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New chiral nitrones as precursors of α,α-disubstituted amino-acids, according to the SRS principle

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Abstract—The preparation of new enantiopure cyclic nitrones based on the 1-oxy-2,3-dihydro-imidazol-4-one ring is described. The addition of arylmagnesium or alkynylzinc reagents to these nitrones can be achieved with total enantio- and diastereoselectivity, leading to α,α-disubstituted amino-acid precursors.

1. Introduction

The de novo design of peptides or peptidomimetics is a major tool for the exploration and understanding of the proteome.[1] Thus, the need for efficient synthetic methods for the preparation of 'tailor-made'[2] α-amino-acids with elaborate side chains or specific geometries[3] is continuous, and a large array of methods have been designed to achieve this goal. Among them, the addition to properly designed α-carboxyl-nitrones[4] has received attention. Several enantiopure chiral cyclic nitrones have been prepared and used as substrates for 1,3-dipolar cycloadditions,[5–10] radical additions[11] or Grignard addition.[12] We have recently applied[13] for the first time the SRS principle to the preparation of 5-substituted oxazolidin-4-one-*N*-oxides **1** starting from natural amino-acids as the only source of chirality. Highly enantioselective nucleophilic addition to these reagents can be achieved. Nevertheless, the acidity of the H atom at the 2-position, as well as some stability issues for the product nitrones **1**, prompted us to develop a second series **2**, in which the C-2 atom is made quaternary. Moreover, related α-quaternary nitrones feature interesting applications as spin-trap agents.[14] Herein, we report our first results on the preparation of some enantiopure nitrones **2**, and the feasibility of the diastereoselective addition of Grignard and alkynylzinc reagents to **2**.

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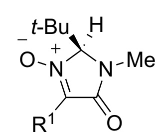

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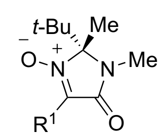


2

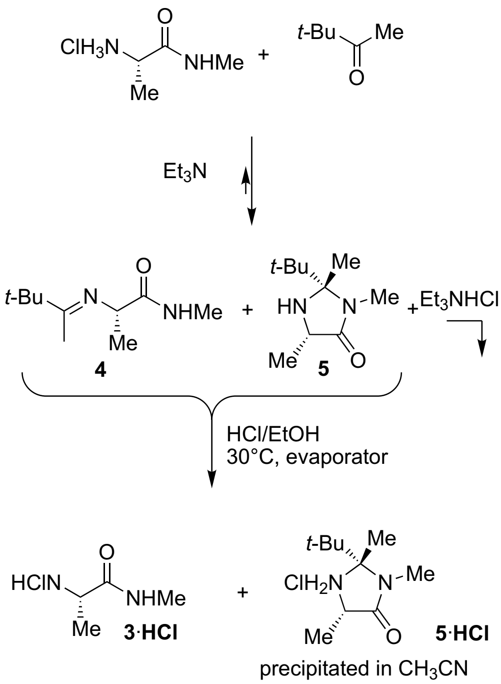
2. Results and discussion

2.1. Preparation of the imidazolidinones

N-Methyl-amide hydrochloride **3** was prepared from the corresponding amino-acid ester.[15] In our previous work, the reaction of pivalaldehyde with **3** led only to the corresponding acyclic imine. Under the same conditions, the reaction of pinacolone with **3** led to a mixture of open-chain amide **4** and cyclic imidazolidinone **5** (about 70%). Treatment of this mixture with dry HCl in ethanol, followed by evaporation of the solvent and precipitation in acetonitrile, provided pure **5·HCl** in limited yields (Table 1), but in diastereomerically pure form.

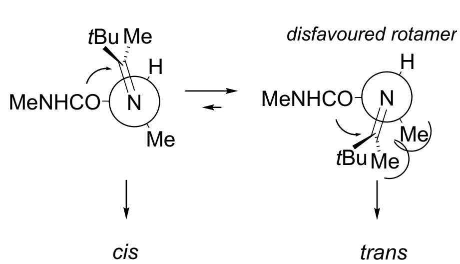
This cyclization appeared to be very easily reversible. We found that as HCl salts, imidazolidinones **5** were very much prone to solvolysis to yield **3·HCl** back. When we repeated the sequence thrice: dissolution of pure **5·HCl** in ethanol followed by concentration on the rotary evaporator, we recovered pure **3·HCl** as the sole product.[16] Attempts to displace the equilibrium by adding an excess of pinacolone led only to a larger amount of crotonization by-product.

Table 1. Preparation of imidazolidinones **5**



Entry	R_1	Yield
a	H	32
b	Me	45
c	CH_2Ph	27
d	3-Indolyl	22
e	CH_2OH	28

NOE experiments of **5b**, **5c**, **5e** and X-ray analysis of **5b** proved that the stereochemistry of **5** is *cis*. This result is the inverse of that obtained with pivalaldehyde[13,15] that led to the more stable *trans* imidazolidinones. Examination of the crystal structure of *cis*-**5b** showed that there is no consequent steric interaction between the *tert*-butyl and the 5-methyl groups. Thus, the final recovery of a single isomer cannot be explained with basic thermodynamic considerations. Most likely, the diastereoselectivity of the cyclization is dictated by the allylic-1,3 strain[17] favouring the reactive rotamer of **4** that leads to the *cis* product (Scheme 1).

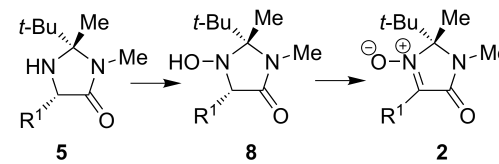


Scheme 1. Allylic 1,3-strain in cyclization.

2.2. Oxidation

For the oxidation of amines **5** into nitrones **2**, we kept to methods developed in our earlier works on nitrones **1**, because the enantioselectivity of these methods had been confirmed. Our first tests, using 2.1 equiv of *m*-CPBA, led efficiently to product **2b**, without any side reactions. However, the large amounts of *m*-CBA by-product caused difficulties in the recovery of **2b** in good yields. Since the oxidation of the intermediate hydroxylamine with MnO_2 was particularly easy in this series, we preferred to use 1.3 equiv *m*-CPBA[18] in order to ensure a total conversion of secondary amine **5** into hydroxylamine **8** (containing 0.15 equiv of nitrone **2**). The transformation of **8** into **2** was completed with excess MnO_2[19] (DCM, 20 °C, 2 h; Table 2).

Table 2. Oxidation of amines **5** to nitrones **2**



Nitrone **2**	R^1	Yield
a	H	60[b]
b	Me	92[a](29[b])
c	CH_2Ph	80[a]
d	3-Indolyl	0[a,b]

[a] 1.3 equiv MCPBA, then MnO_2.
[b] 1.2 equiv UHP/MTO, then MnO_2.

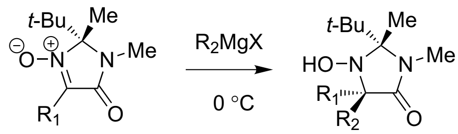
This procedure proved relatively inefficient in the case of nitrone **2a** (based on glycine), because the hydrophilicity of **2a** made the separation of *m*-CBA even more troublesome. We turned to UHP/MTO[20] for the first step. We noticed in our case that with these conditions, the first oxidation step from **5** to **8** was much quicker (less than 1 h) than the second from **8** to **2**. During the slow second step, catalyst decomposition required repeated additions.[20] Thus, we again found it more convenient to use only 1.1 equiv UHP in DCM in the presence of MTO to yield **8a**, then filter off the urea after 1 h and complete the oxidation with MnO_2 in DCM. Curiously, both procedures failed to transform the tryptophane derivative **5d** (starting material was recovered).

The two-step procedure also allowed us to check the diastereopurity of the intermediate hydroxylamine **8b** (>95% ^{1}H NMR).

3. Addition of Grignard reagents

The addition of Grignard reagents to nitrones **2**[21] easily took place in THF at 0 °C with aryl- or vinyl-magnesium halides. The product was always isolated as a single diastereoisomer (NMR detection), in yields ranging from 64% to 78% (Table 3). Adduct **9b** of 4-methoxy-phenylmagnesium bromide and **2c** was a solid and X-ray analysis of **9b** proved that the newly introduced aryl group was *trans* to the *tert*-butyl group. The same stereochemical relationship in **9a** was confirmed by NOE experiments.

Table 3. Addition of organomagnesium reagents



2b,c **9a-d**

9	Nitrone **2**: $R^1 =$	R^2MgBr	Yield (%)
a	Me	*p*-MeOPhMgBr	78
b	CH_2Ph	*p*-MeOPhMgBr	64
c	Me	Vinyl-MgBr	68

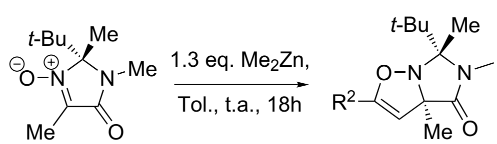
4. Enantioselectivity of the process

We resolved the racemate of adduct **9a** on a CHIRALPAK AD-RH column. The enantiopurity of a sample prepared from optically active **2a** was found superior to 98%. Therefore, the whole process, from starting Alanine to the Grignard adduct, was totally enantioselective.

5. Addition of alkynes

In our preceding work,[13] we have shown that the addition of alkynylzinc reagents prepared in situ from 1-alkynes and dimethylzinc led smoothly and efficiently to the bicyclic products **10** (Table 4). We extended this process to **2b** to produce **10a–c** with excellent yields and total diastereoselectivity.

Table 4. Alkynylation of **2b**



2b **10a-c**

10	Alkyne: $R^2 =$	Yield (%)
a	Ph	95
b	*n*-Bu	98
c	CH_2–OAc	98

6. Conclusion

In conclusion, we have demonstrated the great potential of a new family of enantiopure nitrones, available in a few steps from cheap common amino-acids as the only source of chirality. These compounds can be reacted with organometallic reagents under very mild conditions, leading to α,α-disubstituted amino-acids in protected form with total enantio- and diastereoselectivity.

7. Experimental

7.1. General remarks

^{1}H NMR (200 or 300 MHz) and ^{13}C NMR (50 or 75 MHz) spectra were recorded on Bruker AC200 or Advance300 spectrometers, in $CDCl_3$ with tetramethylsilane as the internal standard. Mass spectra were recorded with a ThermoFinnigan PolarisQ ion-trap spectrometer using DCI (ammonia/isobutane 63/37). IR spectra were recorded with a Nicolet Impact-400 FTIR spectrometer, from sintered KBr discs. HRMS (chemical ionization) and elemental analyses were performed at the Service Central d'Analyses du CNRS, Vernaison, France. Analytical samples for elemental analysis were obtained by chromatography. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates. Spots were visualized with UV or by basic permanganate revelation, or by basic 1% triphenyl tetrazolium chloride (TTC): a strong permanent red colour is characteristic of *N*-hydroxylamines. Forced-flow column chromatography was performed using Macherey-Nagel Silica Gel 60, 230–400 mesh. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. All reactions were performed under nitrogen in oven-dried glassware, with magnetic stirring. All reagents were purchased from Aldrich, Acros or Fluka and used as received. Dichloromethane (DCM) was distilled from CaH_2. Toluene was distilled from sodium. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 605989 (**9b**), 605990 (**10a**) and 605991 (**5b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

7.2. Imidazolidinones 5

The preparation of **5b** is typical. In a 250 mL flask fitted with a reflux condenser were introduced the aminoamide **3b·HCl**[15] (14.54 g, 105 mmol), pinacolone (26 mL, 210 mmol), activated 4 Å molecular sieves (beads, 60 g), triethylamine (14.7 mL, 105 mmol) and EtOH (100 mL). After 16 h at reflux, the sieves were filtered off and the solvent was evaporated under reduced pressure. The crude white slurry was taken in ethyl acetate (150 mL), the precipitated triethylamine hydrochloride was filtered off and the solvent removed under reduced pressure. A solution of 150 mmol of dry HCl in ethanol (150 mL) was prepared by addition of 11.2 mL of acetyl chloride in the solvent. After 30 min, the crude mixture was dissolved in this solution and the solvent was evaporated in vacuo (bath temperature 30 °C; a prolonged heating at this stage decreased the yield). A mixture of **3b·HCl** and **5b·HCl** was obtained. The crude mass was stirred in acetonitrile (50 mL) and filtered. The solid was **3b·HCl**. The solution was concentrated under reduced pressure, and the crude oil was taken in ethyl acetate and treated with a 4 M aqueous solution of $NaHCO_3$. After drying over Na_2SO_4 and concentration, **5b** (8.648 g, 47 mmol, 45% yield) was recovered as a yellow oil, which crystallized on standing. All imidazolidinones **5** were obtained as single isomers (NMR detection).

7.2.1. *rac*-2-*tert*-Butyl-2,3-dimethylimidazolidin-4-one 5a.

Yield 32%. White solid, mp 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.48$ (s, 2H), 2.90 (s, 3H), 1.37 (s, 3H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.2$ (C), 84.8 (C), 49.6 (CH_2), 41.0 (C), 29.1 (CH_3), 26.3 (CH_3), 21.3

(CH_3). IR (KBr pellet): 3329, 2952, 1674, 1436, 1126 cm^{-1}. MS (DCI): 172 (11), 171 (100). Anal. Calcd for $C_9H_{16}N_2O$: C, 63.50; H, 10.66; N, 16.46. Found: C, 62.96; H, 10.59; N, 16.01.

7.2.2. (2*S*,5*S*)-2-*tert*-Butyl-2,3,5-trimethylimidazolidin-4-one 5b. Yield 42%. Pale yellow solid, mp 81–83 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (q, $J = 6.8$ Hz, 1H), 2.88 (s, 3H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.30 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.8$ (C), 82.6 (C), 53.1 (CH), 38.2 (C), 29.0 (CH_3), 26.1 (CH_3), 18.9 (CH_3), 18.0 (CH_3). IR (KBr pellet): 3348, 2979, 2930, 2866, 1695, 1475, 1127 cm^{-1}. MS (DCI) 186 (12), 185 (100), 183 (4). Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 65.69; H, 10.97; N, 15.19. $[\alpha]_D^{25} = +50.7$ (*c* 1.03, CH_2Cl_2). Crystal description CCDC 605991.

7.2.3. (2*S*,5*S*)-2-*tert*-Butyl-5-benzyl-2,3-dimethylimidazolidin-4-one 5c. Yield after chromatography is 27% (in EtOAc 80/EtOH 20, f.r. = 0.57). Oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$–7.18 (m, 5H), 3.73 (dd, $J = 4.5$, 6.5 Hz, 1H), 3.13 (dd, $J = 4.5$, 13.7 Hz, 1H), 3.02 (dd, $J = 6.5$, 13.7 Hz, 1H), 2.86 (s, 3H), 1.25 (s, 3H), 0.82 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.7$ (C), 137.6 (C), 129.6 (CH), 128.5 (CH), 126.6 (CH), 82.0 (C), 58.0 (CH), 37.8 (C), 37.2 (CH_2), 28.4 (CH_3), 25.4 (CH_3), 18.5 (CH_3). IR (KBr pellet): 3334, 3051, 2957, 1690, 1478, 1131 cm^{-1}. MS (DCI) 262 (16), 261 (100), 259 (8). Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.81, H, 9.30, N, 10.76. Found: C, 74.46, H, 9.48, N, 10.78. $[\alpha]_D^{25} = -48.8$ (*c* 1.05, CH_2Cl_2).

7.2.4. (2*S*,5*S*)-5-((1*H*-Indol-3-yl)methyl)-2-*tert*-butyl-2,3-dimethylimidazolidin-4-one 5d. Yield after chromatography is 32% (in EtOAc 80/EtOH 20, f.r. = 0.53). White solid, mp 177 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.3$–7.1 (m, 5H), 3.76 (dd, $J = 4.5$, 5.6 Hz, 1H), 3.34 (dd, $J = 4.5$, 14.7 Hz, 1H), 3.25 (dd, $J = 5.6$, 14.7 Hz, 1H), 2.82 (s, 3H), 1.22 (s, 3H), 0.66 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.2$ (C), 136.6 (C), 128.6 (C), 127.5 (CH), 123.8 (CH), 120.1 (CH), 119.3 (CH), 111.5 (CH), 111.3 (C), 82.8 (C), 58.7 (CH), 37.9 (C), 28.9 (CH_3), 26.3 (CH_2), 25.7 (CH_3), 18.6 (CH_3) cm^{-1}. IR (KBr pellet): 3329, 3053, 2957, 1680, 1426, 1090. MS (DCI) 301 (21), 300 (100). Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.04. Found: C, 71.45; H, 8.58; N, 13.71. $[\alpha]_D^{25} = -70.1$ (*c* 1.01, CH_2Cl_2).

7.2.5. *rac*-(2*S,5*S**)-2-*tert*-Butyl-5-(hydroxymethyl)-2,3-dimethylimidazolidin-4-one 5e.** Yield after chromatography is 28% (in EtOAc 80/EtOH 20, f.r. = 0.37). White solid, mp 108–110 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.98$ (dd, $J = 3.9$, 11.3 Hz, 1H), 3.77 (dd, $J = 4.9$, 11.3 Hz, 1H), 3.60 (dd, $J = 3.9$, 4.9 Hz, 1H), 2.80 (s, 3H), 1.34 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.6$ (C), 82.6 (C), 61.7 (CH_2), 58.3 (CH), 38.1 (C), 28.4 (CH_3), 25.7 (CH_3), 18.8 (CH_3). IR (KBr pellet): 3298, 3205, 2962, 1685, 1478, 1157, 1059 cm^{-1}. MS (DCI) 202 (19), 201 (100). Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.98; H, 10.07; N, 13.99. Found: C, 59.71; H, 10.00; N, 13.85.

7.3. Imidazolidinones *N*-oxides 2

7.3.1. *rac*-2-*tert*-Butyl-1-hydroxy-2,3-dimethyl-imidazolidin-4-one 8a. In a 250 mL fitted flask, aminoamide **5a** (0.723 g, 4.3 mmol) and the urea:hydroperoxide complex (UHP; 1.39 g, 5.16 mmol, 1.2 equiv) were introduced in 20 mL of dichloromethane (DCM). Methyltrioxorhenium (MTO, 5 mg) was added at 20 °C. A yellow coloration developed, then slowly faded over 30 min. Fresh fractions of 5 mg MTO were added every other 30 min. After a total of 1.5 h, anhydrous magnesium sulfate was added, and the reaction mixture filtered. After concentration, chromatography over 50 g silica gel (eluent EtOH/DCM 4/96) yielded 0.477 g (60%) of hydroxylamine **8a**. White solid, mp 125 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.89$ (d, $J = 16.8$ Hz, 1H), 3.56 (d, $J = 16.8$ Hz, 1H), 2.89 (s, 3H), 1.40 (s, 3H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.7$ (C), 91.7 (C), 61.1 (CH_2), 40.7 (C), 29.1 (CH_3), 26.5 (CH_3), 14.2 (CH_3). IR (KBr pellet): 3283, 2967, 1680, 1126 cm^{-1}. MS (DCI): 187 (74), 186 (27), 171 (86), 169 (100). Anal. Calcd for $C_9H_{18}N_2O_2$: C: 58.04, H: 9.74, N: 15.04. Found C: 58.28, H: 9.71, N: 14.87.

7.3.2. *rac*-2-*tert*-Butyl-2,3-dimethyl-2,3-dihydro-imidazol-4-one-1-oxide 2a. Hydroxylamine **8a** (0.477 g) was stirred for 30 min with activated MnO_2 (Fluka, ref. 63548, 0.334 g, 1.5 equiv) in 10 mL of DCM, Then the mixture was diluted with ethyl acetate and anhydrous Na_2SO_4 was added. The solid was filtered over Celite and repeatedly rinsed with ethyl acetate. Concentration of the gathered filtrates yielded 0.471 g (2.56 mmol) of **2b** (60% yield from **8a**) as a yellow solid. Mp 127 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.03$ (s, 1H), 3.06 (s, 3H), 1.68 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.9$ (C), 125.1 (CH), 97.2 (C), 40.0 (C), 30.1 (CH_3), 25.5 (CH_3), 18.3 (CH_3). IR (KBr pellet): 2962, 1705, 1550, 1121 cm^{-1}. MS (DCI) 186 (15), 185 (100), 169 (27), 129 (66). Anal. Calcd for $C_9H_{16}N_2O_2$: C: 58.68, H: 8.76, N: 15.21. Found: C: 58.81, H: 8.80, N: 15.19.

7.3.3. (*S*)-2-*tert*-Butyl-2,3,5-trimethyl-2,3-dihydro-imidazol-4-one-1-oxide 2b. In a 250 mL flask, *m*-chloroperbenzoic acid (7.77 g, shipping grade, 70% purity, 21 mmol) was added in portions at 0 °C to **5b** (3.851 g, 21 mmol) in 50 mL of DCM. After 30 min at 20 °C, MnO_2 (2.75 g, 31.5 mmol) was added and stirring continued for 2 h at 20 °C. The reaction mixture was then filtered over Celite and the precipitate repeatedly rinsed with EtOAc. The organic phase was extracted with a 2 M Na_2CO_3 solution, dried over Na_2SO_4 and concentrated to yield pure nitrone **2b** in 74% yield (3.06 g). Pale yellow solid, mp 63 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.90$ (s, 3H), 1.90 (s, 3H), 1.50 (s, 3H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.3$ (C), 134.1 (C), 94.5 (C), 39.8 (C), 29.7 (CH_3), 25.2 (CH_3), 17.6 (CH_3), 7.3 (CH_3). IR (KBr pellet): 2964, 1707, 1601, 1126 cm^{-1}. MS (DCI): 200 (12), 199 (100), 183 (13), 143 (30). $[\alpha]_D^{25} = -93.7$ (*c* 4.8, CH_2Cl_2). Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.59; H, 9.16, N, 14.13. Found: C, 60.52, H, 9.22, N, 14.06.

7.3.4. (*S*)-5-Benzyl-2-*tert*-butyl-2,3-dimethyl-2,3-dihydro-imidazol-4-one-1-oxide 2c. Same preparation as **2b**. Yield

80%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–7.16 (m, 5H), 3.85 (d, $J = 14.10$ Hz, 1H), 3.82 (d, $J = 14.10$ Hz, 1H), 3.06 (s, 3H), 1.63 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.4$ (C), 136.0 (C), 134.8 (C), 130.3 (CH), 129.1 (CH), 127.3 (CH), 94.9 (C), 40.3 (C) ; 29.7 (CH_3) ; 27.9 (CH_2), 26.3 (CH_3), 18.1 (CH_3). IR (KBr pellet): 3029, 2962, 1705, 1581, 1126. MS (DCI): 276 (16), 275 (100), 259 (14). $[\alpha]_D^{25} = -69.8$ (*a* 1.08, CH_2Cl_2). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C: 70.04, H: 8.08, N: 10.21. Found C: 69.82, H: 8.43, N: 10.27.

7.4. Addition of Grignard reagents to nitrones 2

The preparation of **9a** is typical. In a 20 mL Schlenk vessel under an N_2 atmosphere, **2b** (396 mg, 2 mmol) was dissolved in 5 mL THF. At −40 °C, the solution of *p*-methoxy-phenyl-magnesium bromide in THF (2 mL, 2.4 mmol) was added dropwise. After 4 h at −40 °C, the mixture was quenched with NH_4Cl, extracted with EtOAc, the organic phase dried over Na_2SO_4 and concentrated. The solid obtained was washed with an EtOAc/cyclohexane mixture 10/90, to yield 477 mg (78% yield) of pure **9a**.

7.4.1. (2*R*,5*R*)-2-*tert*-Butyl-1-hydroxy-5-*para*-methoxyphenyl-2,3,5-trimethylimidazolidin-4-one 9a. Yield 78%. White solid, mp 61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.10$–6.74 (m, 4H), 3.72 (s, 3H), 3.02 (s, 3H), 1.63 (s, 3H), 1.06 (s, 3H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.7$ (C), 155.3 (C), 130.5 (CH), 130.0 (C), 113.6 (CH), 87.3 (C), 77.9 (C), 54.9 (CH_3), 40.5 (C), 28.9 (CH_3), 26.4 (CH_3), 24.9 (CH_3), 13.4 (CH_3). IR (KBr pellet): 3371, 3014, 2988, 2967, 1690, 1183 cm^{-1}. MS (DCI): 308 (9), 307 (56), 306 (8), 291 (44), 192 (100). $[\alpha]_D^{25} = +77.3$ (*c* 0.75, CH_2Cl_2). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C: 66.64, H: 8.55, N: 9.14. Found C: 66.57, H: 8.71, N: 9.15. HPLC of enantiomers: Daicel Chiralpak AD-RH column, 4.6×150 mm, eluent acetonitrile 60/water 40, 0.3 mL/min, retention time (2*R*,5*R*)-**9a** 9.7 min, (2*S*,5*S*)-**9a** 12.7 min.

7.4.2. (2*R*,5*R*)-5-Benzyl-2-*tert*-butyl-1-hydroxy-5-*para*-methoxyphenyl-2,3-dimethylimidazolidin-4-one 9b. Yield 64%. White solid, mp 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$–6.78 (m, 9H), 3.73 (s, 3H), 3.39 (d, $J = 13.7$ Hz, 1H), 3.19 (d, $J = 13.7$ Hz, 1H), 2.90 (s, 3H), 0.88 (s, 3H), 0.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.0$ (C), 159.5 (C), 138.2 (C), 132.0 (CH), 131.2 (CH), 129.8 (C), 128.2 (CH), 126.7 (CH), 113.5 (CH), 86.6 (C), 74.1 (C), 55.6 (CH_3), 42.6 (CH_2), 40.1 (C), 28.5 (CH_3), 26.2 (CH_3), 13.4 (CH_3). IR (KBr pellet): 3355, 3005, 2988, 2952, 2915, 1679, 1173 cm^{-1}. MS (DCI): 384 (25), 383 (100), 382 (7), 367 (22), 268 (80). $[\alpha]_D^{25} = +93.9$ (*c* 0.83, CH_2Cl_2). Anal. Calcd for $C_{23}H_{30}N_2O_3$: C: 72.22, H: 7.91, N: 7.32. Found C: 67.62, H: 8.42, N: 6.36. Crystal description CCDC 605989.

7.4.3. (2*R*,5*R*)-2-*tert*-Butyl-1-hydroxy-2,3,5-trimethyl-5-vinylimidazolidin-4-one 9c. Yield 68%. White solid, mp 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.09$ (dd, $J = 10.9$, 17.6 Hz, 1H), 5.24–5.16 (m, 2H), 2.87 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 0.93 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.8$ (C), 136.9 (CH), 117.2 (CH_2), 82.6 (C), 68.1 (C), 38.2 (C), 29.0 (CH_3), 26.5 (CH_3), 23.3 (CH_3), 14.3 (CH_3). IR (KBr pellet): 3376, 3081, 2988, 2967, 2920, 1695, 1059 cm^{-1}. MS (DCI): 228 (16), 227 (100), 226 (29), 211 (36), 196 (74). $[\alpha]_D^{25} = +25.2$ (*c* 1.02, CH_2Cl_2). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C: 63.69, H: 9.80, N: 12.38. Found C: 63.65, H: 9.76, N: 11.91.

7.5. Preparation of 10

The preparation of **10a** is typical. In a 50 mL Schlenk tube under a nitrogen atmosphere, 198 mg (1.0 mmol) of nitrone **2b** and 306 mg (3 mmol) of phenylacetylene were dissolved in 2 mL of toluene. At 20 °C, 0.75 mL of a 2 M commercial solution of dimethylzinc in toluene was added and the mixture was stirred overnight. After hydrolysis with 1 mL saturated NH_4Cl and extractive work-up in ethyl acetate, the excess alkyne was separated on a short column of silica gel, to yield pure **10a** (285 mg, 95%).

7.5.1. (3a*S*,6*R*)-6-*tert*-Butyl-5,6-dimethyl-2-phenyl-5,6-dihydroimidazo[1,5-*b*]isoxazol-4(3a*H*)-one 10a. Yield 95%. White solid, mp 103 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.45$–7.25 (m, 5H), 5.32 (s, 1H), 2.85 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 171.3$ (C), 154.7 (C), 129.3 (CH), 128.4 (CH), 127.3 (C), 125.5 (CH), 98.0 (CH), 90.5 (C), 74.5 (C), 39.5 (C), 28.8 (CH_3), 25.6 (CH_3), 24.0 (CH_3), 13.5 (CH_3). IR (KBr pellet): 3374, 3096, 3062, 2986, 2962, 2924, 1703, 1496, 1481, 1447, 1428, 1392, 1258, 1131, 1055, 1003, 916, 763, 737, 694 cm^{-1}. $[\alpha]_D^{25} = -33$ (*c* 3.2 ; CH_2 Cl_2). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C: 71.97, H: 8.05, N: 9.33. Found C: 72.36, H: 8.44, N: 9.11. Crystal description CCDC 605990.

7.5.2. (3a*S*,6*R*)-2-Butyl-6-*tert*-butyl-5,6-dimethyl-5,6-dihydroimidazo[1,5-*b*]isoxazol-4(3a*H*)-one 10b. Yield 98% (835 mg, 6 mol equiv of 1-hexyne were used). Oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.62$ (t, $J = 1.1$ Hz, 1H), 2.86 (s, 3H), 2.11–2.05 (m, 2H), 1.49–1.23 (m, 4H), 1.36 (s, 3H), 1.29 (s, 3H), 0.98 (s, 9H), 0.85 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.2$ (C), 157.6 (C), 97.8 (CH), 90.4 (C), 74.1 (C), 39.6 (C), 28.9 (CH_3), 28.6 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 25.1 (CH_2), 24.4 (CH_3), 22.4 (CH_2), 13.9 (CH_3). IR (KBr pellet): 3111, 2959, 2928, 2873, 1703, 1446, 1424, 1392, 1372, 1264, 1135, 1103, 1080, 1050, 983, 954, 936, 855, 822, 756, 719. $[\alpha]_D^{25} = -29$ (*c* 5.3, CH_2Cl_2). HRMS (EI) calcd for $C_{16}H_{28}N_2O_2$ ($M^{+\cdot}$) 280.21522. Found 280.21580.

7.5.3. [(3a*S*,6*R*)-6-*tert*-Butyl-5,6-dimethyl-4-oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazol-2-yl]methyl acetate 10c. Yield 98% (673 mg). Oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.05$ (s, 1H), 4.65 (s, 2H), 2.91 (s, 3H), 2.07 (s, 3H), 1.44 (s, 3H,), 1.36 (s, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.8$ (C), 169.7 (C), 151.5 (C), 102.5 (CH), 90.5 (C), 73.9 (C), 56.1 (CH_2), 39.4 (C), 28.7 (CH_3), 25.6 (CH_3), 23.8 (CH_3), 20.3 (CH_3), 13.5 (CH_3). IR (KBr pellet): 3116, 2974, 2927, 2875, 1750, 1701, 1483, 1446, 1427, 1393, 1297, 1245, 1220, 1136, 1050, 1032, 935, 917, 857, 819, 727 cm^{-1}. $[\alpha]_D^{25} = -34$ (*c* 6.9, CH_2Cl_2). HRMS (EI) calcd for $C_{15}H_{24}N_2O_4$ ($M^{+\cdot}$) 296.17361. Found 296.17476.

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