PERKIN 1

The bisected s-*trans* conformation-controlled highly stereoselective addition of Grignard reagents to *C*-cyclopropylaldonitrone. An efficient synthesis of 1-phenyl-2-[(*S*)-1-aminoalkyl]-*N*,*N*-diethylcyclopropanecarboxamides, a new class of potent NMDA receptor antagonists

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An efficient synthesis of 1-phenyl-2-[(*S*)-1-aminoethyl]- and 1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamides [**1a** (PEDC) and **1b** (PPDC), respectively], potent NMDA receptor antagonists having a cyclopropane structure, was achieved. We have shown for the first time that *C*-cyclopropylaldonitrone preferentially exists in the bisected s-*trans* conformation, due to the characteristic stereoelectronic effects of the cyclopropane ring, by X-ray crystallographic analysis, NMR studies, and theoretical calculations. Based on these findings, the highly stereoselective addition reaction of Grignard reagents to *C*-cyclopropylaldonitrone **6** was developed, and the reaction was successfully used as the key step for the preparation of the NMDA receptor antagonists **1a** and **1b** as well as for a newly designed isopropyl-type congener **1c**. The facial selectivity of the addition of Grignard reagents can be explained by the attack of the reagents from the less hindered side of the substrate in the predicted bisected s-*trans* conformation. This Grignard reaction is the first example of a highly stereoselective addition to a nitrone *via* a non-chelation controlled pathway.

Introduction

Stereoselective preparation of biologically important cyclopropane derivatives is of great interest.[1] It is known that compounds with a cyclopropane adjacent to an unsaturated bond, such as vinylcyclopropanes, cyclopropyl ketones, and cyclopropylcarbaldehydes, preferentially exist in the bisected s-*trans* conformer (**I**) or s-*cis* conformer (**II**), due to the characteristic stereoelectronic effects of the cyclopropane ring, as shown in Fig. 1a.[1a,2] We have previously shown that nucleophilic attack of organometallic reagents on the carbonyl groups adjacent to cyclopropane occurs highly stereoselectively *via* the bisected conformation.[3] Highly stereoselective hydride reductions of cyclopropyl ketones[3,4] and hydroboration of cyclopropyl alkenes,[5] which are also likely to occur *via* the bisected conformations, have also been reported. These reactions are very useful for the stereoselective synthesis of functionalized cyclopropanes. In this report, we describe the highly stereoselective addition of Grignard reagents to a *C*-cyclopropylaldonitrone *via* its bisected s-*trans* conformer **III**, as shown in Fig. 1b.

In recent years, we have been working to develop novel effective antagonists of the NMDA (*N*-methyl-D-aspartic acid) receptor,[6] which are expected to be new therapeutic agents for epilepsy, stroke, or ischaemia.[7] During our studies, we found 1-phenyl-2-[(*S*)-1-aminoethyl]- and 1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamides [**1a** (PEDC) and **1b** (PPDC), respectively] to be a new class of potent noncompetitive NMDA receptor antagonists,[6] which selectively inhibited the function of the NMDA receptor expressed by *Xenopus* oocytes.[6d] However, an alternative method for the synthesis of **1a** and **1b** was needed for their further biological evaluation. In the previous synthesis, shown in Scheme 1,[3b] the use of an excess of the explosive and toxic NaN_3[8] was unsuitable for the large scale preparation of the compounds; this also has the disadvantage of limiting the alkyl groups that could be introduced at the 1′-position, which was undesirable for the planned structure–activity relationship study.

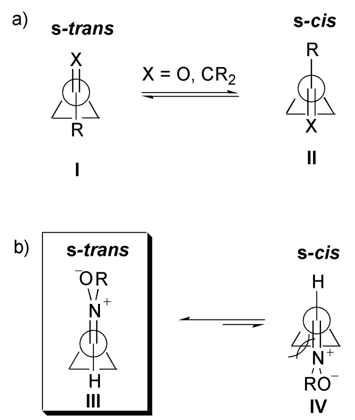

Fig. 1

The chelation-controlled stereoselective addition of organometallic reagents to nitrones has been extensively studied,[9] especially by Merino, Dondoni and co-workers, because of its usefulness in the preparation of a variety of asymmetric amines. In these reactions, the facially selective additions were attributed to chelation between the nitrone oxygen and another oxygen near to the imino group in the substrates, which are shown in Fig. 2.[9b] We planned to develop a stereoselective addition reaction to aldonitrones adjacent to a cyclopropane ring *via* a non-chelation controlled pathway. We hypothesized that *C*-cyclopropylnitrones should preferentially exist in the bisected conformations, due to the stereoelectronic interaction between the imino moiety and the cyclopropane ring, as in cyclopropyl-

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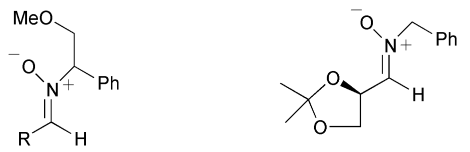
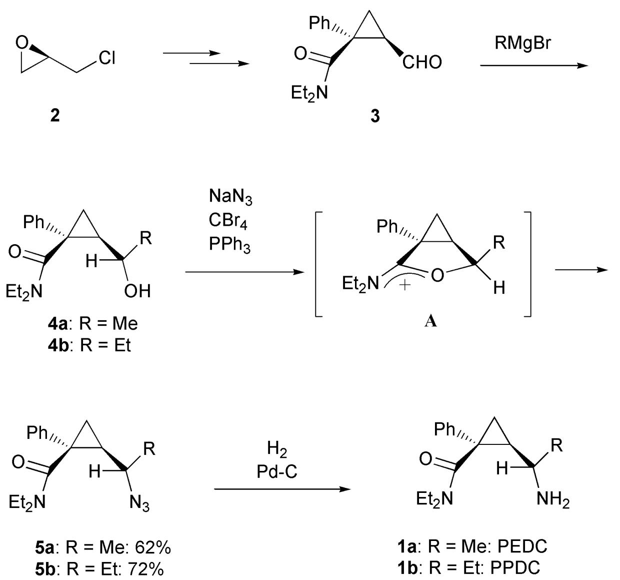


Fig. 2



Scheme 1

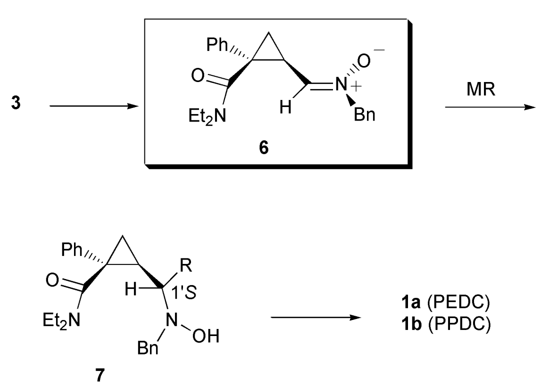
carbonyl compounds and cyclopropyl alkenes; the s-*trans* conformer **III** should predominate, due to the steric repulsion between the nitrone moiety and the cyclopropane ring in the s-*cis* conformation **IV**, as shown in Fig. 1b. If this was indeed the case, stereoselective nucleophilic addition to *C*-cyclopropylnitrones from the less hindered face should occur as in the cyclopropylcarbonyl compounds described above. Thus, we investigated whether the nucleophilic addition of organometallic reagents to the *C*-cyclopropylnitrone **6** would give the desired 1′*S*-product **7**, as shown in Scheme 2. Subsequent deprotection should give the target NMDA receptor antagonists **1a** and **1b**.[10]

Results

Conformation of *C*-cyclopropylnitrone

Treatment of the asymmetric cyclopropylcarbaldehyde **3**,[3b] which was prepared from (−)-epichlorohydrin (**2**), with *N*-benzylhydroxylamine hydrochloride in CH_2Cl_2 gave the *N*-benzyl-*C*-cyclopropylaldonitrone **6** (Scheme 2), the substrate for the reaction with organometallic reagents, in 93% yield.

We wanted to determine whether the bisected s-*trans* conformation would predominate in the nitrone **6** as expected,



Scheme 2

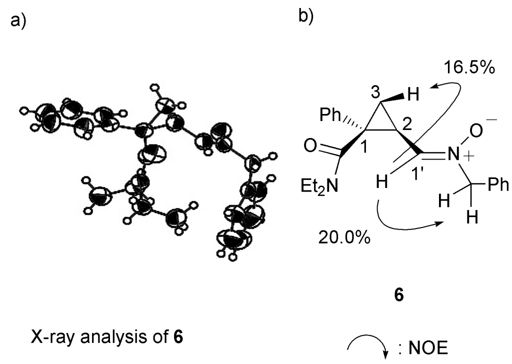


Fig. 3

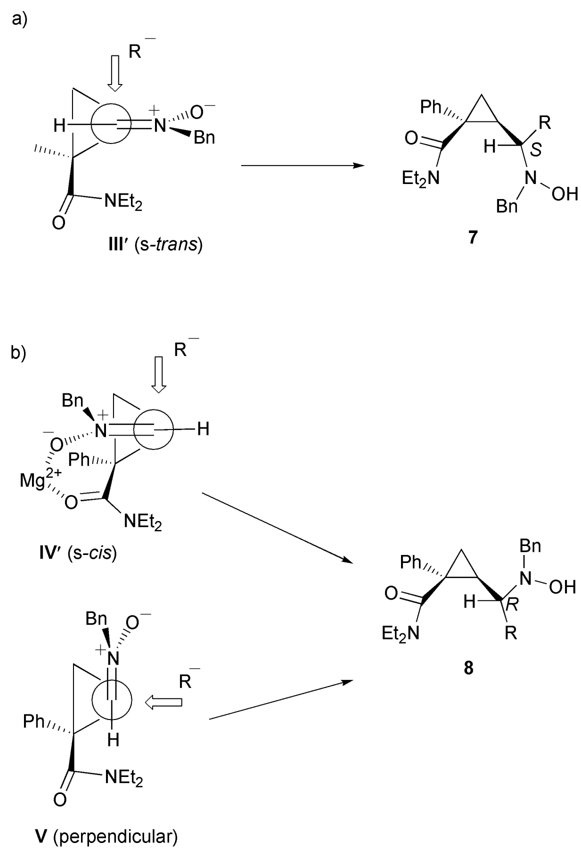


Fig. 4

since no study on the conformation of *C*-cyclopropylnitrones has been reported.

Fig. 3a shows the X-ray crystallographic structure of the nitrone **6**, clearly demonstrating that it exists in the bisected s-*trans* conformation in the solid state. In order to investigate its conformation in solution, NOE experiments on **6** in $CDCl_3$ were also performed. When 1′-H was irradiated, a very strong NOE was observed at 3-H, which was in the position *cis* to the nitrone moiety, of the cyclopropane ring (16.5%), as shown in Fig. 3b. This NOE study suggests that the molecule would be rigidly restricted in the bisected s-*trans* conformation even in solution. As far as we know, these are the first results demonstrating that *C*-cyclopropylnitrone prefers the bisected conformation. In the irradiation of 1′-H, a NOE at the benzyl methylene proton (20.0%) was also observed, which indicated the *Z*-nitrone configuration.

The highly stereoselective addition of Grignard reagents to the nitrone 6

Based on this conformational analysis, we next investigated the addition of organometallic reagents to the *C*-cyclopropylnitrone **6**. If nucleophilic addition to **6** in the bisected s-*trans*

Table 1 The addition reactions of organometallic reagents to *C*-cyclopropylnitrone **6**

Entry	Reagent (equiv.)	Solvent	Temp./°C	Time/h	Additive (equiv.)	Yield (**7** + **8**) (%)	Ratio(**7** : **8**)[a]
1	MeLi (5)	THF	−78	2	—	Trace[b]	
2	Me_2Zn (5)	THF	−78	2	—	Trace[b]	
3	Me_3Al (5)	CH_2Cl_2	−78	2	—	Trace[b]	
4	MeMgBr (5)	THF	−78	2	—	45	95 : 5
5	MeMgBr (5)	THF	0	2	—	53	82 : 18
6	MeMgBr (5)	THF	rt	2	—	56	74 : 26
7	MeMgBr (5)	THF	−78	8	—	56	94 : 6
8	MeMgBr (5)	Et_2O–THF[c]	−78	8	—	83	94 : 6
9	MeMgBr (3)	Et_2O–THF[c]	−78	8	—	63	90 : 10
10	MeMgBr (3)	Et_2O–THF[c]	−78	8	HMPA (5)	32	83 : 17
11	MeMgBr (3)	Et_2O–THF[c]	−78	8	TMSCl (2)	88	86 : 14
12	MeMgBr (3)	Et_2O–THF[c]	−78	8	$ZnBr_2$ (2)	62	87 : 13
13	MeMgBr (3)	Et_2O–THF[c]	−78	8	$MgBr_2$ (2)	81	98 : 2
14	MeMgBr (2)	Et_2O–THF[c]	−78	8	$MgBr_2$ (2)	62	90 : 10
15	EtMgBr (3)	Et_2O–THF[c]	−78	8	$MgBr_2$ (2)	80	**7b** only
16	i-PrMgCl (5)	Et_2O–THF[c]	−78	8	$MgBr_2$ (2)	77	**7c** only

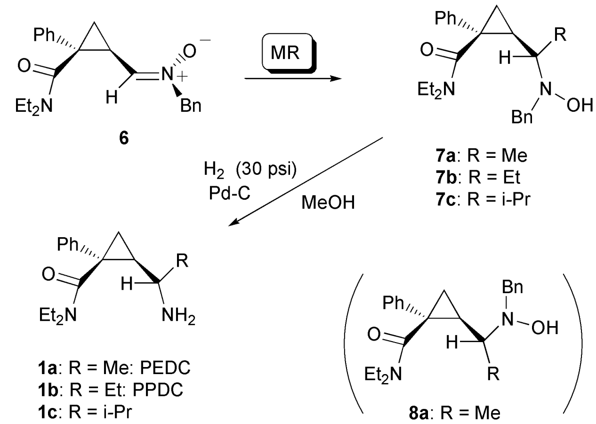
[a] Determined by ^{1}H NMR. [b] The starting material **6** was recovered almost quantitatively. [c] Et_2O–THF (2 : 1).

conformation (**III′**) occurs from the less hindered face, the desired 1′*S*-product **7** should be selectively produced, as shown in Fig. 4a. The results are summarized in Table 1. The addition was first examined by treating **6** with several organometallic reagents (5 equiv.), *i.e.*, MeLi, Me_2Zn, Me_3Al, and MeMgBr, at −78 °C for 2 h (entries 1–4). When MeLi, Me_2Zn, or Me_3Al was used, the addition reaction hardly proceeded and nearly all the nitrone **6** was recovered. Only the reaction with the Grignard reagent (entry 4) gave addition products in which the desired 1′*S* product **7a** was produced with high stereoselectivity ($R : S = 5 : 95$), although the yield was unsatisfactory (45%). The stereochemistry was confirmed by the conversion of **7a** into the final product PEDC (**1a**), as described below. Based on these results, further reactions were investigated with Grignard reagents. Higher temperatures increased the yield slightly, but the stereoselectivity decreased (entries 5 and 6). When the reaction was carried out at −78 °C for 8 h with Et_2O–THF (2 : 1)[11] as the solvent, it gave the addition products in 83% yield with high stereoselectivity (entry 8, $R : S = 6 : 94$), whereas a similar reaction in THF alone gave only a moderate yield (entry 7). We next investigated the effect of additives on the reaction with 3 equiv. of MeMgBr in Et_2O–THF (entries 9–13). Addition of HMPA, $ZnBr_2$, or TMSCl (entries 10–12) did not improve the yield or the stereoselectivity compared to the reaction without an additive (entry 9). The best result was obtained when the reaction was performed with $MgBr_2$[9a,b] as an additive (entry 13, 81%, $R : S = 2 : 98$). A similar reaction with 2 equiv. of MeMgBr lowered both the yield and the stereoselectivity (entry 14). The reaction with EtMgBr instead of MeMgBr under conditions identical to those in entry 13 was also successful and gave the desired 1′*S*-ethyl product **7b** as the sole product in 80% yield (entry 15).

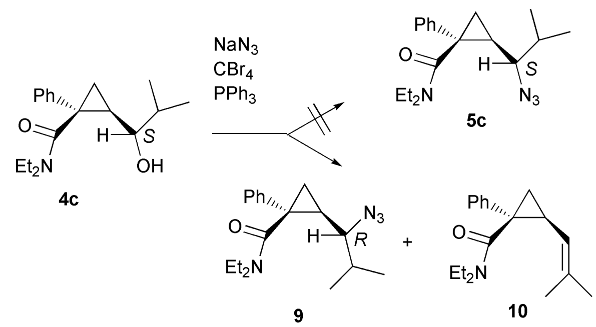
Thus, a highly stereoselective addition reaction to the nitrone **6** has been developed. The *N*-benzyl and *N*-hydroxy groups of the 1′*S*-products **7a** and **7b** were readily removed by hydrogenation with Pd–C in MeOH to give the targets **1a** and **1b** in 98% and 93% yield, respectively. Thus, the overall yields were clearly increased compared with those by the previous method.

Synthesis of the isopropyl-type congener

For the structure–activity relationship study, we needed to synthesize the isopropyl-type congener **1c** (Scheme 3). The compound could not be obtained by the previous procedure, since the stereoselective introduction of an azide group *via* the neighboring group-participation intermediate **A** proved unsuccessful as shown in Scheme 4. When compound **4c**, which was easily prepared by the Grignard reaction of aldehyde **3** with i-PrMgCl,[6b] was treated with NaN_3–CBr_4–Ph_3P in DMF, only the undesired 1′*R*-azide **9**[12] (26%) and the elimination



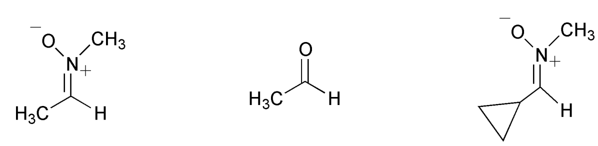
Scheme 3



Scheme 4

product **10** (31%) were produced and none of the desired 1′*S*-azide **5c**. This result is likely due to steric hindrance around the 1′-position.

Therefore we next applied the nitrone method to the synthesis of **1c**. When the *C*-cyclopropylnitrone **6** was treated with i-PrMgCl in the presence of $MgBr_2$ in Et_2O-THF at −78 °C, the desired 1′*S*-product **7c** was successfully obtained in 77% yield as the sole product (Scheme 3, entry 16 in Table 1). The usual reductive treatment of compound **7c** readily gave the target compound **1c**.



11 **12** **13**

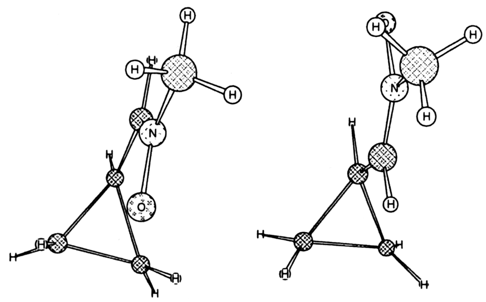


Fig. 5 Minimum energy conformers of the cyclopropylcarbaldonitrile **13**.

Discussion

This study suggests that the reaction pathway of nucleophilic addition to a *C*-cyclopropylnitrone probably occurs *via* the predominant bisected conformation, which can be predicted from stereoelectronic and steric effects. The facial selectivity of the addition of the Grignard reagents can be explained as an attack occurring from the less hindered face (*Si*-face) at the imino carbon of **6**, in the bisected s-*trans* conformation **III′**, to give the desired 1′*S*-product **7** highly stereoselectively, as shown in Fig. 4a. If the reaction proceeded *via* the chelated s-*cis* conformer **IV′** or the perpendicular conformer **V**, the addition reactions are likely to mainly occur from the less hindered *Re*-face and should give the 1′*R*-diastereomer **8** as the major product (Fig. 4b).

When *C*-cyclopropylnitrone exists as the bisected conformer, the orbitals of the cyclopropane ring would effectively interact with the adjacent π* (C=N) orbital. Calculations of the orbital energy of π* (C=N) in acetaldonitrone **11** and of π* (C=O) in acetaldehyde **11** by the PM3 method[13] showed that the energy of π* (LUMO) for the C=N orbital in **11** was 0.3754 eV, which was significantly lower than that for the C=O orbital in **12** (0.8226 eV). These results suggest that the bisected conformation should be very stable in *C*-cyclopropylnitrones. This was further confirmed by the *ab initio* calculation (RHF/3-21G* level)[13] on the *C*-cyclopropylnitrone **13**; only two minimum energy conformers, which were in the s-*cis* and s-*trans* bisected conformations as shown in Fig. 5, were found by this calculation, and the s-*trans* conformer was 2.74 kcal mol^{-1} more stable than the corresponding s-*cis* one.[14] Thus, these theoretical calculations support the above experimental results showing that the *C*-cyclopropylnitrone preferentially exists in the bisected s-*trans* conformation.

In the course of the nucleophilic addition, the electrons of the cyclopropane ring, which can be characterized as strong π-donors,[1a] interact with the antibonding orbital of the incipient bond between the nucleophile and the imino carbon of the nitrone. The nucleophilic addition can be facilitated by this interaction,[15] which is maximized when the nitrone is in the bisected conformation. This interaction would increase significantly when Mg^{2+} is coordinated to the nitrone oxygen. As a result, the reaction should proceed highly stereoselectively, especially in the presence of $MgBr_2$ as an additive.

Conclusion

We have shown for the first time that *C*-cyclopropylaldonitrone preferentially exists in the bisected s-*trans* conformation, due to the characteristic stereoelectronic effects of the cyclopropane ring, by X-ray crystallographic analysis, NMR studies, and theoretical calculations. The highly stereoselective addition reaction of Grignard reagents to the *C*-cyclopropylnitrone **6** was developed, which was used as the key step for the preparation of the potent NMDA receptor antagonists PEDC (**1a**) and PPDC (**1b**) as well as a newly designed isopropyl-type congener **1c**. The facial selectivity of the addition can be explained by the attack of the reagent from the less hindered side of the substrate in the bisected s-*trans* conformation. This Grignard reaction may be the first example of a highly stereoselective addition to nitrones *via* a non-chelation controlled pathway.[16]

Experimental

Mps were measured on a Yanagimoto MP-3 micro-melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 500 MHz (^{1}H), and at 125 MHz (^{13}C). Chemical shifts are reported in ppm downfield from TMS. The ^{1}H NMR assignments reported were in agreement with COSY spectra. Mass spectra were obtained by the electron impact ionization (EI) method. Thin-layer chromatography was done on a Merck coated plate $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

N-[(1*R*,2*S*)-2-(*N*,*N*-Diethylcarbamoyl)-2-phenylcyclopropylmethylene]benzylamine *N*-oxide (6)

A mixture of *N*-benzylhydroxylamine hydrochloride (1.53 g, 9.60 mmol), molecular sieves 4 Å (2 g), and **3** (1.96 g, 8.00 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 1 h. The resulting mixture was evaporated, and the residue was partitioned between AcOEt (100 ml) and H_2O (50 ml). The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$–MeOH 20 : 1) to give **6** (2.60 g, 93%) as white crystals, mp 115–116 °C (hexane–AcOEt); $[\alpha]_D^{23}$ −37.6 (*c* 1.12, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.37 (3 H, t, -NCH_2CH_3, $J = 7.1$ Hz), 1.01 (3 H, t, -NCH_2CH_3, $J = 7.1$ Hz), 1.34 (1 H, dd, H-3a, $J_{3a,3b} = 5.0$, $J_{3a,2} = 9.0$ Hz), 1.95 (1 H, dd, H-3b, $J_{3b,3a} = 5.0$, $J_{3b,2} = 5.8$ Hz), 2.67 (1 H, m, -NCH_2CH_3), 3.19 (1 H, m, -NCH_2CH_3), 3.25 (1 H, m, -NCH_2CH_3), 3.36–3.47 (2 H, m, -NCH_2CH_3 and H-2), 4.86 (2 H, s, -CH_2Ph), 6.48 (1 H, d, H-1′, $J_{1',2} = 8.4$ Hz), 7.20–7.44 (10 H, m, aromatic); NOE (400 MHz, $CDCl_3$) 20.0% (H-1′→-CH_2Ph), 16.5% (H-1′→H-3b); ^{13}C-NMR (125 MHz, $CDCl_3$) 11.99, 12.31, 21.65, 21.87, 38.11, 39.84, 41.61, 68.95, 126.27, 126.87, 128.07, 128.18, 128.60, 128.77, 129.18, 129.71, 132.60, 137.85, 138.71, 168.63; HR-MS (EI) 350.1979 (M^+, $C_{22}H_{26}N_2O_2$ requires 350.1994). Found: C, 75.19; H, 9.79; N, 4.46. $C_{22}H_{26}N_2O_2$ requires C, 75.40; H, 7.48; N, 7.99%.

General procedure for the addition of an organometallic reagent to nitrone 6 (Table 1)

A mixture of nitrone **6** (70 mg, 0.20 mmol) and an additive (2 equiv.) ($MgBr_2$ was insoluble and the others were soluble in the solvent used) in a solvent (3 ml) was stirred at room temperature for 30 min. The mixture was cooled to the temperature indicated in Table 1, and then a solution of an organometallic reagent (Grignard reagents, 1.0 M in Et_2O; MeLi, 1.0 M in Et_2O; Me_2Zn, 1.0 M in hexane; Me_3Al, 1.1 M in hexane). The mixture was stirred for 2–8 h at the same temperature, and then saturated NH_4Cl was added. The mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt–hexane 1 : 4) to give the product.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-(*N*-benzyl-*N*-hydroxyamino)ethyl]-*N*,*N*-diethylcyclopropanecarboxamide (7a)

Mp 135–136 °C (hexane–AcOEt); $[\alpha]_D^{23}$ −115.3 (*c* 1.090, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.69 (3 H, t, $J = 6.4$ Hz), 1.11 (3 H, t, $J = 7.0$ Hz), 1.12 (1 H, br s), 1.29 (3 H, d, $J = 6.3$ Hz), 1.49 (1 H, br s), 1.72 (1 H, br s), 2.68 (1 H, m), 3.21 (1 H, m), 3.30 (1 H, m), 3.39 (1 H, m), 3.57 (1 H, m), 3.67 (1 H, d, J = 13.5 Hz), 4.13 (1 H, d, J = 13.5 Hz), 7.16 (1 H, m), 7.21–7.25 (5 H, m), 7.30 (2 H, t, J = 7.5 Hz), 7.40 (2 H, d, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) 12.48, 12.64, 16.81 (C-3), 22.62, 31.55, 35.01, 39.91, 42.37, 62.74, 63.53, 126.14, 126.47, 126.80, 128.09, 128.56, 129.33, 138.71, 140.46, 171.64; HR-MS (EI) 366.2317 (M^+, $C_{23}H_{30}N_2O_2$ requires 366.2307). Found: C, 75.19; H, 9.79; N, 4.46. $C_{23}H_{30}N_2O_2$ requires C, 75.37; H, 8.25; N, 7.64%.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-(*N*-benzyl-*N*-hydroxyamino)ethyl]-*N*,*N*-diethylcyclopropanecarboxamide (8a)

Obtained as a solid; ^{1}H-NMR (500 MHz, $CDCl_3$) 0.55 (3 H, t, J = 7.3 Hz), 1.11 (3 H, t, J = 7.3 Hz), 1.24 (1 H, dd, J = 4.3, 9.2 Hz), 1.41 (3 H, d, J = 6.6 Hz), 1.64–1.79 (2 H, m), 2.67 (1 H, m), 2.98–3.23 (2 H, m), 3.37 (1 H, m), 3.52 (1 H, m), 3.82 (1 H, d, J = 13.2 Hz), 3.89 (1 H, d, J = 13.2 Hz), 7.17–7.31 (10 H, m); HR-MS (EI) 366.2297 (M^+, $C_{23}H_{30}N_2O_2$ requires 366.2307).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-(*N*-benzyl-*N*-hydroxyamino)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (7b)

Mp 146–147 °C (hexane–AcOEt); $[\alpha]_D^{23}$ −123.2 (c 1.11, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.53 (3 H, t, J = 7.0 Hz), 1.05–1.09 (6 H, m), 1.32 (1 H, dd, J = 5.6, 8.9 Hz), 1.75–1.92 (4 H, m), 2.64 (1 H, m), 3.03 (1 H, m), 3.13 (1 H, m), 3.46–3.58 (2 H, m), 3.89 (1 H, d, J = 13.5 Hz), 4.09 (1 H, d, J = 13.5 Hz), 4.72 (1 H, br s), 7.18–7.38 (10 H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) 11.34, 12.16, 12.26, 20.89, 24.96, 27.42, 32.71, 39.56, 42.16, 60.65, 67.23, 126.26, 126.73, 126.93, 128.18, 128.59, 129.00, 139.39, 142.20, 170.21; HR-MS (EI) 380.2439 (M^+, $C_{24}H_{32}N_2O_2$ requires 380.2464). Found: C, 75.19; H, 9.79; N, 4.46. $C_{24}H_{32}N_2O_2$ requires C, 75.75; H, 8.48; N, 7.36%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-(*N*-benzyl-*N*-hydroxyamino)-2-methylpropyl]-*N*,*N*-diethylcyclopropanecarboxamide (7c)

Mp 78–80 °C (hexane–AcOEt); $[\alpha]_D^{23}$ −55.7 (c 0.65, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.55 (3 H, t, J = 7.0 Hz), 1.06–1.09 (6 H, m), 1.16 (3 H, d, J = 6.9 Hz), 1.45 (1 H, dd, J = 4.1, 8.7 Hz), 1.89–2.01 (3 H, m), 2.81 (1 H, dd, H-1′, J = 5.2, 9.1 Hz), 3.02 (1 H, m), 3.13 (1 H, m), 3.46–3.55 (2 H, m), 3.92 (1 H, d, J = 13.6 Hz), 4.15 (1 H, d, J = 13.6 Hz), 4.54 (1 H, br s), 7.18–7.40 (10 H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) 12.16, 12.21, 19.37, 20.28, 20.85, 26.70, 31.95, 32.39, 39.49, 42.00, 61.74, 69.74, 126.24, 126.54, 126.92, 128.18, 128.62, 129.02, 139.55, 142.23, 170.32; HR-MS (EI) 394.2612 (M^+, $C_{25}H_{34}N_2O_2$ requires 394.2620). Found: C, 76.02; H, 8.63; N, 7.12. $C_{25}H_{34}N_2O_2$ requires C, 76.10; H, 8.69; N, 7.10%.

General procedure for reduction of *N*-benzylhydroxyamines 7

A mixture of hydroxylamine **7a**–**c** (1.0 mmol) and 10% Pd on carbon (50 mg) in MeOH (15 ml) was shaken under H_2 at 30 psi for 3 days. The mixture was filtered through a pad of Celite, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; AcOEt–hexane 1 : 1, then $CHCl_3$–MeOH 9 : 1) to give the free amine of **1** as an oil. The oil was dissolved in MeOH, which was applied to a column of Diaion WA-30 resin (Cl^- form), and the column was eluted with MeOH. The solvent was evaporated, and the residue was treated with Et_2O to give white crystals of **1a**–**c** as a hydrochloride (**1a** 98%, **1b** 93%, **1c** 71%). The ^{1}H and ^{13}C NMR spectra of **1a** and **1b** were identical with those of the compounds previously synthesized by us.[3b]

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-2-methylpropyl]-*N*,*N*-diethylcyclopropanecarboxamide (1c) hydrochloride

Mp 83–84 °C (Et_2O); $[\alpha]_D^{21}$ +105.7 (c 0.90, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) 0.57 (3 H, t, J = 7.0 Hz), 1.00–1.11 (9 H, m), 1.26 (1 H, dd, H-3a, J = 4.7, 6.0 Hz), 1.38 (1 H, ddd, H-2, J = 6.0, 8.6, 8.6 Hz), 1.65 (1 H, dd, J = 4.7, 8.6 Hz), 1.73 (1 H, m), 2.72 (1 H, m), 3.08 (1 H, m), 3.15 (1 H, m), 3.47–3.56 (2 H, m), 7.18–7.33 (5 H, m); ^{13}C-NMR (125 MHz, CD_3OD) 12.26, 12.35, 18.99, 20.22, 31.69, 32.51, 34.89, 39.40, 41.95, 59.74, 126.36, 128.33, 128.65, 136.17, 170.00; HR-MS (EI) 288.2193 (M^+, $C_{17}H_{26}N_2O$ requires 288.2193). Found: C, 59.78; H, 9.21; Cl, 9.72; N, 7.73. $C_{17}H_{27}ClN_2O{\cdot}H_2O$ requires C, 59.90; H, 9.22; Cl, 9.82; N, 7.76%.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-azido-2-methylpropyl]-*N*,*N*-diethylcyclopropanecarboxamide (9) and (1*S*, 2*R*)-1-phenyl-2-(2-methylprop-1-enyl)-*N*,*N*-diethylcyclopropanecarboxamide (10)

A mixture of **4c** (868 mg, 3.00 mmol), PPh_3 (2.36 g, 9.00 mmol), and CBr_4 (2.98 g, 9.00 mmol) in DMF (20 ml) was stirred at 0 °C for 30 min. To the resulting mixture was added NaN_3 (1.95 g, 30.0 mmol), and then the whole was stirred at room temperature for 5 h. After addition of AcOEt and H_2O, the organic layer was separated, washed with brine, dried (Na_2SO_4), evaporated, and purified by flash column chromatography (silica gel; AcOEt–hexane 1 : 9) to give **9** (248 mg, 26%) as white crystals and **10** (251 mg, 31%) as an oil, respectively. Carboxamide **9**: mp (hexane–AcOEt) 89–90 °C; $[\alpha]_D^{23}$ −68.7 (c 1.14, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.71 (3 H, t, J = 7.1 Hz), 1.00 (3 H, d, J = 6.8 Hz), 1.03 (3 H, d, J = 6.8 Hz), 1.11 (3 H, t, J = 7.1 Hz), 1.48 (1 H, dd, J = 4.5, 8.5 Hz), 1.61 (1 H, dd, J = 4.5, 6.0 Hz), 1.63 (1 H, ddd, J = 6.0, 8.5, 8.5 Hz), 2.12 (1 H, m), 3.17 (1 H, m), 3.24 (1 H, m), 3.45–3.53 (3 H, m), 7.20–7.32 (5 H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) 12.37, 12.68, 16.57, 17.71, 20.37, 29.77, 33.10, 33.30, 39.43, 41.88, 68.00, 126.15, 126.64, 128.76, 140.79, 169.30; HR-MS (EI) 314.2096 (M^+, $C_{18}H_{26}N_4O$ requires 314.2107). Found: C, 68.78; H, 8.28; N, 17.57. $C_{18}H_{26}N_4O$ requires C, 68.76; H, 8.33; N, 17.82%. Carboxamide **9**: $[\alpha]_D^{22}$ −177.6 (c 2.34, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.56 (3 H, t, J = 7.1 Hz), 1.07 (1 H, dd, J = 4.7, 9.0 Hz), 1.08 (3 H, t, J = 7.1 Hz), 1.70 (3 H, s), 1.72 (1 H, dd, J = 4.7, 6.0 Hz), 1.83 (3 H, s), 2.64 (1 H, ddd, J = 6.0, 9.0, 9.6 Hz), 2.99 (1 H, m), 3.14 (1 H, m), 3.37 (1 H, m), 3.60 (1 H, m), 4.71 (1 H, d, J = 9.6 Hz), 7.19–7.30 (5 H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) 12.04, 12.39, 18.18, 23.46, 24.13, 25.51, 36.66, 38.80, 40.92, 123.03, 125.83, 126.23, 128.58, 133.99, 141.24, 170.16; HR-MS (EI) 271.1937 (M^+, $C_{18}H_{25}NO$ requires 271.1936).

X-Ray crystallogaraphic data of 6 †

$C_{22}H_{26}N_2O_2$, M = 340.45, orthorhombic, $P2_12_12_1$, a = 10.093 (2), b = 19.840 (4), c = 9.895 (2) Å, V = 1981.4 (7) Å^3, Z = 4, D_x = 11.175 Mg cm^{-1}. Cell parameters were determined and refined from 26 reflections in the range 28.3° < θ < 29.9°. A colorless crystal (0.30 × 0.25 × 0.11 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å). Data collection using the $\omega/2\theta$ scan technique gave 3490 reflections at room temperature, 3340 unique, of which 2928 with $I > 3.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption or the extinction effect. The structure was solved by direct methods and refined by the full-matrix least squares technique (Crystan-GM system[17] as the computer program and SIR92[18] as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. The unweighted and weighted values (with a weighting scheme $W = \exp(15\sin^2\theta/\lambda^2)/\sigma^2(F_o)$) were 0.050 and 0.065, respectively. There was no peak above 0.13 e Å^{-3} in the last Fourier-difference map.

† CCDC reference number 207/507.

Computations

All calculations were performed with the Gaussian 98 program. The energy of π* was calculated by the PM-3 method. Preoptimization of **12** was performed at the RHF/STO-3G level to find two minimum energy conformers, and their final optimizations and single point energy calculations were performed at the RHF/3-21G* level.

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References

1 (*a*) H. N. C. Wong, M.-Y. Hon, C.-Y. Tse and Y.-C. Yip, *Chem. Rev.*, 1989, **89**, 165; (*b*) S. H. Stammer, *Tetrahedron*, 1990, **46**, 2231; (*c*) M. P. Doyle and M. N. Protopopova, *Tetrahedron*, 1998, **54**, 7919.
2 (*a*) J. K. Gerasimos and J. Nelsom, *J. Am. Chem. Soc.*, 1965, **87**, 2864; (*b*) J. L. Pierre and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1966, 1690; (*c*) L. S. Bartell, J. P. Guillory and A. T. Parks, *J. Phys. Chem.*, 1965, **69**, 3043; (*d*) L. S. Bartell and J. P. Guillory, *J. Phys. Chem.*, 1965, **43**, 647; (*e*) J. Bordner, L. A. Jones and R. L. Johnson, *Cryst. Struct. Commun.*, 1972, **1**, 389; (*f*) C. N. A. Lute and C. H. Stam, *Recl. Trav. Chim. Pays-Bas*, 1976, **95**, 130; (*g*) R. Roques, F. Crasnier, J. P. Declercq, G. Germain, H. Cousse and G. Mouzin, *Acta Crystallogr., Sect. B*, 1982, **38**, 1375; (*h*) F. Crasnier, J. F. Labarre, H. Cousse, L. D. D'Hinterland and G. Mouzin, *Tetrahedron*, 1975, **31**, 825.
3 S. Ono, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 221; (*b*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama, H. Takada, K. Yamashita and A. Matsuda, *J. Org. Chem.*, 1996, **61**, 915.
4 (*a*) A. I. Meyers, J. L. Romine and S. A. Fleming, *J. Am. Chem. Soc.*, 1988, **110**, 7245; (*b*) M. Lautens and P. H. M. Delanghe, *J. Org. Chem.*, 1995, **60**, 2474; (*c*) T. Yokomatsu, T. Yamaghishi, K. Suemune, H. Abe, T. Kihara, S. Soeda, H. Shimeno and S. Shubuya, *Tetrahedron*, 2000, **56**, 7099.
5 J. Cossy, N. Blanchard, C. Hamel and C. Meyer, *J. Org. Chem.*, 1999, **64**, 2608.
6 (*a*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 641; (*b*) S. Shuto, S. Ono, Y. Hase, Y. Ueno, T. Noguchi, K. Yoshii and A. Matsuda, *J. Med. Chem.*, 1996, **39**, 4844; (*c*) S. Shuto, S. Ono, H. Imoto, K. Yoshii and A. Matsuda, *J. Med. Chem.*, 1998, **41**, 3507; (*d*) T. Noguchi, K. Ishii, H. Imoto, Y. Otubo, S. Shuto, S. Ono, A. Matsuda and K. Yoshii, *Synapse*, 1999, **31**, 87.
7 G. L. Collingridge and J. C. Watkins, *The NMDA Receptor*, IRL Press at Oxford University Press, Oxford, UK, 1994.
8 K. Turnbull, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley & Sons, Chichester, UK, 1995, vol. 7, pp. 4509–4512.
9 For examples see: (*a*) Y. Ukaji, T. Hatanaka, A. Ahmed and K. Inomata, *Chem. Lett.*, 1993, 1313; (*b*) A. Dondoni, S. Franco, F. Junquera, F. L. Merchan, P. Merino, T. Tejero and V. Bertolasi, *Chem. Eur. J.*, 1995, **1**, 505; (*c*) P. Merino, E. Castillo, F. L. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1997, **8**, 1725; (*d*) A. Dondoni, S. Franco, F. Junquera, F. L. Merchan, P. Merino and F. Tejero, *J. Org. Chem.*, 1997, **62**, 5497; (*e*) P. Merino, E. Castillo, S. Franco, F. L. Merchan and T. Tejero, *J. Org. Chem.*, 1998, **63**, 2371; (*f*) P. Merino, E. Castillo, S. Franco, F. L. Merchan and T. Tejero, *Tetrahedron*, 1998, **54**, 12301; (*g*) A. Dondoni and D. Perrone, *Aldrichimica Acta*, 1997, **30**, 35; (*h*) A. Dondomi, *Synthesis*, 1998, 1681.
10 A part of this study has been described in a communication: Y. Kazuta, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 2000, **41**, 5373.
11 Compound **6** was insoluble in Et_2O.
12 Hydrogenation of **8** with Pd–C gave the 1′-diastereomer of **1c**, which was synthesized *via* the nitrone **6.**
13 Calculations were performed with the Gaussian 98 program. Gaussian 98, Revision A. 6 : M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, O. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople Gaussian, Inc., Pittsburgh, PA, 1998.
14 The heat of formation: s-*trans* conformer, −321.9412253 hartree; s-*cis* conformer, −321.94559514 hartree.
15 The importance of the antibonding orbital in nucleophilic additions to unsaturated bonds has been recognized: (*a*) A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540; (*b*) A. S. Cieplak and B. D. Tait, *J. Am. Chem. Soc.*, 1989, **111**, 5875; (*c*) M. Satoh, M. Murakami, S. Sunami, C. Kaneko, T. Furuya and H. Kurihara, *J. Am. Chem. Soc.*, 1995, **117**, 4279.
16 Although addition of Grignard reagents to nitrones, the stereoselectivity of which could be explained by the Felkin–Anh model, has been reported, the stereoselectivity was not high: M. P. Cowling, P. R. Jenkins and K. Cooper, *J. Chem. Soc., Chem. Commun.*, 1988, 1503.
17 A computer program for the solution and refinement of crystal structures from X-ray diffraction data; Mac Science Co., Ltd., maXus (version 2.0).
18 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.