Tetrahedron: *Asymmetry* 22 (2011) 1274–1281

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Totally diastereoselective addition of aryl Grignard reagents to the nitrone-based chiral glycine equivalent MiPNO

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ARTICLE INFO

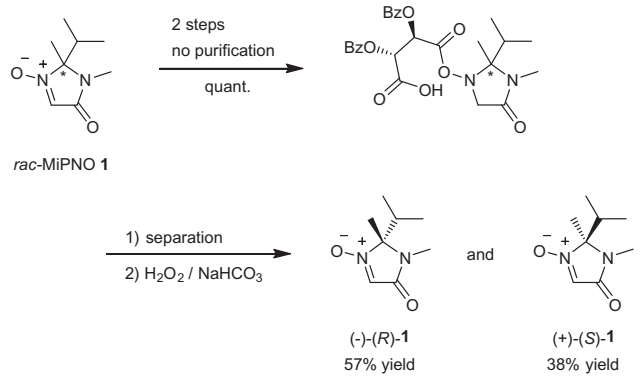
Article history:
Received 5 May 2011
Accepted 25 July 2011

ABSTRACT

The reaction of the chiral nitrone MiPNO (2-isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one) with Grignard reagents is totally diastereoselective. Using simple and functionalized arylmagnesium reagents, enantiopure hydroxylamines were obtained in fair to good yields, which in turn could be easily transformed into new chiral ketonitrones. The preparation of enantiopure L-phenylglycine derivatives is also described.

1. Introduction

We recently reported that chiral nitrone **1** (2-isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one, aka MiPNO)[1] exhibits a high degree of facial differentiation in 1,3-dipolar cycloaddition reactions. Both enantiomers of MiPNO are available on a multigram-scale through a rapid, 3-stage sequence (Scheme 1): selective reduction into the corresponding racemic hydroxylamine/resolution of the hydroxylamine with *O,O′*-dibenzoyl-L-tartaric anhydride via the formation of covalent diastereomers/one-pot removal of the chiral auxiliary and oxidation into a nitrone.[2]



Scheme 1. Preparation of enantiopure MiPNO **1**.

Several other α-carbonyl aldonitrones, both cyclic[3,4] and acyclic,[5] have been described in the literature and their reactivity in 1,3-dipolar cycloaddition reactions studied. However, little attention has been paid to their reactivity toward the nucleophilic addition of organometallic reagents.[6] To the best of our knowledge, the only report concerns the patented addition of organomagnesium and organolithium reagents to a menthol-derived cyclic α-alkylaminocarbonyl nitrone.[7] Our work on related ketonitrones has shown that the presence of an acidic proton on the carbon atoms at the α-position of the nitrone group is detrimental to the nucleophilic addition reaction.[8] Alkynylzinc reagents react smoothly on the electrophilic carbon atom, whereas deprotonation can occur with more basic organometallic species. We thus wondered whether synthetically useful yields of hydroxylamine adducts could be obtained in the reaction of Grignard reagents with MiPNO **1** and whether high diastereoselectivities could be achieved.

Given its structure, MiPNO **1** is a nitrone-based chiral glycine equivalent, and we have demonstrated in the case of 1,3-dipolar cycloaddition reactions that the products can be transformed into γ-hydroxy α-amino acids.[1] By taking advantage of the electrophilic nature of the nitrone carbon atom, we would have access to other α-amino acids. We chose to focus our study on the reaction of MiPNO **1** with arylmagnesium reagents, as the adducts should be precursors of arylglycines, α-amino acids that cannot be easily synthesized from the well-known chiral glycine enolate developed by Seebach.[9,10] Herein we report our investigation into this topic.

2. Results and discussion

2.1. Addition of Grignard reagents to MiPNO

A variety of aryl Grignard reagents were added to racemic or enantiopure MiPNO **1** (Scheme 2 and Table 1), leading in all cases to a single isomer of *N*-hydroxy imidazolidinone **2**. The sole

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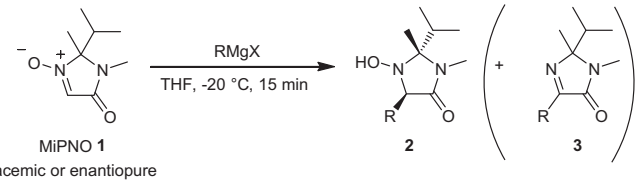
doi:10.1016/j.tetasy.2011.07.022



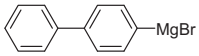
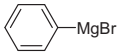
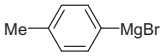
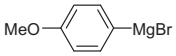
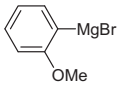
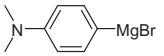
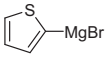
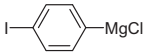
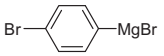
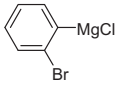
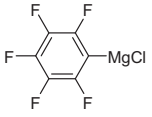
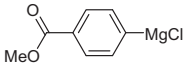
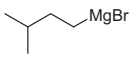
Scheme 2. Addition of Grignard reagents to racemic or enantiopure MiPNO **1** (relative stereochemistry shown).

imidazolidinone-based impurities present in the reaction mixture were unreacted MiPNO **1** and imine.

Simple and electron-rich aryl Grignard reagents led to *N*-hydroxy imidazolidinones **2a–f** in fair to good yields (entries 1–14). The *ortho*-substituted (+)-**2e** (entry 12) was prepared from anisole via *ortho*-lithiation followed by magnesium/lithium exchange. The direct addition of the lithium species onto MiPNO caused degradation. The addition of a heteroaromatic group was possible, for example α-thienyl hydroxylamine **2g** was isolated in high yield (entries 15 and 16).

We were particularly interested in functionalized aryl Grignard reagents bearing electron-withdrawing substituents. Such species can be prepared from the corresponding aryl iodides by magnesium–iodine exchange according to the procedure reported by

Table 1
Addition of Grignard reagents to MiPNO **1**

Entry	Grignard reagent[a]		MiPNO	**1**:**2**:**3** ratio[b]	Hydroxylamine **2**	Isolated yield (%)
1		B	*rac*-**1**	5:95:0	*rac*-**2a**	69
2				5:90:5[c]		51[c]
3				0:79:21[d]		—[e]
4			(*R*)-**1**	9:91:0	(−)-**2a**	62
5		A	*rac*-**1**	0:97:3	*rac*-**2b**	65
6			(*R*)-**1**	7:90:3	(−)-**2b**	71
7			(*S*)-**1**	3:95:2[f]	(+)-**2b**	75[f]
8		A	*rac*-**1**	5:92:3	*rac*-**2c**	65
9			(*R*)-**1**	1:94:5	(−)-**2c**	60
10		A	*rac*-**1**	3:91:6	*rac*-**2d**	64
11			(*R*)-**1**	1:94:5	(−)-**2d**	67
12		C	(*S*)-**1**	9:91:0	(+)-**2e**	72
13		B	*rac*-**1**	5:95:0	*rac*-**2f**	65
14			(*R*)-**1**	5:89:6	(−)-**2f**	65
15		B	*rac*-**1**	7:90:3	*rac*-**2g**	77
16			(*R*)-**1**	4:94:2	(−)-**2g**	79
17		D	*rac*-**1**	0:100:0	*rac*-**2h**	84
18			(*R*)-**1**	0:100:0	(−)-**2h**	89
19		B	*rac*-**1**	6:87:7	*rac*-**2i**	49
20			(*R*)-**1**	8:86:6	(−)-**2i**	52
21		D	*rac*-**1**	37:49:14	*rac*-**2j**	—[e]
22		D	*rac*-**1**	10:90:0	*rac*-**2k**	71
23			(*R*)-**1**	6:94:0	(−)-**2k**	78
24		D[g]	(*R*)-**1**	30:67:3	(−)-**2l**	46
25		A[h]	*rac*-**1**	—[e]	*rac*-**2m**	44
26			(*R*)-**1**	—[e]	(−)-**2m**	41
27		B	(*S*)-**1**	25:68:7	**2n**	40[i]

[a] Preparation and amount of Grignard reagents. Method A: commercial source; 1.1 equiv. Method B: prepared from the aryl bromide and Mg^0; 1.1 equiv. Method C: prepared from anisole via *ortho*-lithiation followed by magnesium–lithium exchange; 1.5 equiv. Method D: prepared from the aryl iodide via magnesium–iodine exchange; 2.0 equiv.
[b] The ratio of **1**:**2**:**3** was determined on the basis of the ^1H NMR spectrum of the crude product.
[c] 1.3 equiv of Grignard reagent were used.
[d] 2.0 equiv of Grignard reagent were used.
[e] Not determined.
[f] PhMgCl was used.
[g] 1.1 equiv of Grignard reagent were used.
[h] The ^{i}PrMgCl·LiCl complex was used.
[i] Hydroxylamine **2m** was contaminated with its imine counterpart (10%).

Knochel and Cahiez,[11] but their addition to nitrones has not yet been investigated. The *p*-iodophenyl adduct **2h** and pentafluorophenyl adduct **2k** were isolated in very good yields (entries 17–18 and 22–23). On the other hand, the reaction of MiPNO **1** with hindered *o*-bromo phenylmagnesium chloride was very sluggish and was accompanied by imine formation to a large extent (entry 21). Better results were obtained in the case of an ester group at the *para*-position (entry 24), although the corresponding hydroxylamine **2l** was isolated in modest yield. Since methyl 4-iodobenzoate underwent a rapid magnesium-iodine exchange, we wondered whether this exchange could be performed in the presence of MiPNO, that is, with in situ quenching.[12] However, the addition of isopropylmagnesium chloride onto the mixture of MiPNO **1** and methyl 4-iodobenzoate led only to the isopropyl adduct **2m** and not the aryl adduct **2l**.

Finally, we investigated the reaction of MiPNO with alkylmagnesium reagents (entries 25–27). Again, the reaction produced a single diastereomer, albeit in modest yield.

2.2. Diastereoselectivity

The relative configuration of hydroxylamines **2** was determined by 2D NOESY NMR experiments on the crude materials. Distinct correlations between the protons of the isopropyl group and the hydrogen atom on the imidazolidinone ring showed that the aryl group was transferred *anti* to the bulky isopropyl group (the observed correlations in the instance of *rac*-**2c** are depicted in Scheme 3). In the case of *p*-anisyl adduct (−)-**2d**, crystals suitable for X-ray diffraction analysis were obtained, and the *trans*-stereochemistry was again confirmed (Fig. 1).

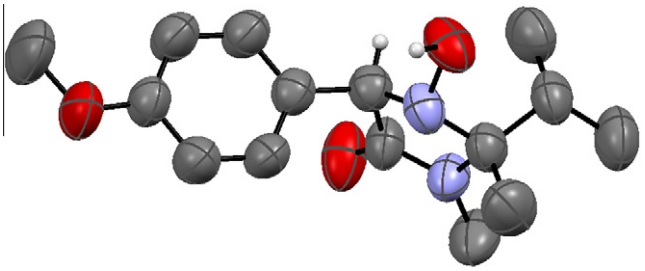
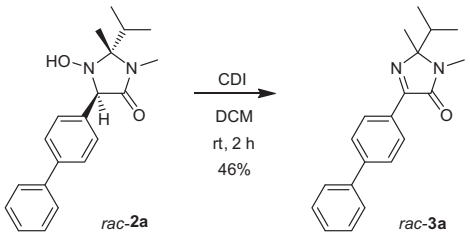


Figure 1. ORTEP drawing of (−)-**2d** (H atoms omitted for clarity).[13] The ellipsoids are plotted at the 70% probability level.

The diastereoselectivity of the reaction appeared very high in all runs. No other hydroxylamine could be detected by TLC[14] in the isolated or crude material, or in minor chromatography fractions. The ^{1}H NMR analysis of crude reaction mixtures showed only **1**, **2,** and **3**. In order to prove the absence of the *cis*-diastereomer, we prepared an authentic sample in the case of the *p*-tolyl adduct (Table 1, entry 8). For this, hydroxylamine *rac*-**2c** was oxidized with MnO_2 into nitrone *rac*-**4c** in quantitative yield[15] (Scheme 3; we also quantitatively prepared ketonitrones **4a**, **b**, **f**, **g** from **2a**, **b**, **f**, **g** by this very efficient procedure, see Section 4). The reduction of ketonitrone **4c** into hydroxylamine proved difficult. Nitrone **4c** was recovered unchanged after reaction with $NaBH_4$, BH_3·THF, BH_3·DMS or BH_3·*N*,*N*-diethylaniline. Finally, the use of $LiAlH_4$ allowed the partial conversion (72%) of **4c** into a new compound, identified by ^{1}H NMR and mass spectroscopy as *N*-hydroxy imidazolidinone **2′c**.[16] A 2D NOESY NMR experiment showed a distinct correlation between the protons of the methyl group and the hydrogen atom introduced, which was consistent with a *cis*-stereochemistry for **2′c** (Scheme 3). The chemical shifts for **2′c** are clearly different compared to **2c** (see Section 4). Thus, we could confirm that **2′c** was indeed not present in the crude material from the *p*-tolylmagnesium addition onto MiPNO (Table 1, entry 8) and that the diastereoselectivity of this addition was above 98%.

2.3. Imine side product

As mentioned in Table 1, we supposed that the single imidazolidinone-based side product in the crude materials was imine **3**. This was proven in the case of **3a** by comparison with an authentic sample prepared by 1,1′-carbonyldiimidazole-mediated dehydration of hydroxylamine **2a** (Scheme 4).[7] Compounds **3a–l** curiously exhibited a very large difference in ^{1}H NMR chemical shift between the diastereotopic methyl groups of the isopropyl (0.60–0.70 ppm, compare with 0.03–0.04 for hydroxylamines **2** or 0–0.07 for nitrones **4**). The separation of hydroxylamine **2** from **3** proved difficult, thus affecting the yield.

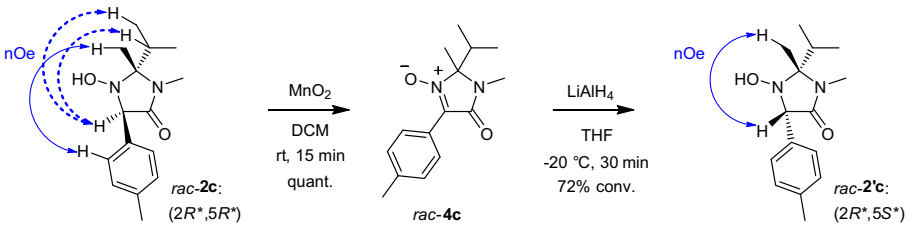


Scheme 4. Preparation of authentic imine **3a** from hydroxylamine **2a** (relative configuration shown).

Our attempts to suppress the formation of **3** were unsuccessful. Changes in the hydrolysis protocol produced only non-significant variations in the ratios. More interestingly, we noticed that a greater amount of **3** was obtained when a larger excess of arylmagnesium reagent was used (for instance, see Table 1, entries 1–3). This suggests that imine **3** is formed before hydrolysis, with the excess Grignard reagent acting as a base.

2.4. Enantioselective preparation of L-phenylglycine derivatives

Arylglycines are a class of α-amino acids that are difficult to synthesize in enantiopure form due to the high acidity of the α-aryl proton.[17] Elegant approaches to the asymmetric construction of the chiral center leading to arylglycine derivatives have been

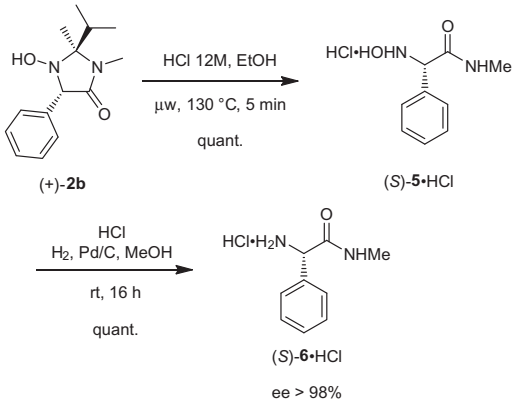


Scheme 3. Preparation of the opposite diasteromer **2′c**; NOESY correlations for each diastereomer (relative stereochemistry shown).

disclosed[18–20] but the subsequent obtention of the enantiopure α-aryl amino acids remains challenging.[21]

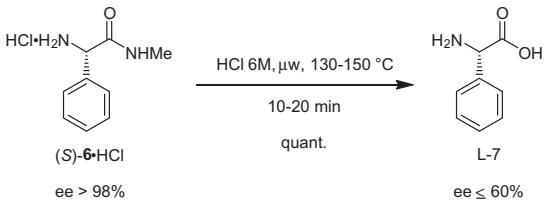
We investigated the transformation of *N*-hydroxy imidazolidinone (+)-**2b** into L-phenylglycine. The hydrolytic cleavage of the two C–N bonds of the aminal was performed in 5 min under microwave irradiation (Scheme 5). Under these conditions, no cleavage of the amide C–N bond was observed; the sole side product, 3-methyl-2-butanone was easily eliminated under reduced pressure to give the *N*-hydroxy α-amino amide hydrochloride salt (*S*)-**5**·HCl in quantitative yield.

Attempts to hydrolyze the amide group at the *N*-hydroxy α-amino amide stage resulted in partial degradation. The hydroxylamine group was thus reduced first. The hydrogenation over Pd/C of the crude (*S*)-**5**·HCl quantitatively yielded the amine hydrochloric salt. However, some racemization occurred: the phenylglycine derivative was recovered in 84% ee as determined by ^{1}H NMR analysis of **6** with (*S*)-*O*-acetylmandelic acid as a chiral solvating agent.[22] Performing the hydrogenolytic N–O bond cleavage in the presence of excess HCl (1.6 additional equivalents) suppressed the racemization (ee >98%, Scheme 5).



Scheme 5. Transformation of *N*-hydroxy imidazolidinone (+)-**2b** into enantiopure L-phenylglycine derivatives.

We have previously performed the epimerization-free hydrolysis of a similar amide group on a related compound produced via a 1,3-dipolar cycloaddition reaction between MiPNO **1** and cyclohexene.[1] When the same conditions (HCl_{aq} 6 M, microwave irradiation, 150 °C) were applied, amino amide (*S*)-**6** was converted into phenylglycine **7** in 10 min (Scheme 6). However the enantiomeric excess of the amino acid was only 60% as determined by HPLC analysis. With lower reaction temperatures, longer reaction times were required for complete conversion and the extent of racemization could not be reduced.



Scheme 6. Amide group hydrolysis.

3. Conclusions

The reaction of the chiral glycine equivalent MiPNO **1** with Grignard reagents is totally diastereoselective and, with arylmagnesium reagents, gives the hydroxylamine adducts **2** in fair to good yields. With both enantiomers of MiPNO **1** being equally accessible,[2] both enantiomers of the adducts **2** are also equally accessible. The hydroxylamines can be easily oxidized into new chiral ketonitrones **4**. The transformation of the *N*-hydroxy imidazolidinone (+)-**2b** into L-phenylglycine shows that enantiopure arylglycine derivatives, namely the *N*-hydroxy amino amide and the amino amide, could be prepared via this methodology. *N*-Hydroxy amino acid derivatives are particularly valuable compounds: their introduction in peptides allows the easy grafting of side chains on the peptide backbone leading to other classes of pseudopeptides or cyclized peptides.[23]

4. Experimental

4.1. General

Non-aqueous reactions were performed under a positive pressure of N_2 in oven-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl. Technical grade dichloromethane, ethanol and methanol were purchased from Carlo Erba reagents and used without further purification. All reagent-grade chemicals were purchased from either Acros or Aldrich chemical companies (magnesium turnings: Aldrich, ref. 20,090-5; Pd/C 10%: Fluka, ref. 15990) and used without purification. GC analyses were performed on a Shimadzu C17 apparatus equipped with a flame ionization detector and a BPX1 column (15 m × 0.25 mm, SGE; He). Thin layer chromatography (TLC) was performed using commercial aluminium-backed silica gel plates (Merck, Kieselgel 60 F_{254}). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with an appropriate staining solution ($KMnO_4$, ninhydrine for amines, basic TTC (2,3,5-triphenyltetrazolium chloride) for hydroxylamines). Product purification by column chromatography was performed using Macherey Nagel Silica Gel 60 M (230–400 mesh). Microwave irradiation experiments were conducted in a CEM Discover S-Class apparatus (single mode technology). Melting points (mp) were determined in capillary tubes with a Büchi B-540 apparatus and are uncorrected. Optical rotations [α] were measured on a Perkin Elmer 341 polarimeter, the corresponding concentration is given in g per 100 cm^3. Infrared spectra (IR) were recorded on a Nicolet 'Magna 550' spectrometer using ATR (Attenuated Total Reflexion) or a Nicolet Impact-400 Fourier transform infrared spectrometer from a thin film. Data are reported in reciprocal centimeters (cm^{-1}). 1D and 2D NMR spectra were recorded on either a Bruker Advance 300 or Advance 400 spectrometer. Chemical shifts (δ) are given in ppm using internal references or TMS as external reference for $CDCl_3$. Multiplicities are declared as follows: s (singlet), d (doublet), t (triplet), hept (heptuplet), m (multiplet), dd (doublet of doublet), tt (triplet of triplet), qq (quadruplet of quadruplet). Coupling constants (*J*) are given in Hertz. Low Resolution Mass Spectra (LRMS) were recorded on a Bruker Daltonics Esquire 3000 Plus ion-trap spectrometer (ESI) or a Thermo Fischer Scientific Polaris Q spectrometer, using ammonia/isobutene—63:37 for chemical ionization. High Resolution Mass Spectra (HRMS) were recorded on a Thermoquest Orbitrap spectrometer at the LCOSB, UMR 7613, Université Pierre et Marie Curie, Paris. Experimental errors for HRMS data are estimated between 1 and 2 ppm. Elemental analysis were performed at the Service d'Analyse Elémentaire du Département de Chimie Moléculaire, Grenoble. Crystal data were collected on a Bruker AXS-Enraf-Nonius MACH3 diffractometer working at the Cu Kα wavelength (1.54178 Å) and at 296 K.

4.2. Synthesis of hydroxylamines 2

4.2.1. Preparation of Grignard reagents

Method A: Commercial organomagnesium reagents.

Method B: The organomagnesium reagents were freshly prepared by the slow addition of the corresponding bromides (1.0 equiv) in THF (Et_2O for 2-bromothiophene and 1-bromo-3-methylbutane) onto magnesium turnings (1.3 equiv) previously activated with 1,2-dibromoethane. *p*-Bromomagnesium bromide was prepared by the dropwise addition (over 15 min) of *p*-dibromobenzene (4.72 g, 20.0 mmol) in THF (30 mL) onto magnesium turnings (486 mg, 20 mmol) that were previously activated with a crystal of iodine. The insoluble dimagnesium compound precipitated in the reaction mixture.[24] The organomagnesium solutions were titrated prior to use according to Watson and Eastham (1.05 M solution of *iso*propanol in toluene and orthophenantroline).[25]

Method C: In an oven-dried, N_2-flushed Schlenk vessel were introduced magnesium turnings (182 mg, 7.50 mmol) and Et_2O (11 mL). 1,2-Dibromoethane (390 μL, 4.50 mmol) was slowly added and the reaction mixture was stirred at room temperature until ethylene evolution ceased (2 h). The reaction mixture became biphasic. In an oven-dried, N_2-flushed Schlenk vessel, a solution of *t*-BuLi in heptane (1.1 M, 2.05 mL, 2.25 mmol) was slowly added to anisole (740 μL, 6.75 mmol) in THF (1 mL) at 0 °C. The reaction mixture was kept at this temperature for 2.5 h. This solution was then added in two portions to the previously prepared pre-cooled solution of $MgBr_2$ (4.50 mmol) in Et_2O (11 mL) at 0 °C. The resulting solution was stirred for 15 min before use.

Method D: The preparation was carried out in an oven-dried, N_2-flushed, 25 mL two-necked flask fitted with an internal thermometer. To a −30 °C (liquid N_2/EtOH bath) pre-cooled solution of appropriate iodobenzene (3.30 mmol) in dry THF (3 mL) was added dropwise a commercial solution of isopropylmagnesium chloride–lithium chloride complex in THF (1.01 M, 2.96 mL, 3.00 mmol). The pot temperature raised to −20 °C and was kept at this temperature until the I/Mg exchange was complete (as checked by GC analysis of reaction aliquots; conditions: 2 min at 75 °C, then 75–280 °C at 10 °C per min and 4 min at 280 °C, internal standard: dodecane) at which point the reagent was used immediately.

4.2.2. (2*R*,5*R*)-5-Biphenyl-4-yl-1-hydroxy-2-isopropyl-2,3-dimethyl-imidazolidin-4-one (−)-2a

The reaction was performed in an oven-dried, nitrogen-flushed, 25 mL cylindrical three-necked flask fitted with an internal thermometer. Nitrone (*R*)-**1** (170 mg, 1.0 mmol) was dissolved in anhydrous THF (2 mL). The reaction mixture was cooled to −20 °C (liquid N_2/EtOH bath) and a solution of organomagnesium reagent in THF (1.1 mmol, method B) was added. During the addition, the temperature was kept below −20 °C. After 15 min, a saturated aqueous solution of NH_4Cl (2 mL) was added, followed by ethyl acetate (10 mL) and water (2 mL). The aqueous layer was separated and extracted with ethyl acetate (15 mL). The gathered organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The resulting crude material was purified by flash chromatography (cyclohexane/ethyl acetate—70:30) to yield hydroxylamine **2a**. Yield: 62%; white solid, mp: 182 °C; $[\alpha]_D^{25} = -123.9$ (*c* 0.96, acetone); R_f 0.62 (ethyl acetate); IR (thin film): 3345, 3050, 3028, 2963, 2937, 1682; δ_H (400 MHz; $CDCl_3$) 7.60–7.58 (4H, m), 7.46–7.41 (4H, m), 7.34 (1H, tt, ^4J = 2.0, ^3J = 7.4 Hz), 4.89 (1H, s), 2.92 (3H, s), 2.35 (1H, qq, J = 6.8, 7.2 Hz), 1.51 (3H, s), 1.17 (3H, d, J = 6.8 Hz), 1.13 (3H, d, J = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 169.5, 141.3, 141.1, 136.1, 129.5, 128.9, 127.4, 127.3, 84.9, 70.9, 35.1, 27.2, 23.0, 19.0, 18.6; LRMS (DCI) *m/z*: 325.2 (100, $(M+H)^+$); Anal. $C_{20}H_{24}N_2O_2$ requires C, 74.05; H, 7.46; N, 8.64. Found: C, 74.06; H, 7.54; N, 8.61.

4.2.3. (2*R*,5*R*)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-phenyl-imidazolidin-4-one (−)-2b

The title compound was prepared as described for **2a** (organomagnesium reagent: method A). Yield: 71%; beige solid, mp: 110 °C; $[\alpha]_D^{25} = -108.2$ (*c* 0.98, acetone); R_f 0.57 (ethyl acetate); IR (thin film): 3297, 3063, 3020, 2985, 2959, 2933, 1681; δ_H (400 MHz; $CDCl_3$) 7.38–7.37 (4H, m), 7.34–7.31 (1H, m), 4.84 (1H, s), 4.83 (1H, s), 2.89 (3H, s), 2.34 (1H, hept, J = 7.2 Hz), 1.49 (3H, s), 1.15 (3H, d, J = 7.2 Hz), 1.12 (3H, d, J = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 169.3, 136.9, 129.0, 128.4, 128.1, 84.7, 71.0, 34.9, 27.0, 22.9, 18.8, 18.5; LRMS (ESI^+) *m/z*: 249.1 (59, $(M+H)^+$), 271.1 (100, $(M+Na)^+$), 497.2 (5, $(2M+H)^+$), 519.3 (67, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 271.14183 (M+Na); $C_{14}H_{20}N_2O_2Na$ requires 271.14170; Anal. $C_{14}H_{20}N_2O_2$ requires C, 67.72; H, 8.12; N, 11.29. Found: C, 67.39; H, 8.15; N, 10.95.

4.2.4. (2*R*,5*R*)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-*p*-tolyl-imidazolidin-4-one (−)-2c

The title compound was prepared as described for **2a** (organomagnesium reagent: method A), then recrystallized from cyclohexane/ethyl acetate. Yield: 60%; white crystals, mp: 135 °C; $[\alpha]_D^{25} = -115.0$ (*c* 1.00, acetone); R_f 0.28 (cyclohexane/ethyl acetate—60:40); IR (ATR): 3250, 3054, 2977, 2936, 2933, 1679; δ_H (400 MHz; $CDCl_3$) 7.26 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 4.80 (1H, s), 4.74 (1H, s), 2.89 (3H, s), 2.36 (3H, s), 2.32 (1H, qq, J = 6.8, 7.2 Hz), 1.49 (3H, s), 1.14 (3H, d, J = 6.8 Hz), 1.11 (3H, d, J = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 169.7, 138.0, 134.0, 129.3, 129.1, 84.8, 71.0, 35.0, 27.1, 22.8, 21.3, 18.9, 18.6; LRMS (ESI^+) *m/z*: 263.1 (95, $(M+H)^+$), 285.1 (100, $(M+Na)^+$), 301.1 (5, $(M+K)^+$), 525.3 (5, $(2M+H)^+$), 547.3 (35, $(2M+Na)^+$). HRMS (ESI^+) *m/z*: found, 287.15731 (M+Na); $C_{15}H_{22}N_2O_2Na$ requires 287.15735; Anal. $C_{15}H_{22}N_2O_2$ requires C, 68.68; H, 8.46; N, 10.68. Found: C, 69.00; H, 8.60; N, 10.86.

4.2.5. (2*R*,5*R*)-1-Hydroxy-2-isopropyl-5-(4-methoxy-phenyl)-2,3-dimethyl-imidazolidin-4-one (−)-2d

The title compound was prepared as described for **2a** (organomagnesium reagent: method A), then recrystallized from cyclohexane/dichloromethane. Yield: 67%; beige solid, mp: 147 °C; $[\alpha]_D^{25} = -104.1$ (*c* 1.04, acetone); R_f 0.32 (cyclohexane/ethyl acetate—50:50); IR (thin film): 3354, 3054, 2985, 2963, 2933, 1691; δ_H (400 MHz; $CDCl_3$) 7.29 (2H, d, J = 8.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 4.79 (1H, s), 4.67 (1H, s), 3.80 (3H, s), 2.90 (3H, s), 2.32 (1H, qq, J = 6.8, 7.2 Hz), 1.49 (3H, s), 1.14 (3H, d, J = 6.8 Hz), 1.11 (3H, d, J = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 169.9, 159.7, 130.4, 128.9, 114.0, 84.8, 70.6, 55.4, 35.1, 27.1, 22.5, 18.9, 18.6; LRMS (ESI^+) *m/z*: 279.1 (15, $(M+H)^+$), 301.1 (100, $(M+Na)^+$), 579.3 (84, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 301.15152 (M+Na); $C_{15}H_{22}N_3O_2Na$ requires 301.15226; Anal. $C_{15}H_{22}N_2O_3$ requires C, 64.73; H, 7.97; N, 10.07. Found: C, 64.40; H, 8.06; N, 9.91. The relative configuration of (−)-**2d** was determined by X-ray crystallography of an analytical sample recrystallized in ethanol (pale yellow crystals). $C_{15}H_{22}N_2O_3$, M = 278.35 g mol^{-1}, monoclinic, $P2_1$, a = 10.448(4), b = 7.451(2), c = 20.442(6) Å, β = 97.63(4)°, V = 1577.2(8) Å^3, Z = 4, Dx = 1.172 g cm^{-3}. A total of 3497 reflections were collected; 3445 independent reflections (R_{int} = 0.0455). The structure was solved by direct methods with SIR92[26] and refined against F by least-squares method implemented by TeXsan.[27] The C, N, and O atoms were refined anisotropically by the full matrix least-squares method. The H atoms were set geometrically and recalculated before the last refinement cycle. There are two independent molecules in the asymmetric unit. These two molecules are linked by a hydrogen bond. The final R values obtained for

3022 reflections with $I > 2\sigma(I)$ and 361 parameters are $R_1 = 0.0643$, $wR_2 = 0.1008$ and for all 3445 unique reflections $R_1 = 0.0702$, $wR_2 = 0.1033$. The data have been deposited at the Cambridge Crystallographic Data Centre (Reference No. CCDC 819593).

4.2.6. (2*S*,5*S*)-1-Hydroxy-2-isopropyl-5-(2-methoxy-phenyl)-2,3-dimethyl-imidazolidin-4-one (+)-2e

The title compound was prepared as described for **2a** except that the solution of nitrone (*S*)-**1** (255 mg, 1.50 mmol) in THF (3 mL) was added to the organomagnesium reagent obtained from method C. Yield: 72%; white solid, mp: 160 °C; $[\alpha]_D^{25} = +61.7$ (*c* 1.04, acetone); R_f 0.55 (ethyl acetate); IR (ATR): 3391, 3018, 2968, 2838, 1666; δ_H (400 MHz; $CDCl_3$) 7.30–7.25 (2H, m), 6.93 (1H, t, *J* = 7.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 5.97 (1H, br s), 5.15 (1H, s), 3.78 (3H, s), 2.83 (3H, s), 2.19 (1H, qq, *J* = 6.8, 7.2 Hz), 1.04 (3H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.99 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 170.2, 158.6, 132.1, 129.7, 124.2, 120.6, 111.1, 86.0, 66.5, 55.7, 34.9, 27.2, 20.2, 18.8, 18.4; LRMS (ESI^+) *m/z*: 279.2 (100, $(M+H)^+$), 301.2 (71, $(M+Na)^+$), 579.3 (54, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 301.15175 (M+Na); $C_{15}H_{22}N_2O_3Na$ requires 301.15226. Anal. $C_{15}H_{22}N_2O_3$ requires C, 64.73; H, 7.97; N, 10.07. Found: C, 65.05; H, 8.10; N, 10.08.

4.2.7. (2*R*,5*R*)-5-(4-Dimethylamino-phenyl)-1-hydroxy-2-isopropyl-2,3-dimethyl-imidazolidin-4-one (−)-2f

The title compound was prepared as described for **2a** (organomagnesium reagent: method B). The resulting crude material was purified by trituration in boiling ethyl acetate to yield hydroxylamine (−)-**2f** (65%) as a beige solid. mp: 184 °C; $[\alpha]_D^{25} = -111.3$ (*c* 1.10, acetone); R_f 0.34 (ethyl acetate/cyclohexane—70:30); IR (ATR): 3251, 3006, 2987, 2965, 2796, 1679; δ_H (400 MHz; $CDCl_3$) 7.20 (2H, d, *J* = 8.8 Hz), 6.72 (2H, d, *J* = 8.8 Hz), 4.96 (1H, s), 4.74 (1H, s), 2.93 (6H, s), 2.88 (3H, s), 2.28 (1H, qq, *J* = 6.8, 7.2 Hz), 1.41 (3H, s), 1.11 (3H, d, *J* = 6.8 Hz), 1.08 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 170.3, 150.8, 130.2, 124.3, 112.8, 84.8, 70.7, 40.8, 35.1, 27.1, 22.2, 18.9, 18.6; LRMS (ESI^+) *m/z*: 292.2 (100, $(M+H)^+$), 314.2 (14, $(M+Na)^+$), 583.4 (9, $(2M+H)^+$), 605.3 (13, $(2M+Na)^+$); Anal. $C_{16}H_{25}N_3O_2$ requires C, 65.96; H, 8.65; N, 14.43. Found: C, 65.75; H, 8.97; N, 14.48.

4.2.8. (2*R*,5*R*)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-thiophen-2-yl-imidazolidin-4-one (−)-2g

The title compound was prepared as described for **2a** (organomagnesium reagent: method B). Yield: 79%; pink solid, mp: 118 °C; $[\alpha]_D^{25} = -64.9$ (*c* 1.24, acetone); R_f 0.62 (ethyl acetate); IR (thin film): 3338, 3111, 3067, 2963, 2933, 1688; δ_H (300 MHz; $CDCl_3$) 7.28 (1H, dd, *J* = 1.2, 5.1 Hz), 7.15 (1H, dd, *J* = 1.2, 3.5 Hz), 7.01 (1H, dd, *J* = 3.5, 5.1 Hz), 5.12 (1H, s), 4.97 (1H, s), 2.89 (3H, s), 2.30 (1H, hept, *J* = 9.2 Hz), 1.49 (3H, s), 1.13 (3H, d, *J* = 9.2 Hz), 1.10 (3H, d, *J* = 9.2 Hz); δ_C (100 MHz; $CDCl_3$) 168.5, 140.0, 127.3, 127.1, 125.7, 85.1, 66.8, 35.1, 27.2, 22.2, 18.8, 18.5; LRMS (ESI^+) *m/z*: 255.0 (25, $(M+H)^+$), 277.1 (100, $(M+Na)^+$), 293.0 (17, $(M+K)^+$), 531.2 (67, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 277.09861 (M+Na); $C_{12}H_{18}N_2O_2SNa$ requires 277.09812; Anal. $C_{12}H_{18}N_2O_2S$ requires C, 56.67; H, 7.14; N, 11.02. Found: C, 56.99; H, 7.44; N, 11.18.

4.2.9. (2*R*,5*R*)-1-Hydroxy-5-(4-iodo-phenyl)-2-isopropyl-2,3-dimethyl-imidazolidin-4-one (−)-2h

The title compound was prepared as described for **2a** except that the solid nitrone (*R*)-**1** (255 mg, 1.50 mmol) was added in one portion to the solution of organomagnesium reagent obtained from method D (2.0 equiv) cooled to −30 °C. Yield: 89%; white solid, mp: 151 °C; $[\alpha]_D^{25} = -104.8$ (*c* 1.14, acetone); R_f 0.26 (cyclohexane/ethyl acetate—60:40); IR (thin film): 3345, 3054, 2976, 2959, 2933, 1682; δ_H (400 MHz; $CDCl_3$) 7.69 (2H, d, *J* = 8.2 Hz), 7.14 (2H, d, *J* = 8.2 Hz), 4.77 (1H, s), 4.76 (1H, s), 2.88 (3H, s), 2.33 (1H, qq, *J* = 6.8, 7.2 Hz), 1.50 (3H, s), 1.15 (3H, d, *J* = 6.8 Hz), 1.12 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 169.0, 137.5, 136.7, 130.9, 94.0, 84.9, 70.5, 35.1, 27.1, 22.9, 18.9, 18.5; LRMS (ESI^+) *m/z*: 375.1 (45, $(M+H)^+$), 397.1 (79, $(M+Na)^+$), 749.0 (3, $(2M+H)^+$), 771.1 (100, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 397.03914 (M+Na); $C_{14}H_{19}IN_2O_2Na$ requires 397.03834; Anal. $C_{14}H_{19}IN_2O_2$ requires C, 44.94; H, 5.12; N, 7.49. Found: C, 45.05; H, 5.17; N, 7.56.

4.2.10. (2*R*,5*R*)-5-(4-Bromo-phenyl)-1-hydroxy-2-isopropyl-2,3-dimethyl-imidazolidin-4-one (−)-2i

The title compound was prepared as described for **2a** (organomagnesium reagent: method B). Yield: 52%; white solid, mp: 153 °C; $[\alpha]_D^{25} = -106.9$ (*c* 1.38, acetone); R_f 0.67 (ethyl acetate); IR (thin film): 3336, 3054, 2985, 1693; δ_H (400 MHz; $CDCl_3$) 7.49 (2H, d, *J* = 8.4 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 4.79 (1H, s), 4.78 (1H, s), 2.88 (3H, s), 2.33 (1H, qq, *J* = 6.8, 7.2 Hz), 1.50 (3H, s), 1.15 (3H, d, *J* = 6.8 Hz), 1.12 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 168.9, 136.1, 131.6, 130.6, 122.3, 84.9, 70.5, 35.1, 27.2, 23.1, 18.9, 18.6; LRMS (ESI^+) *m/z*: 327.1 (100, $(M+H)^+$), 329.1 (92, $(M+H)^+$), 349.1 (92, $(M+Na)^+$), 351.1 (93, $(M+Na)^+$), 655.1 (5, $(2M+H)^+$), 677.1 (43, $(2M+Na)^+$), 679.1 (20, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 349.05286 and 351.05049 (M+Na); $C_{14}H_{19}BrN_2O_2Na$ requires 349.05221 and 351.05017.

4.2.11. (2*R*,5*R*)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-pentafluorophenyl-imidazolidin-4-one (+)-2k

The title compound was prepared as described for **2a** except that the solid nitrone (*R*)-**1** (255 mg, 1.50 mmol) was added in one portion to the solution of organomagnesium reagent obtained from method D (2.0 equiv) cooled to −30 °C. Yield: 78%; white solid, mp: 178 °C; $[\alpha]_D^{25} = +14.8$ (*c* 0.94, acetone); R_f 0.22 (cyclohexane/ethyl acetate—70:30); IR (thin film): 3331, 2976, 2985, 2938, 1693, 1003; δ_H (400 MHz; $CDCl_3$) 5.21 (1H, s), 4.86 (1H, s), 2.92 (3H, s), 2.28 (1H, hept, *J* = 7.2 Hz), 1.49 (3H, s), 1.15 (3H, d, *J* = 7.2 Hz), 1.10 (3H, d, *J* = 7.2 Hz); δ_C (100 MHz; $CDCl_3$) 167.1, 146.4 (d, *J* = 190 Hz), 141.5 (d, *J* = 190 Hz), 137.6 (d, *J* = 187 Hz), 111.2, 86.3, 62.0, 35.3, 27.1, 22.2, 18.4, 18.2; δ_F (282 MHz; $CDCl_3$) −141.2 (br), −153.7 (tt, ^4J = 2.3 Hz, ^3J = 21.4 Hz), −162.4 (td, ^5J = 8.1 Hz, ^3J = 21.4 Hz); LRMS (ESI^+) *m/z*: 339.1 (34, $(M+H)^+$), 361.1 (100, $(M+Na)^+$), 699.2 (20, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 361.09507 (M+Na); $C_{14}H_{15}F_5N_2O_2Na$ requires 361.09459.

4.2.12. (2*R*,5*R*)-1-Hydroxy-5-(4-methoxycarbonylphenyl)-2-isopropyl-2,3-dimethylimidazolidin-4-one (−)-2l[28]

The title compound was prepared as described for **2a** except that a solution of nitrone (*R*)-**1** (340 mg, 2.0 mmol) in THF (3 mL) was added to the solution of organomagnesium reagent obtained from method D (1.1 equiv). Yield: 46%; white solid, mp: 162 °C; $[\alpha]_D^{25} = -82.9$ (*c* 1.00, acetone); R_f 0.67 (ethyl acetate); IR (ATR): 3424, 2987, 2959, 1715, 1686; δ_H (400 MHz; $CDCl_3$) 7.95 (2H, d, *J* = 8.3 Hz), 7.43 (2H, d, *J* = 8.3 Hz), 5.69 (1H, s), 4.83 (1H, s), 3.89 (3H, s), 2.84 (3H, s), 2.32 (1H, hept, *J* = 7.1 Hz), 1.47 (3H, s), 1.13 (3H, d, *J* = 7.1 Hz), 1.10 (3H, d, *J* = 7.1 Hz); δ_C (100 MHz; $CDCl_3$) 169.0, 167.2, 142.2, 129.6 (2C), 128.7, 84.9, 70.7, 52.2, 35.0, 27.1, 23.2, 18.9, 18.5; LRMS (ESI^+) *m/z*: 307.1 $(M+H)^+$, 329.1 $(M+Na)^+$.

4.2.13. (2*R*,5*R*)-1-Hydroxy-2,5-diisopropyl-2,3-dimethylimidazolidin-4-one (−)-2m

The title compound was prepared as described for **2a** using ^{i}PrMgCl·LiCl (method A). Yield: 41%; white solid, mp: 126 °C; $[\alpha]_D^{25} = -1.7$ (*c* 1.06, acetone); R_f 0.26 (cyclohexane/ethyl acetate—60:40); IR (thin film): 3284, 2965, 2933, 1675; δ_H (400 MHz; $CDCl_3$) 4.69 (1H, s), 3.66 (1H, d, *J* = 3.6 Hz), 2.80 (3H, s), 2.25 (1H, qq, *J* = 6.8, 7.2 Hz), 2.17–2.13 (1H, m), 1.41 (3H, s), 1.07 (3H, d, *J* = 6.8 Hz), 1.05 (3H, d, *J* = 6.8 Hz), 1.04 (3H, d,

J = 7.2 Hz), 0.95 (3H, d, J = 6.8 Hz); δ_C (100 MHz; $CDCl_3$) 170.6, 84.4, 71.4, 35.0, 29.2, 26.6, 23.6, 19.2, 18.8, 18.5, 17.7; LRMS (ESI^+) *m/z*: 215.1 (100, $(M+H)^+$), 237.1 (54, $(M+Na)^+$), 253.1 (6, $(M+K)^+$), 429.2 (10, $(2M+H)^+$), 451.3 (29, $(2M+Na)^+$); HRMS (ESI^+) *m/z*: found, 237.15760 (M+Na); $C_{11}H_{22}N_2O_2Na$ requires 237.15735.

4.2.14. (2*S*,5*S*)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-(3-methyl-butyl)-imidazolidin-4-one 2n

The title compound was prepared as described for **2a** starting from (*S*)-MiPNO (organomagnesium reagent: method B). Hydroxylamine **2n** (white solid, 40% yield) was contaminated with its imine counterpart (10%). R_f 0.59 (ethyl acetate); δ_H (400 MHz; $CDCl_3$) 4.82 (1H, br s), 3.72 (1H, t, J = 6.4 Hz), 2.80 (3H, s), 2.11 (1H, qq, J = 6.8, 7.2 Hz), 1.80–1.71 (2H, m), 1.58–1.51 (1H, m), 1.45–1.25 (2H, m), 1.42 (3H, s), 1.03 (3H, d, J = 7.2 Hz), 0.99 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.4 Hz), 0.90 (3H, d, J = 6.4 Hz); δ_C (100 MHz; $CDCl_3$) 172.2, 86.3, 66.5, 35.4, 35.2, 28.4, 27.1, 26.5, 22.8, 22.6, 19.7, 18.8, 18.3; LRMS (ESI^+) *m/z*: 243.2 (100, $(M+H)^+$), 265.2 (62, $(M+Na)^+$), 485.3 (3, $(2M+H)^+$), 507.3 (42, $(2M+Na)^+$).

4.2.15. Complementary data for racemic hydroxylamines 2

Compound *rac*-**2a**: white solid, mp: 162 °C; *rac*-**2b**: yellow oil that solidified upon standing, mp: 95 °C; *rac*-**2c**: beige solid, mp: 128 °C; *rac*-**2d**: white solid, mp: 139 °C; *rac*-**2f**: yellow solid, mp: 155 °C; *rac*-**2g**: beige solid, mp: 108 °C; *rac*-**2h**: white solid, mp: 135 °C; *rac*-**2i**: white solid, mp: 103 °C; *rac*-**2k**: white solid, mp: 155 °C; *rac*-**2m**: beige solid, mp: 85 °C.

4.3. *rac*-5-Biphenyl-4-yl-2-isopropyl-2,3-dimethyl-2,3-dihydro-imidazol-4-one *rac*-3a

In a 25-mL flask under an N_2 atmosphere, hydroxylamine *rac*-**2a** (481 mg, 1.48 mmol) was dissolved in dichloromethane (2 mL) and 1,1′-carbonyldiimidazole (384 mg, 2.37 mmol) was added. The reaction mixture was stirred for 2 h at room temperature after which a 0.25 M aqueous solution of hydrochloric acid (8 mL) was added. After decantation, the aqueous layer was extracted three times with dichloromethane (10 mL). The gathered organic layers were washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (silica gel, cyclohexane/ethyl acetate—70:30) gave imine *rac*-**3a** as a beige solid (209 mg, 682 μmol, 46%). R_f 0.62 (ethyl acetate); δ_H (400 MHz; $CDCl_3$) 8.54 (2H, d, J = 8.4 Hz), 7.70 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 7.2 Hz), 7.47 (2H, t, J = 7.2 Hz), 7.38 (1H, t, J = 7.2 Hz), 2.98 (3H, s), 2.18 (1H, hept, J = 6.8 Hz), 1.53 (3H, s), 1.24 (3H, d, J = 6.8 Hz), 0.58 (3H, d, J = 6.8 Hz); δ_C (100 MHz; $CDCl_3$) 163.0, 162.4, 144.2, 140.6, 130.0, 129.00, 128.95, 128.0, 127.35, 127.30, 87.7, 34.7, 26.1, 22.5, 17.9, 15.7; LRMS (ESI^+) *m/z*: 307.2 (100, $(M+H)^+$), 329.2 (21, $(M+Na)^+$), 635.3 (60, $(2M+Na)^+$).

4.4. Preparation of ketonitrones 4 from hydroxylamines 2

4.4.1. *rac*-5-Biphenyl-4-yl-2-isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one *rac*-4a

In a 10 mL flask, hydroxylamine *rac*-**2a** (204 mg, 629 μmol) was dissolved in dichloromethane (4 mL). Manganese dioxide (219 mg, 2.52 mmol, 4 equiv) was added. The reaction mixture was stirred at room temperature for 15 min, then diluted with ethyl acetate (4 mL), and anhydrous $MgSO_4$ was added. The solids were filtered over Celite and thoroughly rinsed with ethyl acetate. The gathered filtrates were concentrated under reduced pressure to yield nitrone *rac*-**4a** as a white solid in quantitative yield. An analytical sample was recrystallized from cyclohexane/ethyl acetate: white crystals, mp: 101 °C; R_f 0.62 (ethyl acetate); IR (thin film): 3059, 3033, 2967, 2924, 1702, 1557; δ_H (400 MHz; $CDCl_3$) 8.89 (2H, m), 7.73–7.71 (2H, m), 7.66–7.64 (2H, m), 7.48–7.44 (2H, m), 7.37 (1H, tt, ^4J = 0.3, ^3J = 7.6 Hz), 3.11 (3H, s), 2.44 (1H, qq, J = 6.8, 7.2 Hz), 1.74 (3H, s), 1.04 (3H, d, J = 7.2 Hz), 0.99 (3H, d, J = 6.8 Hz); δ_C (100 MHz; $CDCl_3$) 163.1, 143.4, 140.4, 130.5, 129.0, 128.05, 128.00, 127.3, 127.0, 125.0, 91.2, 35.2, 26.7, 21.6, 16.4, 15.7; LRMS (ESI^+) *m/z*: 323.2 (100, $(M+H)^+$), 345.2 (94, $(M+Na)^+$), 645.4 (3, $(2M+H)^+$), 667.3 (42, $(2M+Na)^+$); Anal. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 6.96; N, 8.63.

4.4.2. *rac*-2-Isopropyl-2,3-dimethyl-1-oxy-5-phenyl-2,3-dihydro-imidazol-4-one *rac*-4b

The title compound was prepared as described for **4a** starting from hydroxylamine *rac*-**2b** (1.35 g, 5.47 mmol). Yield: 95%, beige solid; δ_H (400 MHz; $CDCl_3$) 8.79–8.77 (2H, m), 7.48–7.46 (3H, m), 3.09 (3H, s), 2.44 (1H, qq, J = 6.8, 7.2 Hz), 1.73 (3H, s), 1.03 (3H, d, J = 7.2 Hz), 0.98 (3H, d, J = 6.8 Hz).

4.4.3. *rac*-2-Isopropyl-2,3-dimethyl-1-oxy-5-*p*-tolyl-2,3-dihydro-imidazol-4-one *rac*-4c

The title compound was prepared as described for **4a** starting from hydroxylamine *rac*-**2c** (262 mg, 1 mmol). Yield: quant.; brown solid; δ_H (400 MHz; $CDCl_3$) 8.70 (2H, d, J = 8.1 Hz), 7.28 (2H, d, J = 8.1 Hz), 3.08 (3H, s), 2.42 (1H, hept, J = 7.0 Hz), 2.40 (3H, s), 1.71 (3H, s), 1.02 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 7.0 Hz).

4.4.4. *rac*-5-(4-Dimethylamino-phenyl)-2-isopropyl-2,3-dimethyl-1-oxy-2,3-dihydro-imidazol-4-one *rac*-4f

The title compound was prepared as described for **4a** from hydroxylamine *rac*-**2f** (100 mg, 343 μmol). Yield: quant.; yellow solid; δ_H (300 MHz; $CDCl_3$) 8.83 (2H, d, J = 9.2 Hz), 6.76 (2H, d, J = 9.2 Hz), 3.07 (3H, s), 3.04 (6H, s), 2.44 (1H, qq, J = 6.9, 7.2 Hz), 1.70 (3H, s), 1.02 (3H, d, J = 7.2 Hz), 0.95 (3H, d, J = 6.9 Hz).

4.4.5. *rac*-2-Isopropyl-2,3-dimethyl-1-oxy-5-thiophen-2-yl-2,3-dihydro-imidazol-4-one *rac*-4g

The title compound was prepared as described for **4a** from hydroxylamine *rac*-**2g** (110 mg, 432 μmol). Yield: quant.; yellow oil; δ_H (400 MHz; $CDCl_3$) 8.52 (1H, d, J = 4.2 Hz), 7.58 (1H, d, J = 4.8 Hz), 7.23 (1H, dd, J = 4.2, 4.8 Hz), 3.10 (3H, s), 2.41 (1H, hept, J = 6.8 Hz), 1.73 (3H, s), 0.99 (6H, d, J = 6.8 Hz).

4.5. (2*R**,5*S**)-1-Hydroxy-2-isopropyl-2,3-dimethyl-5-*p*-tolyl-imidazolidin-4-one *rac*-2′c

In a 25 mL flask, nitrone **4c** (210 mg, 0.81 mmol) was dissolved in anhydrous THF (10 mL). The reaction mixture was cooled to −20 °C (liquid N_2/EtOH bath) and $LiAlH_4$ (31 mg, 0.81 mmol) was added. After 30 min at −20 °C, the medium was diluted with Et_2O (20 mL), carefully hydrolyzed with a saturated aqueous Na_2SO_4 solution (10 mL) and filtered. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford an inseparable mixture of the desired compound and the starting material. A selected set of peaks belonging to the title compound from the ^1H NMR and LRMS of the crude material are as follows: δ_H (400 MHz; $CDCl_3$) 7.27 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 4.96 (1H, s), 4.42 (1H, s), 2.79 (3H, s), 2.34 (3H, s), 1.95 (1H, hept, J = 7.1 Hz), 1.44 (3H, s), 1.08 (3H, d, J = 7.1 Hz), 0.96 (3H, d, J = 7.1 Hz); LRMS (ESI^+) *m/z*: 263.1 (100, $(M+H)^+$), 285.1 (20, $(M+Na)^+$), 525.3 (40, $(2M+H)^+$), 547.3 (70, $(2M+Na)^+$).

4.6. Synthesis of L-phenylglycine

4.6.1. (*S*)-2-Hydroxyamino-*N*-methyl-2-phenyl-acetamide hydrochloride (*S*)-5·HCl

In a 10 mL microwave vial were introduced hydroxylamine (+)-**2b** (743 mg, 3 mmol), a 12 M aqueous solution of hydrochloric acid

(1.25 mL, 15 mmol) and ethanol (5 mL). The reaction mixture was heated for 5 min at 130 °C under microwave irradiation. Removal of the solvents under reduced pressure yielded (*S*)-**5**·HCl (yellow oil, quantitative). δ_H (400 MHz; CD_3OD) 7.58–7.56 (2H, m), 7.50–7.48 (3H, m), 5.05 (1H, s), 2.77 (3H, s); δ_C (100 MHz; CD_3OD) 167.7, 131.5, 130.5, 130.3, 130.1, 58.5, 26.5; LRMS (ESI^+) *m/z*: 148.0 (71), 163.0 (97, $(M+H-H_2O)^+$), 181.0 (100, $(M+H)^+$), 203.0 (51, $(M+Na)^+$).

4.6.2. (*S*)-2-Amino-*N*-methyl-2-phenyl-acetamide hydrochloride (*S*)-6·HCl

The above crude hydrochloride salt of *N*-hydroxy amino amide (*S*)-**5**·HCl was taken up in methanol (7 mL). A 12 M aqueous solution of HCl (370 μL, 4.5 mmol) and Pd/C 10% (200 mg) were added. The reaction mixture was stirred under an atmospheric pressure of H_2 at room temperature for 16 h, then filtered through Celite and concentrated to give (*S*)-**6**·HCl (yellow oil, quantitative). Peaks corresponding to two rotamers were distinguishable in the NMR spectra. δ_H (400 MHz; CD_3OD) 7.51–7.46 (5H, m), 4.92 (1H, s), 2.76 and 2.75 (3H, s); δ_C (100 MHz; CD_3OD) 169.3, 134.5, 130.9, 130.3, 129.1, 57.8 and 57.6, 26.6 and 26.5; LRMS (ESI^+) *m/z*: 148.0 (36, $(M+H-NH_3)^+$), 165.1 (100, $(M+H)^+$), 187.0 (42, $(M+Na)^+$), 351.2 (9, $(2M+Na)^+$). The enantiomeric purity of the free amino amide (>98%) was determined by ^1H NMR analysis ($CDCl_3$, 400 MHz) of **6** with (*S*)-(+)-*O*-acetylmandelic acid as a chiral solvating agent;[22] the separation between the two *N*-methyl signals was 0.05 ppm [upfield signal for the (*S*)-enantiomer].

4.6.3. (*S*)-Amino-phenyl-acetic acid (L-phenylglycine) L-7

In a 10 mL microwave vial were introduced the hydrochloride salt of the amino amide (*S*)-**6**·HCl (138 mg, 688 μmol) and a 6 M aqueous solution of hydrochloric acid (1 mL). The reaction mixture was heated for 10 min at 150 °C under microwave irradiation. After concentration of the reaction mixture, the crude hydrochloride salt of amino acid was adsorbed onto a DOWEX 50W-X8 ion-exchange column. After washing with H_2O and then ethanol until neutrality, elution with a 1 M aqueous solution of NH_4OH and concentration under vacuum gave the free amino acid L-**7** (98 mg, 649 μmol, 94% yield) as a white solid. IR (ATR): 3114, 2980, 2800, 1606, 1577, 1495, 1391; δ_H (400 MHz; 1 N LiOD in D_2O) 7.39–7.29 (5H, m), 4.32 (1H, s); δ_C (100 MHz; 1 N LiOD in D_2O) 178.9, 139.8, 129.0, 127.2, 128.1, 60.0; LRMS (ESI^+) *m/z*: 135.0 (63, $(M+H-NH_3)^+$), 152.0 (100, $(M+H)^+$); HRMS (ESI^+) *m/z*: found, 152.07048 (M+H); $C_8H_{10}NO_2$ requires 152.07061. The enantiomeric purity of the amino acid L-**7** (60%) was determined by chiral HPLC on a Chirex 3126 (D)-penicillamine column, 150 × 4.6 mm, eluent methanol/2 mM $CuSO_4$ in water—20:80, 1 mL/min, retention times: 11.05 min for the (*S*)-enantiomer and 19.18 min for the (*R*)-enantiomer.

Acknowledgments

The authors thank Beatrice Gennaro for her assistance in NMR and Emilien Demory for his support. We are grateful to Université Joseph Fourier and the CNRS for financial support.

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