DOI: 10.1039/c1ob06144e

Table 1 Uncatalyzed 1,3-DCs of *N*-Me, α-aryl nitrones **1a–n** and methacrolein (**3**)[a]



1a-n **3** **2a-n-*endo*** **2a-n-*exo***

Entry	Ar	Nitrone	Yield (%)[b]	*endo*/*exo*[c]
1	4-NMe_2-C_6H_4-	**1a**	40	17/83
2	4-OMe-C_6H_4-	**1b**	65	31/69
3	4-Me-C_6H_4-	**1c**	75	37/63
4	4-H-C_6H_4-	**1d**	65	40/60
5	4-F-C_6H_4-	**1e**	85	43/57
6	4-Cl-C_6H_4-	**1f**	87	49/51
7	4-Br-C_6H_4-	**1g**	90	52/48
8	4-CF_3-C_6H_4-	**1h**	92	62/38
9	4-CN-C_6H_4-	**1i**	78	72/28
10	4-NO_2-C_6H_4-	**1j**	75	73/27
11	2-F-C_6H_4-	**1k**	85	55/45
12	C_6F_5-	**1l**	93	43/57
13	η^6-C_6H_4-$Cr(CO)_3$-	**1m**	95	86/14
14	2-Py-	**1n**	94	95/5

[a] All reactions were carried out under N_2, using **1a–n** (0.5 mmol) and **3** (1 mmol), in 1 mL of dry solvent. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis.

The cycloaddition reactions were carried out with a 50% excess of the enal (with respect to the nitrone), in CH_2Cl_2, at r. t. At the end of the reaction (checked by TLC, 72 h reaction time on average), the unreacted nitrones were precipitated with pentane and the crude product was filtered through a plug of cotton.

Signals for the *endo* and *exo* diastereomers were assigned by ^{1}H NMR analysis. Analysis was complicated by signal broadening in the case of the *endo* diastereomers. This phenomenon is known to occur due to inversion at the nitrogen atom taking place on the ^{1}H NMR-timescale.[19] NOE analysis was inconclusive for the assignment of the signals corresponding to the two diastereomers. However, based on an analogy of chemical shifts for isoxazolidines previously obtained from diarylnitrones,[13] we could distinguish and assign ^{1}H NMR shifts to each of the two diastereomers.

Low to moderate yields reflect the long reaction times needed in the case of nitrones bearing electron donating groups (EDGs). The reactions were frequently accompanied by decomposition of the dipole and/or polymerization of methacrolein (Table 1, entries 1–4).

Interestingly, both the *endo* and the *exo* diastereomers of the 3,5-substituted regioisomer were obtained in ratios varying with the electronic properties of the substituents on the nitrone. Thus, EDGs on the nitrone α-aryl substituent led to a mixture of products with the *exo* product being the major diastereoisomer, while in the cases where electron withdrawing groups (EWGs) are placed on the nitrone α-aryl substituent, it is the *endo* product that becomes the major diastereoisomer. Similar observations are reported in the literature.[20]

In order to evaluate the effects of substitution on reaction rate for the non-catalyzed and the ruthenium-catalyzed 1,3-DCs, the EWG-substituted aryl was replaced with other EWG-like aromatic moieties. Nitrones **1m** and **1n** reacted smoothly at r. t. in CH_2Cl_2 (5 days) with methacrolein (**3**) to give the expected isoxazolidines in quantitative yield. Nitrone **1m**, bearing a $Cr(CO)_3$ moiety, was previously prepared in this laboratory.[21] Nitrone **1m** led to a mixture of diastereomers **2m** (*endo* major). On the other hand, nitrone **1n**,[22] bearing a 2-pyridyl fragment as the EWG aromatic part, proved to be particularly reactive in its reaction with methacrolein (**3**). Isoxazolidine **2n** was isolated in quantitative yield and with excellent regio- and diastereoselectivity (*endo*).

Keeping only the 4-substituted derivatives (steric factors and/or more complex effects occur in the case of 2-F-Ph and the pentafluoro examples) and ordering the diastereomeric ratios according to the Hammett electronic parameter, a linear correlation between diastereoselectivity and substitution can be observed for the series.[23] The correlation can be quantified by plotting the σ_P^+ electronic parameter[24] as a function of log[(*endo*-R/*exo*-R)/(*endo*-H/*exo*-H)] (Fig. 2).[25] A correlation factor (R^2) of 0.9354 was obtained, suggesting a significant degree of linearity of the dependence.

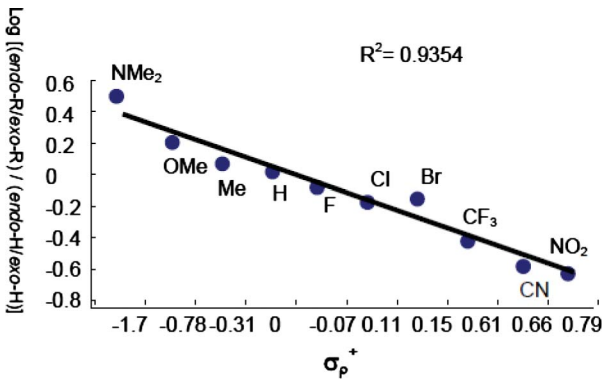


Fig. 2 Hammett plot showing the linear correlation between the electronic parameter of the substituents on the nitrones and the *endo*/*exo* ratio of the products obtained in the non-catalyzed 1,3-DCs of *N*-Me, α-aryl nitrones **1a–n** with methacrolein (**3**).

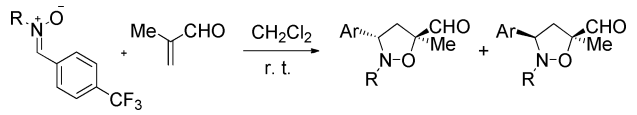
No such effects were observed for the non-catalyzed reactions of methacrolein (**3**) with diarylnitrones carried out in the same conditions.[13b] However, in the case of the Ru-catalyzed asymmetric 1,3-DC of methacrolein (**3**) with substituted diarylnitrones, the regioselectivity was found to vary with the electronic properties of the nitrone.[13] Interestingly, in the case of the *N*-Me nitrones, in the absence of a catalyst this trend is observed in the diastereoselectivity. The variation is not as extreme as for the diarylnitrones, but shows how small variations can have important effects on the outcome of the cycloaddition reaction.

The standardized trendline assigned to this semilogarithmic equation in Fig. 2 gives ρ (the reaction constant) equal to –0.11 (0.93 correlation factor). The very small value of the reaction constant indicates that there is little, if any, charge transfer in the transition state (TS). Moreover, the moderate correlation factor for the linear dependence does not allow for a clear picture of the reaction mechanism.

Variation of the substituents at the nitrogen of the nitrone. Nitrones bearing various substituents at the nitrogen atom of the nitrone were synthesized in order to expand the range of transformations that can be carried out on the isoxazolidine core following the 1,3-DC reaction.

In this series, the *N*-*i*-Pr and -*t*-Bu nitrones **1o** and **1p**, respectively, gave the products in moderate yields despite long

Table 2 Non-catalyzed 1,3-DCs of *N*-substituted, α-aryl nitrones **1o–s** and methacrolein (**3**)[a]



1o-s **3** **2o-s-*endo*** **2o-s-*exo***

Entry	R	Nitrone	Yield (%)[b]	*endo*/*exo*[c]
1	*i*-Pr	**1o**	65	>95/5
2	*t*-Bu	**1p**	75	93/7
3	Bn	**1q**	65	84/16
4	PMB	**1r**	85	79/21
5	DPM	**1s**	87	93/7

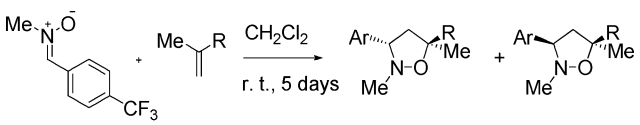
[a] All reactions were carried out under N_2, using **1o–s** (0.5 mmol) and **3** (1 mmol), in 1 mL of dry solvent. [b] Isolated yield, full conversion of the nitrone (up to 2 weeks). [c] Determined by ^{1}H NMR analysis. *i*-Pr: *iso*-propyl; *t*-Bu: *tert*-butyl; Bn: benzyl; PMB: *para*-methoxy-benzyl; DPM: diphenylmethyl.

reaction times (up to 2 weeks at r. t., Table 2, entries 1 and 2) and a two-fold excess of methacrolein (**3**). On the other hand, the *N*-Bn, -PMB, and -DPM-substituted nitrones **1q**, **1r**, and **1s**, respectively, proved to be more reactive, giving stable 3,5-substituted isoxazolidines in good yields (entries 3–5).

Good yields and diastereoselectivities (in favor of the *endo* isomer) can be obtained in the non-catalyzed reaction using these dipoles. No particular trend is observed when changing substitution and solely the 3,5-substituted regioisomers are isolated.

Variation of the dipolarophiles. Non-catalyzed reactions of *N*-Me, α-(4-CF_3)-Ph nitrone **1h** with various activated alkenes were also carried out in order to assess the effects on selectivity (Table 3). Only the 3,5-substituted isoxazolidines are obtained with methacrolein (**3**), methyl methacrylate (**4**), 2-methyl-3-buten-2-one (**5**), and methacrylonitrile (**6**). Also, in this case, diastereoselectivity was found to be in good correlation with the Hammett parameter of the group in the 2-substituted-propylene; an increase in the EWG character of the substituent leads to an increased amount of the *exo* diastereomer being formed. However, the comparison with the classic Hammett correlations does not apply in this case and remains purely illustrative.[23] Despite extended

Table 3 Non-catalyzed 1,3-DCs of nitrone **1h** and dipolarophiles **3–6**[a]



1h **3-6** **2h, 8-10-*endo*** **2h, 8-10-*exo***

Entry	R	Yield (%)[b]	*endo*/*exo*[c]	σ_p^+[24]
1	CHO (**3**)	92	60/40	+0.42
2	CO_2Me (**4**)	64	56/44	+0.45
3	COMe (**5**)	60	50/50	+0.50
4	CN (**6**)	30	33/67	+0.66

[a] All reactions were carried out under N_2, using **1h** (0.5 mmol) and **3–6** (1 mmol), in 1 mL of dry solvent. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis.

reaction times, non-activated alkenes did not give any product under the mild conditions used here.

While difficult to interpret, the observed correlation between the *endo*/*exo* ratio of the products and the electronic character of the substituents confirms that for a type II 1,3-DC both types of frontier molecular orbital interactions are important in the TS. Minute modifications of the electronic properties of either of the reaction partners appear to strongly influence the TS and thus the outcome of the reaction.

The observed variation of diastereoselectivity with the electronic properties of the dipole is rather rare.[20] In the past, we have shown how electronic factors can influence regioselectivity (with diarylnitrones)[13] and enantioselectivity (with aryl nitrile oxides).[10] Interestingly, no catalyst is employed in this case and the reaction is carried out under mild conditions. Although a number of groups have attempted to rationalize regio- and diastereoselectivity through computational studies, no clear picture has emerged so far.[20a,26]

Two factors should be taken into account when considering diastereoselectivity: the structure of the reaction partners (*i.e.* *E*/*Z* isomerism), and the interactions in the TS. For this specific transformation, the general opinion is that *E*/*Z* isomerism is responsible for the observed selectivities. However, with few exceptions,[27] all examples use high temperatures, making indeed nitrone isomerization a possiblity.[28] Our results and recent studies suggest that at r. t. the nitrones are found exclusively in the *Z*-configuration.[29] Thus, we can conclude that the geometry of the reaction partners is not responsible for the observed selectivity inversion.

Information about the reaction mechanism can be extracted from the data presented above. While the Hammett plot does not show a perfectly linear correlation, it suggests an asynchronous concerted mechanism with little or no charge transfer in the TS (confirmed by computational studies).[30,31] In addition, the lack of solvent effects reinforces the argument for a concerted transformation.[2,32–33] Interestingly, a similar inversion of diastereoselectivity is observed when varying the electronic properties in the dipolarophile (Table 3); this is typical for type II 1,3-DCs, where HOMO–LUMO interactions of both reacting partners are possible and can influence the outcome of the reaction.[2] Finally, increasing the bulk on the dipole has little influence on the selectivity (as shown in Table 2), suggesting that steric factors do not play a role in the diastereoselection process.

Thus, subtle variations in the electronic properties of either reaction partners lead to important changes in the ratio of the *endo*/*exo* isomers formed, possibly through secondary orbital interactions that occur in the TS. Unfortunately, computational studies so far have not provided more answers.

Ru-catalyzed reactions

The catalyst of choice for this transformation is (*R*,*R*)-**11**, a robust and easy to prepare monocationic ruthenium complex[5] that has proved active and selective for a number of transformations.[5–11,13,17]

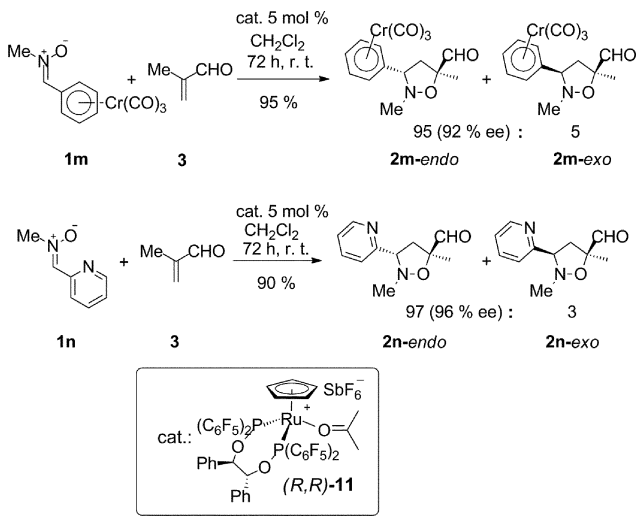
Variation of substituents on the α-aryl part of the nitrone. An optimized set of conditions[33] was previously applied to the reaction of methacrolein (**3**) with a series of substituted *N*-methyl, α-aryl nitrones **1a–l**.[17] As noted above, reactivity is a function of the

electronic character of the nitrone, even in the presence of the ruthenium catalyst.

Electron-rich dipoles **1a–c** proved unreactive and could be recovered quantitatively at the end of the reaction, together with the intact catalyst. Applying harsher reaction conditions or increasing the catalyst loading did not improve the results. Conversely, nitrones **1d–l**, bearing EWG substituents, led to formation of 3,5-substituted isoxazolidines with very good diastereo- and enantioselectivity. The best selectivity was obtained when using the *N*-Me, α-(4-Br-Ph) nitrone **1g**, with 97.7% ee.[17]

Within the series, two dipoles stood apart: while reaction with nitro-substituted nitrone **1j** proved sluggish and provided the product in moderate yield and with decreased diastereoselectivity, reaction with the nitrile-substituted nitrone **1i** led to no product whatsoever. This reinforces our previous findings on substrates bearing Lewis-basic groups that lead to competitive binding to the Lewis acid, thus reducing efficiency or even shutting down the catalytic cycle.[13]

Less common EWG-like aromatic moieties can also be used with good results. The authors have a long-standing interest in the chemistry of chromium arene complexes.[34] When attaching a $Cr(CO)_3$ moiety on an arene, the electron density on the aromatic ring is markedly decreased, rendering the whole fragment electron-poor. Confirming this hypothesis, nitrone **1m**, bearing the $Cr(CO)_3$ moiety on the aryl part, gave excellent yield and selectivities (Scheme 1, top).

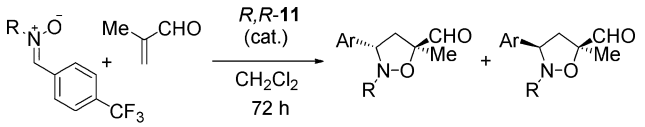


Scheme 1 Ru-catalyzed 1,3-DC reactions of methacrolein (**3**) with *N*-Me, α-aryl nitrones **1m–n** (the reactions were carried out under N_2, using (*R*,*R*)-**11** (0.025 mmol), **1m–n** (0.5 mmol) and **3** (0.75 mmol), in 1 mL of dry solvent; isolated yields reported, diastereomeric ratio determined by ^{1}H NMR analysis and enantiomeric ratio determined by HPLC analysis).

On the same principle, using a 2-pyridyl fragment as the aryl part on the nitrone led to exclusive formation of the *endo*-3,5-substituted adduct **2n** with excellent enantioselectivity (Scheme 1, bottom).

Variation of the substituents at the nitrogen of the nitrone. The variation of the substituents on the nitrogen of the nitrone greatly influences both the electronic and steric properties of a dipole, leading to important changes in the reaction outcome. In order to investigate such effects, the range of dipoles was extended to nitrones bearing *i*-Pr, *t*-Bu, Bn, PMB, and DPM groups at the *N* (Table 4).

Table 4 Ru-catalyzed 1,3-DCs of *N*-substituted, α-aryl nitrones **1h,o–s** and methacrolein (**3**)[a]



Entry	R (nitrone)	*T*/°C	Yield (%)[b]	*endo*/*exo*[c]	ee (%) *endo*[d]
1[17]	Me (**1h**)	−5	85	94/6	92
2	*i*-Pr (**1o**)	r. t.	50[e]	95/5	79
3	*t*-Bu (**1p**)	r. t.	19[e]	95/5	59
4	Bn (**1q**)	+5	95	>95/5	87
5	PMB (**1r**)	+5	80	>95/5	90
6	DPM (**1s**)	+10	94	>95/5	69

[a] All reactions were carried out under N_2, using (*R*,*R*)-**11** (5 mol%), **1h,o–s** (0.5 mmol) and **3** (1 mmol), in 1 mL of dry CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis of the corresponding primary alcohol. *i*-Pr: *iso*-propyl; *t*-Bu: *tert*-butyl; Bn: benzyl; PMB: *para*-methoxy-benzyl; DPM: diphenylmethyl. [e] Full conversion not reached.

As in the case of the non-catalyzed reactions, the *N*-*i*-Pr (**1o**) and -*t*-Bu (**1p**) nitrones reacted very slowly at r. t. and decomposed during the long reaction time; despite the good *endo* selectivity, enantioselectivities were moderate with these dipoles (entries 2 and 3) when compared with the *N*-Me analogue (entry 1).

Nitrones bearing benzyl groups on the nitrogen atom are extremely valuable for applications in synthesis as these moieties act as versatile protecting groups. We were pleased to find that the *N*-Bn (**1q**) and -PMB (**1r**) nitrones afforded the expected *endo*-3,5-substituted isoxazolidines **2q–r** with high yields and enantioselectivities (entries 4 and 5).

Maruoka and coworkers recently provided new examples of nitrones bearing removable groups at the nitrogen atom of the nitrone, moving from the *N*-Bn to the *N*-DPM nitrones. Contrary to the *N*-Bn nitrones (which give the *endo*-3,5-substituted adducts), the *endo*-3,4-isoxazolidines were obtained exclusively with good yields and enantioselectivity. Moreover, the DPM group could be easily removed through oxidation, leaving the isoxazolidine ring intact.[11n–o] We tested an analogous nitrone (**1s**) with our catalytic system; unfortunately, not only the nitrone reacts slowly, but the *endo*-3,5-substituted isoxazolidine **2s** is obtained with moderate enantioselectivity (entry 6). Too much steric bulk on the nitrone appears to slow down the catalytic cycle and leads to an erosion of the enantioselectivity by formation of racemic product through background (thermal) reaction.

Determination of the absolute configuration of the adducts and rationalization of selectivity. The reaction of methacrolein (**3**) with nitrone **1g** bearing a *para*-bromo substituent on the α-aryl part of the dipole led, in the presence of pre-catalyst (*R*,*R*)-**11**, to the *endo*-3,5-substituted isoxazolidine **2g** in high yield and excellent enantiopurity. The product readily crystallized at r. t. by vapor diffusion from an Et_2O–pentane system yielding transparent prisms. A single crystal was analyzed by X-ray diffraction.[17]

The absolute configuration thus determined corresponds to C1(*S*), C3(*S*) and is the one expected from a top-*endo* approach of the *Z*-nitrone to the more accessible C_α-*Si*$_{CC}$ face of the double bond of methacrolein (**3**) coordinated in the chiral pocket of the [RuCp(*R*,*R*-BIPHOP-F)(acetone)][SbF_6] complex (*R*,*R*)-**11**. This can be visualized by means of the X-ray-based models (Fig. 3).

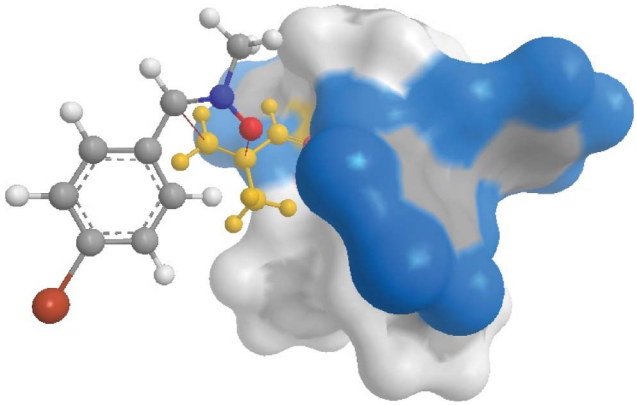


Fig. 3 Model showing the approach of *N*-Me, α-(4-Br-Ph) nitrone (**1g**) to the accessible C_α-*Si* face of the C–C double bond of methacrolein (**3**) coordinated in the chiral pocket of the catalyst (*R*,*R*)-**11**.[17]

The same results were previously obtained when using diarylnitrones[13] and nitrile oxides[10] as dipoles. Diastereo- and enantioselectivity are exclusively under catalyst control. Regioselectivity in this case is under dipole control and appears to be directed by the substituent at the *N* of the nitrone.

Conclusions

The study of the scope and versatility of the 1,3-DCs with *N*-alkyl and *N*-benzyl nitrones with enals exposed intriguing and unprecedented trends in diastereoselectivity in the non-catalyzed reactions.

On the other hand, the Ru-catalyzed reactions proved to be robust, efficient, and selective for a whole range of substrates. Electronic effects are key to activating the dipoles for the cycloaddition reaction. Synthetically relevant isoxazolidines bearing the methyl and benzyl groups at the *N* could thus be obtained in good yields and with high regio-, diastereo-, and enantioselectivity.

Experimental section—selected examples[33]

General experimental procedure for non-catalyzed reactions

In a 50 mL Schlenk tube equipped with a magnetic stirring bar, a solution of the nitrone (0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) is stirred at r. t. to give a clear solution. Methacrolein (1 mmol, 2 equiv.) is added dropwise, by syringe, at r. t. The reaction mixture is stirred at r. t. until TLC analysis (SiO_2, AcOEt/cyclohexane 2/3 or CH_2Cl_2) shows no unreacted nitrone. Addition of dry pentane (10 mL), filtration of the precipitated nitrone through a plug of cotton in a Pasteur pipette and *in vacuo* removal of solvents leads to an oil. Purification by a quick filtration through a SiO_2 plug (H_{dry} = 5 cm, Φ_e = 1 cm) with CH_2Cl_2 gives viscous, clear oils that solidify at −30 °C. Diastereomeric ratios are determined by ^{1}H NMR of the crude mixture. Clear signals for the racemic mixture can be observed in the HPLC analysis of the corresponding primary alcohols obtained by a standard $NaBH_4$ reduction in ethanol (CHIRACEL OD, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254 nm or CHIRALPACK AD, Grad 99+1–85+15, 0.5 mL min^{-1}, 80 min, 254); ν values are given in cm^{-1}, δ values are given in ppm, J values are given in Hz, t_R (retention times) are given in minutes. Some products proved too unstable for MS analysis; data for the corresponding primary alcohols is available in the ESI.†

***rac*-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-methyl-isoxazoline-5-carbaldehyde (*rac*-2h).** Obtained according to the general procedure in 92% yield (*endo*/*exo* 62/38): ν_{max}/cm^{-1} (film) 762, 839, 894, 979, 1019, 1068, 1123, 1165, 1324, 1378, 1421, 1474, 1520, 1620, 1735, 2853, 2963; δ_H (300 MHz, $CDCl_3$) 1.46 (3H, s, Me), 2.18–2.23 (1H, dd, *J* 9, 13, H-C_4), 3.01–3.06 (1H, bdd, *J* 9, 13, H-C_4), 3.76 (1H, bs, *J* 9, H-C_3), 7.48–7.50 (2H, d, *J* 9, H-C_m), 7.61–7.63 (2H, d, *J* 9, H-C_o), 9.68 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 21.1, 33.5, 47.5, 85.4, 122.8, 125.5, 125.9, 128.1, 130.3, 130.6, 142.8, 201.5.

***rac*-5-Methyl-3-(2-pyridyl)-2-methyl-isoxazoline-5-carbaldehyde (*rac*-2n).** Obtained according to the general procedure in 94% yield (*endo*/*exo* 95/5): ν_{max}/cm^{-1} (CH_2Cl_2) 621, 639, 698, 749, 761, 807, 978, 1020, 1036, 1090, 1133, 1290, 1381, 1435, 1472, 1519, 1590, 1641, 1732, 2871, 2930, 2960, 3061; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 2.53–2.59 (1H, dd, *J* 8, 12, H-C_4), 2.76 (3H, s, N-CH_3), 2.77–2.82 (1H, dd, *J* 8, 12, H-C_4-*endo*), 3.83–3.88 (1H, bt, *J* 8, H-C_3), 7.24-7.27 (1H, m, H-C*arom*), 7.34–7.36 (1H, bd, H-C*arom*), 7.70-7.74 (1H, m, H-C*arom*), 8.57–8.58 (1H, bm, H-C*arom*), 9.78 (1H, s, CHO-*endo*); δ_C (100.6 MHz, $CDCl_3$) 19.1, 43.3, 74.5, 84.7, 86.0, 121.9, 123.0, 123.2, 137.1, 149.4, 158.8, 204.8; HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}N_2O_2$ [M + H]$^+$: 207.1128. Found: 207.1132.

***rac*-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-*iso*-propyl-isoxazoline-5-carbaldehyde (*rac*-2o).** Obtained according to the general procedure in 34% yield (*endo*/*exo* >95/5): ν_{max}/cm^{-1} (CH_2Cl_2) 734, 838, 909, 1019, 1067, 1124, 1165, 1324, 1369, 1421, 1457, 1619, 1733, 2978; δ_H (400 MHz, $CDCl_3$) 1.00–1.02 (6H, d, *J* = 6 Hz, CH_3), 2.07–2.12 (1H, ddd, *J* 0.5, 7, 13, H-C_4), 2.80–2.89 (1H, hept, *J* 6, CH), 3.11–3.16 (1H, dd, *J* 7, 13, H-C_4), 4.22–4.25 (1H, t, *J* 7, H-C_3), 7.53–7.55 (2H, d, *J* 8, H-C*arom*), 7.58–7.60 (2H, d, *J* 8, H-C*arom*), 9.66 (1H, d, *J* 0.5, CHO); δ_C (100.6 MHz, $CDCl_3$) 16.7, 19.7, 19.9, 21.6, 46.9, 125.7, 128.0, 128.1, 129.7, 130.0, 205.5; MS (TS) *m*/*z* = 302.5 (M+1), 216.3, 191.3, 190.3, 174.5, 172.5, 159.3; HRMS (ESI+): Exact mass calculated for $C_{15}H_{19}F_3NO_2$ [M + H]$^+$: 302.1371. Found: 302.1362.

***rac*-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-diphenylmethyl-isoxazoline-5-carbaldehyde (*rac*-2s).** Obtained according to the general procedure in 68% yield (*endo*/*exo* 93/7): ν_{max}/cm^{-1} (CH_2Cl_2) 730, 904, 1019, 1068, 1124, 1165, 1326, 1455, 1735, 2969; δ_H (400 MHz, $CDCl_3$) 1.32 (4H, bs, CH and CH_3), 3.25–3.30 (1H, bdd, *J* 9, 13, H-C_4), 4.31–4.34 (1H, dd, *J* 5, 9, H-C_4), 4.75 (1H, bs, H-C_3), 7.14–7.54 (14H, m, H-C*arom*), 9.57 (1H, bs, CHO); δ_C (100.6 MHz, $CDCl_3$) 17.7, 19.6, 21.2, 31.2, 46.9, 125.4, 125.7, 127.7, 128.0, 128.3, 128.6, 128.7, 129.7, 130.0, 194.2.

General procedure for reactions catalyzed by (*R*,*R*)-11

In a 50 mL Schlenk tube equipped with a magnetic stirring bar, the catalyst (36 mg, 0.025 mmol, 5 mol%) is loaded and CH_2Cl_2 (1 mL) is added. The solution is stirred at the appropriate temperature and methacrolein (62 µL, 0.75 mmol, 1.5 equiv.) is added. The mixture is stirred for further 20 min before addition of the corresponding nitrone (0.5 mmol, 1 equiv.) as a solid and in one portion. The extent of the reaction is followed by TLC analysis (SiO_2, AcOEt/cyclohexane 2/3 or CH_2Cl_2) until no traces of nitrone are observed. Pentane is added to precipitate the catalyst and most of the unreacted nitrone, and the reaction mixture is passed through a plug of Celite 545 (P3-frit, Celite 545, H_{dry} = 1.5 cm, Φ_e = 2 cm) followed by *in vacuo* removal of volatiles. Purification by a quick filtration through a SiO_2 plug (H_{dry} = 5 cm, Φ_e = 1 cm) with CH_2Cl_2 gives viscous, clear oils that solidify at −30 °C. Diastereomeric ratios are determined by ^{1}H NMR of the crude mixture. Enantiomeric excess is determined by HPLC analysis of the corresponding primary alcohols obtained by a standard $NaBH_4$ reduction in ethanol (CHIRACEL OD, Grad. 99+1–90+10, 0.75 mL min^{-1}, 100 min, 254 nm or CHIRALPACK AD, Grad 99+1–85+15, 0.5 mL min^{-1}, 80 min, 254). Given data is for the 3,5-*endo* isomer in the mixture. Some products proved too unstable for MS analysis; data for the corresponding primary alcohols is available in the ESI.†

(3*S*,5*S*)-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-methyl-isoxazoline-5-carbaldehyde (*S*,*S*-2h).[17] Obtained according to the general procedure in 85% yield (*endo*/*exo* 94/6): ν_{max}/cm^{-1} (film) 762, 839, 894, 979, 1019, 1068, 1123, 1165, 1324, 1378, 1421, 1474, 1520, 1620, 1735, 2853, 2963; δ_H (300 MHz, $CDCl_3$) 1.46 (3H, s, Me), 2.18–2.23 (1H, dd, *J* 9, 13, H-C_4), 3.01–3.06 (1H, bdd, *J* 9, 13, H-C_4), 3.76 (1H, bs, *J* 9, H-C_3), 7.48–7.50 (2H, d, *J* 9, H-C_m), 7.61–7.63 (2H, d, *J* 9, H-C_o), 9.68 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 21.1, 33.5, 47.5, 85.4, 122.8, 125.5, 125.9, 128.1, 130.3, 130.6, 142.8, 201.5.

(3*S*,5*S*)-5-Methyl-3-(2-pyridyl)-2-methyl-isoxazoline-5-carbaldehyde (*S*,*S*-2n). Obtained according to the general procedure in 94% yield (*endo*/*exo* 95/5): ν_{max}/cm^{-1} (CH_2Cl_2) 621, 639, 698, 749, 761, 807, 978, 1020, 1036, 1090, 1133, 1290, 1381, 1435, 1472, 1519, 1590, 1641, 1732, 2871, 2930, 2960, 3061; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 2.53–2.59 (1H, dd, *J* 8, 12, H-C_4), 2.76 (3H, s, N-CH_3), 2.77–2.82 (1H, dd, *J* 8, 12, H-C_4-*endo*), 3.83-3.88 (1H, bt, *J* 8, H-C_3), 7.24–7.27 (1H, m, H-C*arom*), 7.34–7.36 (1H, bd, H-C*arom*), 7.70–7.74 (1H, m, H-C*arom*), 8.57–8.58 (1H, bm, H-C*arom*), 9.78 (1H, s, CHO-*endo*); δ_C (100.6 MHz, $CDCl_3$) 19.1, 43.3, 74.5, 84.7, 86.0, 121.9, 123.0, 123.2, 137.1, 149.4, 158.8, 204.8; HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}N_2O_2$ [M + H]$^+$: 207.1128. Found: 207.1132.

(3*S*,5*S*)-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-*iso*-propyl-isoxazoline-5-carbaldehyde (*S*,*S*-2o). Obtained according to the general procedure in 50% yield (*endo*/*exo* 95/5): ν_{max}/cm^{-1} (CH_2Cl_2) 734, 838, 909, 1019, 1067, 1124, 1165, 1324, 1369, 1421, 1457, 1619, 1733, 2978; δ_H (400 MHz, $CDCl_3$) 1.00–1.02 (6H, d, *J* 6, CH_3), 2.07–2.12 (1H, ddd, *J* 0.5, 7, 13, H-C_4), 2.80–2.89 (1H, hept, *J* 6, CH), 3.11–3.16 (1H, dd, *J* 7, 13, H-C_4), 4.22–4.25 (1H, t, *J* 7, H-C_3), 7.53–7.55 (2H, d, *J* 8, H-C*arom*), 7.58–7.60 (2H, d, *J* 8, H-C*arom*), 9.66 (1H, d, *J* 0.5, CHO); δ_C (100.6 MHz, $CDCl_3$) 16.7, 19.7, 19.9, 21.6, 46.9, 125.7, 128.0, 128.1, 129.7, 130.0, 205.5; MS (TS) *m*/*z* = 302.5 (M+1), 216.3, 191.3, 190.3, 174.5, 172.5, 159.3; HRMS (ESI+): Exact mass calculated for $C_{15}H_{19}F_3NO_2$ [M + H]$^+$: 302.1371. Found: 302.1362.

(3*S*,5*S*)-5-Methyl-3-(4-trifluoromethyl-phenyl)-2-diphenylmethyl-isoxazoline-5-carbaldehyde (*S*,*S*-2s). Obtained according to the general procedure in 94% yield (*endo*/*exo* 95/5): ν_{max}/cm^{-1} (CH_2Cl_2) 730, 904, 1019, 1068, 1124, 1165, 1326, 1455, 1735, 2969; δ_H (400 MHz, $CDCl_3$) 1.32 (4H, bs, CH and CH_3), 3.25–3.30 (1H, bdd, *J* 9, 13, H-C_4), 4.31–4.34 (1H, dd, *J* 5, 9, H-C_4), 4.75 (1H, bs, H-C_3), 7.14–7.54 (14H, m, H-C*arom*), 9.57 (1H, bs, CHO); δ_C (100.6 MHz, $CDCl_3$) 17.7, 19.6, 21.2, 31.2, 46.9, 125.4, 125.7, 127.7, 128.0, 128.3, 128.6, 128.7, 129.7, 130.0, 194.2.

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