Ruthenium Lewis Acid Catalyzed Asymmetric 1,3-Dipolar Cycloadditions between *N*-Methylnitrones and Enals

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Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Abstract: *N*-Methylisoxazolidines are formed in good yields and high regio-, diastereo- and enantioselectivity via asymmetric 1,3-dipolar cycloaddition of nitrones with enals catalyzed by a chiral ruthenium Lewis acid. Electronic effects in the dipole are the key to activation of these substrates for efficient catalysis.

Key words: asymmetric catalysis, Lewis acid, ruthenium, *N*-methyl nitrones, 1,3-dipolar cycloaddition

Functionalized, chiral N,O-heterocyclic compounds hold great synthetic value due to their high versatility either on their own or, after the reductive cleavage of the N–O bond, as acyclic chiral building blocks.[1] In this class of compounds, isoxazolidines stand out due to their ready access through asymmetric catalytic 1,3-dipolar cycloaddition (1,3-DC) reactions and the potential of this reaction to generate up to three contiguous stereogenic centers.[2]

Our work in the field of asymmetric Lewis acid catalysis focused on the development of monocationic one-point binding cyclopentadienyl complexes of iron and cyclopentadienyl and indenyl complexes of ruthenium that proved efficient and selective for the Diels–Alder reactions of enals[3,4] and enones[5] with dienes.

We also detailed the first examples of chiral Lewis acid catalyzed 1,3-DC of nitrones with enals.[6] In the following, several groups have reported other catalytic systems for this reaction.[7] We note that this transformation has also been successfully carried out with organocatalysts.[8] Recently we reported more fully on the scope, regioselectivity, and enantioselectivity of reactions of diarylnitrones,[9] and also extended the studies to nitrile oxides.[10]

Less reactive than cyclic or diarylnitrones, *N*-alkyl- and *N*-benzylnitrones are synthetically more appealing in view of the synthesis of chiral amino alcohols and amino acids. Our initial attempts to extend reactions to alkylnitrones failed to give the expected products in reasonable yields. Subsequently, two groups reported the successful use of *N*-methyl- and *N*-benzylnitrones in catalytic 1,3-DC reactions. While Carmona et al. concentrated their efforts on the synthesis and development of rhodium and iridium Lewis acids,[7g–l] Maruoka, using titanium-based catalysts, considerably expanded the substrate range both in terms of nitrones and enals and demonstrated successfully ring opening of the isoxazolidine products.[7m–o] An *N*-diphenylmethyl group on the nitrone afforded selectively the 3,4-substituted isoxazolidine, an unique trait for these transformations.[7n,o]

Intrigued by these results, and by our observation of important changes in reactivity, regioselectivity and enantioselectivity in the 1,3-DC reactions upon variation of the *para* aryl-substituent in the nitrone,[9,10] we decided to reinvestigate. This article reports our results with α-aryl,*N*-methylnitrones.

The nitrones were readily synthesized by condensation of the corresponding substituted benzaldehydes with *N*-methylhydroxylamine.[11] Next, these dipoles were submitted to 1,3-DC reactions with methacrolein (**2**) in the presence of the ruthenium complex (*R*,*R*)-**1** (Table 1).[12]

With electron-poor substituted nitrones, the 3,5-substituted isoxazolidines were obtained selectively in good yields and with excellent diastereo- and enantioselectivity (entries 1–6). Despite long reaction times, nitrone **3g** provides isoxazolidine **4g** in poor yield and with decreased diastereoselectivity (entry 7). Moreover, no product is formed in the reaction of methacrolein (**2**) with the nitrile-substituted nitrone **3h** (entry 8). This is in agreement with our previous finding that substrates bearing Lewis-basic groups lead to competitive binding to the Lewis acid, thus reducing efficiency or even shutting down the catalytic cycle.[9]

N-Methyl,α-phenylnitrone (**3i**) affords the expected product **4i** with similar levels of selectivity as did **3a**–**e**, but with a reduced yield of 60% (entry 9). The moderate to fair yields obtained in these cycloaddition reactions reflect the sensitivity of these adducts during isolation and purification.[13] No cycloaddition products were isolated from reaction mixtures involving methacrolein (**2**) and electron-rich substituted nitrones **3j**–**l** (entries 10–12), revealing the reactivity limits with this particular catalytic system. Both the nitrones and the acetone precatalyst could be recovered quantitatively at the end of the reaction, suggesting low reactivity rather than catalyst inhibition.

A crystal of isoxazolidine **4d** was analyzed by X-ray diffraction (Figure 1). The compound crystallizes in the orthorhombic system with no inclusion of solvent.

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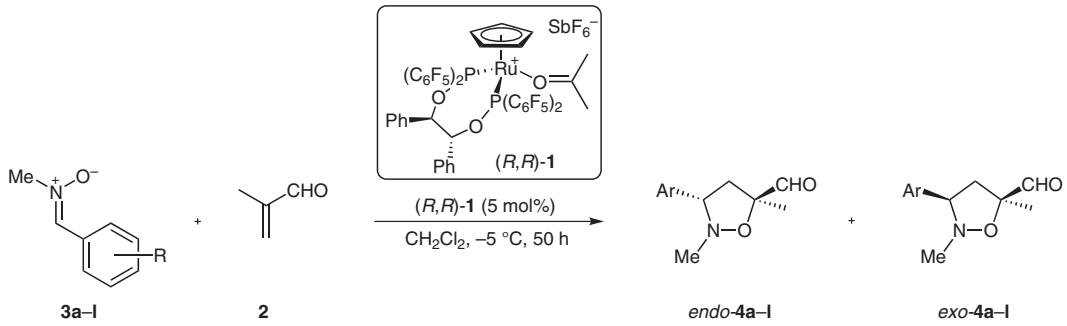
Table 1 Ruthenium-Catalyzed Asymmetric 1,3-DC of Methacrolein (**2**) with α-Aryl, N-methylnitrones **3a–l**[a]



3a–l **2** *endo*-**4a–l** *exo*-**4a–l**

Entry	R	Yield (%)[b]	*endo*/*exo*[c]	*endo* ee (%)[d]
1	2-F (**3a**)	74	>95:5	93
2	4-F (**3b**)	73	94:6	91
3	4-Cl (**3c**)	79	94/6	90
4	4-Br (**3d**)	73	>95:5	97.7
5	4-CF_3 (**3e**)	85	94:6	92
6	pentafluoro (**3f**)	60	91:9	78
7	4-NO_2 (**3g**)	43	80:20	92
8	4-CN (**3h**)	–	–[e]	–
9	4-H (**3i**)	60	94:6	94
10	4-Me (**3j**)	–	–[e]	–
11	4-OMe (**3k**)	–	–[e]	–
12	4-NMe_2 (**3l**)	–	–[e]	–

[a] Reaction conditions: (*R*,*R*)-**1** (5 mol%), **2** (0.75 mmol), and **3** (0.5 mmol) in CH_2Cl_2 (1 mL).
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis of the corresponding primary alcohol.
[e] No reaction; quantitative recovery of unreacted nitrone.

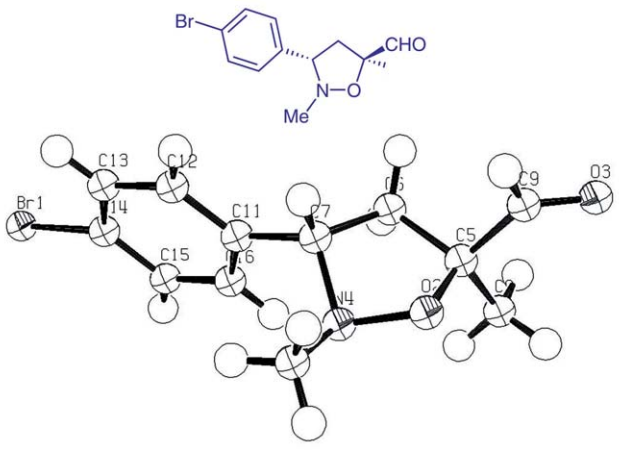


Figure 1 ORTEP representation of the X-ray structure of the isoxazolidine **4d**, obtained by ruthenium-catalyzed 1,3-DC of methacrolein (**2**) with α-(4-bromophenyl)-*N*-methylnitrone (**3d**)

The absolute configuration corresponds to C5 (*S*), C7 (*S*) and is the one expected from an top-*endo* approach of the *Z*-nitrone to the accessible C_α-$Si_{C=C}$ face of the double bond of methacrolein (**2**) coordinated in the chiral pocket of the [Ru(acetone)(*R*,*R*-BIPHOP-F)(Cp)][SbF_6] complex **1**. This can be visualized by means of the X-ray-based model shown below (Figure 2).[14]

This correlates perfectly with the previous results obtained with the diarylnitrones[6,9] and the nitrile oxides.[10] Diastereo- and enantioselectivity are exclusively under catalyst control.

Enantioselectivities were determined by HPLC analysis of the isoxazolidine alcohols **5** obtained in high yields by reduction of aldehydes **4** with sodium borohydride (see experimental section).

In conclusion, we have developed an efficient and selective ruthenium-catalyzed 1,3-DC of *N*-methylnitrones with enals. Electronic effects proved to be the key to activating the dipoles for the cycloaddition reaction. Synthet-

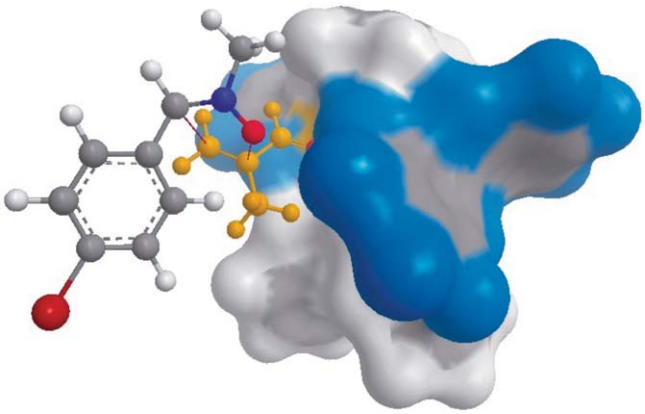


Figure 2 Model showing the approach of α-(4-bromophenyl),*N*-methylnitrone (**3d**) to the accessible C_α-*Si* face of the C=C bond of methacrolein (**2**) coordinated in the chiral pocket of the catalyst (*R*,*R*)-**1**[14]

ically relevant isoxazolidines bearing the methyl group at the nitrogen could thus be obtained in good yields and with high regio-, diastereo-, and enantioselectivity.

Complex (*R*,*R*)-**1** was prepared by using our previously published procedures.[4] Reactions were carried out under a positive pressure of N_2, unless otherwise stated. Glassware was oven-dried at 70 °C. Purification of CH_2Cl_2 was carried out by using a Solvtek purification system. All other solvents used were commercially available synthesis grade. The nitrones **3a–l** were synthesized by the condensation of the appropriate substituted benzaldehyde with methylhydroxylamine.[11] Commercially available chemicals were used as supplied, unless stated otherwise. Flash column chromatography was carried out using silica gel (60L, 32–63 mesh, Brunschwig SA, Basel). TLC was performed on precoated aluminum plates (Merck silica 60F254), and visualized using UV light, aq $KMnO_4$, or ceric ammonium molybdate acidic solution. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on Bruker AMX 300, 400, and 500 spectrometers. Chemical shifts are quoted relative to tetramethylsilane and referenced to the residual solvent peaks as appropriate. IR spectra were recorded on a PerkinElmer Spectrum One spectrophotometer as neat liquids using a Golden Gate accessory. Polarimetry was performed using a PerkinElmer 241 polarimeter with a Na lamp (589 nm, continuous). LRMS were acquired using a Varian CH4 or SM1 spectrometer with the ionizing voltage at 70 eV, whereas HRMS were measured using a positive TOF mode in the ESI-MS mode using an Applied Biosystems/Scix (QSTA) spectrometer. HPLC analyses were recorded on an Agilent HP 1100 Series instrument (hexanes–propan-2-ol mixtures).

Ruthenium-Catalyzed 1,3-DC Reaction of Nitrones 3 with Methacrolein (2); General Procedure

In a 50 mL Schlenk tube equipped with a magnetic stirring bar, the catalyst (*R*,*R*)-**1** (36 mg, 0.025 mol, 5 mol%) was loaded and CH_2Cl_2 (1 mL) was added. The mixture was stirred at the appropriate temperature, methacrolein (**2**; 62 μL, 0.75 mmol, 1.5 equiv) was added and the mixture stirred for further 20 min before addition of the corresponding nitrone **3** (0.5 mmol, 1 equiv) in one portion as a solid. The mixture was stirred at the appropriate temperature and the extent of the reaction was followed by TLC analysis (SiO_2, EtOAc–cyclohexane, 2:3 or CH_2Cl_2) until no traces of nitrone were observed. Pentane was added to precipitate the catalyst and any unreacted nitrone, and the mixture was passed through a plug of Celite 545 (P3-frit, 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 gave viscous, clear oils that solidified at –30 °C. Diastereomeric ratios were determined by ^{1}H NMR of the crude mixture.

Note: In all cases, partial data for the *endo* diastereomer is given (in the mixture). Most isoxazolidines proved to be too unstable for MS analysis (data is given for the corresponding primary alcohols).

(3*S*,5*S*)-3-(2-Fluorophenyl)-5-methyl-2-methylisoxazoline-5-carbaldehyde (4a)

Obtained according to the general procedure in 74% yield (*endo*/*exo* = 95:5).

IR (film): 727, 757, 798, 816, 853, 895, 941, 978, 1034, 1091, 1135, 1179, 1231, 1277, 1376, 1455, 1473, 1489, 1519, 1587, 1617, 1733, 2876, 2963 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3 H, CH_3), 2.18–2.23 (dd, *J* = 9, 13 Hz, 1 H, H-C_4), 2.65 (s, 3 H, NCH_3), 3.01–3.06 (br dd, *J* = 9, 13 Hz, 1 H, H-C_4), 4.12 (br s, *J* = 9 Hz, 1 H, H-C_3), 7.02–7.06 (m, 1 H, CH_{arom}), 7.14–7.18 (m, 1 H, CH_{arom}), 7.24–7.30 (m, 1 H, CH_{arom}), 7.51–7.54 (m, 1 H, CH_{arom}), 9.68 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.1, 43.9, 45.6, 85.5, 115.6, 115.8, 124.7, 125.8, 125.9, 128.5, 129.5, 159.7, 162.2, 201.0.

(3*S*,5*S*)-3-(4-Fluorophenyl)-5-methyl-2-methylisoxazoline-5-carbaldehyde (4b)

Obtained according to the general procedure in 73% yield (*endo*/*exo* = 94:6).

IR (film): 718, 761, 772, 837, 893, 979, 1015, 1091, 1134, 1158, 1223, 1295, 1378, 1473, 1509, 1606, 1640, 1733, 2850, 2963 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3), 2.17–2.23 (dd, *J* = 9, 13 Hz, 1 H, H-C_4), 2.59 (s, 3 H, NCH_3), 2.93–2.97 (br dd, *J* = 9, 13 Hz, 1 H, H-C_4), 3.65 (br s, *J* = 9 Hz, 1 H, H-C_3), 7.02–7.06 (m, 2 H, CH_{arom}), 7.31–7.34 (m, 2 H, CH_{arom}), 9.67 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.1, 47.7, 72.8, 85.1, 128.1, 129.4, 129.7, 129.9, 161.5, 163.9, 205.0.

(3*S*,5*S*)-3-(4-Chlorophenyl)-5-methyl-2-methylisoxazoline-5-carbaldehyde (4c)

Obtained according to the general procedure in 79% yield (*endo*/*exo* = 94:6).

IR (film): 700, 717, 825, 850, 893, 922, 979, 1015, 1089, 1134, 1174, 1296, 1376, 1411, 1474, 1491, 1519, 1599, 1640, 1733, 2849, 2962 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3 H, CH_3), 2.15–2.20 (dd, *J* = 9, 13 Hz, 1 H, H-C_4), 2.59 (s, 3 H, NCH_3), 2.94–2.98 (br dd, *J* = 9, 13 Hz, 1 H, H-C_4), 3.65 (br s, *J* = 9 Hz, 1 H, H-C_3), 7.27–7.33 (m, 4 H, CH_{arom}), 9.65 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.0, 47.6, 61.2, 85.2, 128.3, 128.5, 129.1, 129.4, 134.0, 137.0, 204.9.

(3*S*,5*S*)-3-(4-Bromophenyl)-5-methyl-2-methylisoxazoline-5-carbaldehyde (4d)

Obtained according to the general procedure in 73% yield (*endo*/*exo* = >95:5); $[\alpha]_D^{20}$ –67.6 (*c* = 0.42, CH_2Cl_2).

IR (film): 822, 851, 893, 979, 1011, 1071, 1091, 1134, 1296, 1376, 1409, 1474, 1488, 1519, 1734, 2847, 2960 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3), 2.16–2.21 (dd, *J* = 9, 13 Hz, 1 H, H-C_4), 2.60 (s, 3 H, NCH_3), 2.95–3.00 (br dd, *J* = 9, 13 Hz, 1 H, H-C_4), 3.65 (br s, *J* = 9 Hz, 1 H, H-C_3), 7.23–7.25 (d, *J* = 9 Hz, 2 H, CH_{arom}), 7.47–7.49 (d, *J* = 9 Hz, 2 H, CH_{arom}), 9.67 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.5, 21.2, 47.6, 66.1, 85.2, 122.2, 128.3, 129.1, 129.5, 132.1, 137.5, 200.2.

Crystallographic Data for 4d[15]

$C_{12}H_{14}BrNO_2$; M_r = 284.2, orthorhombic, $P2_12_12_1$, a = 6.0612(3), b = 8.8059(5), c = 23.3962(10) Å, V = 1248.8(11) Å^3; Z = 4, μ = 3.28 mm^{-1}, d_x = 1.511 g cm^{-3}, MoK_α radiation (λ = 0.71073 Å); 7984 reflections measured at 150 K on a STOE IPDS diffractometer, 2414 unique reflections of which 1839 with $|Fo| > 4\ \sigma\ (Fo)$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min}, T_{max} = 0.5341, 0.7789). The structure was solved by direct methods (SIR97).[16] All calculations were performed with the XTAL system.[17] Full-matrix least-squares refinement based on F using weights of $1/[\sigma^2\ (Fo) + 0.0001(Fo^2)]$ gave final values R = 0.024, ωR = 0.024, and S = 1.49(3) for 146 variables and 1839 contributing reflections. Flack parameter × = 0.005(4).

(3*S*,5*S*)-5-Methyl-3-(4-trifluoromethylphenyl)-2-methylisoxazoline-5-carbaldehyde (4e)

Obtained according to the general procedure in 85% yield (*endo*/*exo* = 94:6).

IR (film): 762, 839, 894, 979, 1019, 1068, 1123, 1165, 1324, 1378, 1421, 1474, 1520, 1620, 1735, 2853, 2963 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3), 2.18–2.23 (dd, J = 9, 13 Hz, 1 H, H-C_4), 3.01–3.06 (br dd, J = 9, 13 Hz, 1 H, H-C_4), 3.76 (br s, J = 9 Hz, 1 H, H-C_3), 7.48–7.50 (d, J = 9 Hz, 2 H, arom-CH_m), 7.61–7.63 (d, J = 9 Hz, 2 H, arom-CH_o), 9.68 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 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-(pentafluorophenyl)-2-methylisoxazoline-5-carbaldehyde (4f)

Obtained according to the general procedure in 60% yield (*endo*/*exo* = 91:9).

IR (film): 736, 771, 842, 973, 1009, 1095, 1134, 1149, 1292, 1372, 1476, 1504, 1523, 1655, 1736, 2970 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 2.37–2.43 (dd, J = 9, 13 Hz, 1 H, H-C_4), 2.64 (s, 3 H, NCH_3), 2.83–2.89 (dd, J = 9, 13 Hz, 1 H, H-C_4), 3.95–3.99 (t, J = 9 Hz, 1 H, H-C_3), 9.74 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.5, 19.6, 43.3, 62.4, 66.1, 85.0, 111.3, 136.8, 144.5, 146.9, 205.1.

(3*S*,5*S*)-5-Methyl-3-(4-nitrophenyl)-2-methylisoxazoline-5-carbaldehyde (4g)

Obtained according to the general procedure in 43% yield (*endo*/*exo* = 80:20).

IR (film): 751, 856, 981, 1016, 1092, 1292, 1347, 1382, 1474, 1520, 1601, 1641, 1734, 2929 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 3 H, CH_3), 2.16–2.21 (dd, J = 9, 13 Hz, 1 H, H-C_4), 2.64 (s, 3 H, NCH_3), 3.07–3.12 (br dd, J = 9, 13 Hz, 1 H, H-C_4), 3.86 (br s, J = 9 Hz, 1 H, H-C_3), 7.55–7.57 (d, J = 9 Hz, 2 H, CH_{arom}), 8.21–8.24 (d, J = 9 Hz, 2 H, CH_{arom}), 9.68 (s, 1 H, CHO).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.1, 18.6, 31.2, 42.7, 46.4, 46.9, 59.5, 61.3, 72.4, 77.2, 100.1, 123.4, 124.0, 127.7, 128.3, 128.7, 204.2.

(3*S*,5*S*)-5-Methyl-3-(phenyl)-2-methylisoxazoline-5-carbaldehyde (4i)

Obtained according to the general procedure in 84% yield (*endo*/*exo* = 93:7).

IR (film): 699, 753, 793, 845, 894, 914, 956, 973, 1025, 1073, 1091, 1139, 1177, 1290, 1307, 1361, 1374, 1455, 1494, 1604, 1732, 2808, 2849, 2963 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 2.40–2.46 (br dd, J = 9, 12 Hz, 1 H, H-C_4), 2.61 (s, 3 H, NCH_3), 2.66–2.71 (br dd, J = 9, 12 Hz, 1 H, H-C_4), 3.51–3.55 (br t, J = 8 Hz, 1 H, H-C_3), 7.25–7.33 (m, 5 H, CH_{arom}), 9.76 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 34.6, 48.5, 85.6, 121.8, 125.8, 125.9, 128.1, 128.3, 130.9, 141.9, 200.5.

Reduction of Products 4; General Procedure

In a 10 mL round-bottomed flask equipped with a magnetic stirring bar, the corresponding aldehyde **4** (50 mg, 1.35 equiv) was added to EtOH (2 mL), followed by $NaBH_4$ (5.3 mg, 1 equiv). The mixture was stirred for 1–12 h at r.t. and then the excess $NaBH_4$ was quenched with H_2O (2 mL). The mixture was extracted with Et_2O (3 × 10 mL), the combined Et_2O layers were dried ($MgSO_4$ or Na_2SO_4), filtered, and concentrated to give a dense clear oil. Purification by column chromatography (SiO_2, H_{dry} = 15 cm, Φ_e = 1 cm), gradient cyclohexane–EtOAc (9:1, 30 mL; 8:2, 20 mL; 7:3, 20 mL) (R_f = 0.45 in 7:3 mixture) gave viscous, clear oils that solidified at –30 °C.

Note: In all cases, partial data for the *endo* diastereomer is given (in the mixture).

(3*S*,5*S*)-3-(2-Fluorophenyl)-5-methyl-2-methylisoxazoline-5-methanol (5a)

Obtained according to the general procedure in 92% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 25.13 (94.50%), 29.84 (3.45%).

IR (film): 756, 818, 857, 886, 931, 1054, 1130, 1231, 1277, 1367, 1455, 1492, 1587, 1617, 2872, 2965, 3403 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 2.04–2.10 (m, 1 H, H-C_4), 2.18 (br s, 1 H, OH), 2.59 (s, 3 H, NCH_3), 2.78–2.83 (dd, J = 8, 16 Hz, 1 H, H-C_4), 3.47–3.50 (br d, J = 11 Hz, 1 H, CH_2OH), 3.60–3.63 (br d, J = 11 Hz, 1 H, CH_2OH), 3.87 (br s, 1 H, H-C_3), 7.02–7.06 (m, 1 H, CH_{arom}), 7.14–7.18 (m, 1 H, CH_{arom}), 7.23–7.27 (m, 1 H, CH_{arom}), 7.50–7.54 (m, 1 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.7, 24.3, 29.7, 30.3, 31.2, 43.0, 45.8, 46.4, 47.8, 59.1, 59.5, 65.6, 70.7, 115.2, 115.3, 115.4, 115.5, 123.8, 123.9, 124.4, 124.5, 124.6, 128.2, 128.4, 129.0, 129.1, 129.2, 129.3, 129.4, 132.3.

MS (TS): m/z = 226.3 (M + 1), 222.3, 180.3, 176.3, 165.3, 161.3, 152.3.

HRMS (ESI+): m/z calcd for $C_{12}H_{17}FNO_2$ [M + H]$^+$: 226.1233; found: 226.1237.

(3*S*,5*S*)-3-(4-Fluorophenyl)-5-methyl-2-methylisoxazoline-5-methanol (5b)

Obtained according to the general procedure in 96% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 19.42 (4.56%), 28.58 (95.43%).

IR (film): 718, 837, 859, 883, 929, 1056, 1131, 1158, 1225, 1297, 1367, 1458, 1509, 1607, 2870, 2965, 3413 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 2.02–2.07 (m, 1 H, H-C_4), 2.12 (br s, 1 H, OH), 2.52 (s, 3 H, NCH_3), 2.72–2.77 (dd, J = 8, 16 Hz, 1 H, H-C_4), 3.44–3.47 (br d, J = 11 Hz, 2 H, CH_2OH + H-C_3), 3.59–3.61 (br d, J = 11 Hz, 1 H, CH_2OH), 7.01–7.05 (m, 2 H, CH_{arom}), 7.32–7.35 (m, 2 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.3, 22.8, 29.7, 30.3, 31.2, 42.6, 47.3, 47.8, 59.5, 65.6, 65.8, 71.2, 73.6, 115.1, 115.2, 115.4, 115.5, 115.6, 115.7, 129.2, 129.3, 129.4, 129.5, 131.2, 131.3.

MS (TS): m/z = 226.3 (M + 1), 203.3, 179.3, 177.3, 161.3, 152.3.

HRMS (ESI+): m/z calcd for $C_{12}H_{17}FNO_2$ [M + H]$^+$: 226.1230; found: 226.1237.

(3*S*,5*S*)-3-(4-Chlorophenyl)-5-methyl-2-methylisoxazoline-5-methanol (5c)

Obtained according to the general procedure in 90% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 21.28 (5.24%), 28.97 (91.48%).

IR (film): 717, 804, 826, 858, 882, 929, 1015, 1055, 1090, 1131, 1216, 1298, 1368, 1411, 1458, 1492, 1599, 2869, 2964, 3409 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 2.00–2.06 (m, 1 H, H-C_4), 2.18 (br s, 1 H, OH), 2.52 (s, 3 H, NCH_3), 2.73–2.78 (dd, *J* = 8, 16 Hz, 1 H, H-C_4), 3.44–3.47 (br d, *J* = 11 Hz, 2 H, CH_2OH + H-C_3), 3.58–3.61 (br d, *J* = 11 Hz, 1 H, CH_2OH), 7.28–7.32 (m, 4 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.3, 22.8, 29.7, 31.2, 42.7, 47.3, 47.9, 59.5, 65.6, 65.8, 71.1, 73.6, 128.5, 128.8, 128.9, 129.1, 129.2, 130.9.

MS (TS): *m*/*z* = 242.5 (M + 1), 232.1, 205.1, 197.3, 175.5, 173.5, 168.3, 165.5, 156.1, 154.3.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{17}ClNO_2$ $[M + H]^+$: 242.0940; found: 242.0942.

(3*S*,5*S*)-3-(4-Bromophenyl)-5-methyl-2-methylisoxazoline-5-methanol (5d)

Obtained according to the general procedure in 93% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 22.71 (1.12%), 29.35 (96.14%).

IR (film): 714, 822, 858, 881, 929, 1011, 1069, 1131, 1215, 1298, 1367, 1408, 1456, 1488, 1592, 2869, 2962, 3426 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 2.00–2.06 (m, 1 H, H-C_4), 2.15 (br s, 1 H, OH), 2.52 (s, 3 H, NCH_3), 2.73–2.78 (dd, *J* = 8, 16 Hz, 1 H, H-C_4), 3.43–3.46 (br d, *J* = 11 Hz, 2 H, CH_2OH + H-C_3), 3.58–3.61 (br d, *J* = 11 Hz, 1 H, CH_2OH), 7.24–7.26 (d, *J* = 9 Hz, 2 H, CH_{arom}), 7.46–7.48 (d, *J* = 9 Hz, 2 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.8, 29.68, 30.30, 31.22, 42.7, 47.3, 48.0, 59.5, 65.7, 71.0, 73.7, 129.4, 129.5, 131.2, 131.4, 131.8, 131.9.

MS (TS): *m*/*z* = 286.3 (M + 1), 214.3, 212.3, 200.3, 199.3, 198.3, 183.1, 171.3, 172.5, 169.3.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{17}ClNO_2$ $[M + H]^+$: 286.3035; found: 286.3029.

(3*S*,5*S*)-5-Methyl-3-(4-trifluoromethylphenyl)-2-methylisoxazoline-5-methanol (5e)

Obtained according to the general procedure in 90% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 23.74 (95.57%), 26.61 (4.43%).

IR (film): 761, 804, 837, 860, 884, 931, 994, 1019, 1067, 1121, 1163, 1323, 1369, 1421, 1458, 1620, 2872, 2964, 3432 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 2.78–2.83 (dd, *J* = 8, 16 Hz, 1 H, H-C_4), 3.46–3.49 (m, 1 H, H-C_4), 3.56 (br s, 1 H, H-C_3), 3.60–3.63 (m, 2 H, CH_2OH), 7.49–7.51 (d, *J* = 8 Hz, 2 H, CH_{arom}), 7.60–7.62 (d, *J* = 8 Hz, 2 H, C_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.7, 24.4, 29.7, 42.8, 43.1, 47.5, 48.5, 67.6, 71.0, 73.7, 125.5, 125.6, 125.7, 127.9, 128.1.

MS (TS): *m*/*z* = 276.3 (M + 1), 204.3, 202.3, 188.5, 186.5, 159.3.

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{17}F_3NO_2$ $[M + H]^+$: 276.1209; found: 276.1205l.

(3*S*,5*S*)-5-Methyl-3-(pentafluorophenyl)-2-methylisoxazoline-5-methanol (5f)

Obtained according to the general procedure in 94% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 18.53 (5.44%), 19.63 (44.68%).

IR (film): 736, 771, 806, 837, 894, 956, 978, 1005, 1043, 1131, 1149, 1215, 1302, 1372, 1461, 1502, 1524, 1655, 2971, 3392 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 2.05 (br s, 1 H, OH), 2.25–2.30 (m, *J* = 8, 12 Hz, 1 H, H-C_4), 2.56 (s, 3 H, NCH_3), 2.66–2.72 (dd, *J* = 10, 16 Hz, 1 H, H-C_4), 3.55–3.58 (d, *J* = 11 Hz, 2 H, CH_2OH), 3.77–3.80 (br d, *J* = 11 Hz, 1 H, CH_2OH), 3.95–4.00 (dd, *J* = 8, 10 Hz, 1 H, H-C_3).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.2, 22.7, 42.5, 43.2, 63.2, 65.8, 68.9.

MS (TS): *m*/*z* = 298.5 (M + 1), 226.3, 224.3, 211.3, 210.3, 208.1, 192.3, 190.3, 181.3, 179.1, 163.3.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{13}F_5NO_2$ $[M + H]^+$: 298.0864; found: 298.0860.

(3*S*,5*S*)-5-Methyl-3-(4-nitrophenyl)-2-methylisoxazoline-5-methanol (5g)

Obtained according to the general procedure in 99% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 48.66 (67.49%), 51.32 (2.86%).

IR (film): 732, 804, 845, 884, 915, 1056, 1092, 1174, 1235, 1295, 1348, 1475, 1521, 1604, 2872, 2969, 3426 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 2.02–2.08 (m, 1 H, H-C_4), 2.18 (br s, 1 H, OH), 2.57 (s, 3 H, NCH_3), 2.81–2.87 (m, 1 H, H-C_4), 3.46–3.49 (br d, *J* = 11 Hz, 2 H, CH_2OH + H-C_3), 3.61–3.64 (m, 1 H, CH_2OH), 7.49–7.57 (m, 2 H, CH_{arom}), 8.15–8.29 (m, 2 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.1, 22.7, 24.4, 31.2, 43.0, 43.1, 47.6, 48.5, 61.3, 67.6, 70.8, 73.4, 77.2, 100.1, 123.4, 124.0, 127.7, 128.4, 128.6.

MS (TS): *m*/*z* = 253.1 (M + 1), 235.1, 219.1, 203.1, 188.1, 179.3, 168.1, 165.1, 162.3.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{17}N_2O_4$ $[M + H]^+$: 253.1182; found: 253.1189.

(3*S*,5*S*)-5-Methyl-3-(phenyl)-2-methylisoxazoline-5-methanol (5i)

Obtained according to the general procedure in 90% yield. HPLC (CHIRACEL OD-H, Grad. 99 + 1 to 90 + 10, 0.75 mL/min, 100 min, 254 + 340 nm): t_R (min) = 21.32 (96.47%), 27.45 (3.53%).

IR (film): 763, 814, 825, 894, 930, 1005, 1016, 1086, 1142, 11683, 1323, 1379, 1481, 1453, 1621, 2875, 2974, 3458 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 2.09–2.14 (m, 1 H, H-C_4), 2.50 (br s, 1 H, OH), 2.54 (s, 3 H, NCH_3), 2.75–2.78 (dd, *J* = 8, 16 Hz, 1 H, H-C_4), 3.46–3.49 (br d, *J* = 11 Hz, 2 H, CH_2OH + H-C_3), 3.60–3.63 (br d, *J* = 11 Hz, 1 H, CH_2OH), 7.30–7.45 (m, 5 H, CH_{arom}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 16.3, 23.3, 28.5, 32.2, 45.7, 48.5, 49.1, 59.5, 67.8, 68.5, 71.5, 74.3, 127.7, 127.9, 128.4, 128.5, 128.7, 130.5.

MS (TS): *m*/*z* = 208.6 (M + 1), 190.6, 184.6, 161.6.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$: 208.1332; found: 208.1333.

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