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Highly Stereoselective Grignard Addition to *Cis*-Substituted *C*-Cyclopropylaldonitrones. The Bisected *s-Trans* Transition State Can Be Stabilized Effectively by the Lewis Acid-Coordination

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We previously found that Grignard addition to a *C*-cyclopropylaldonitrone, *C*-[*cis*-2-(*N,N*-diethylcarbamoyl)-*trans*-2-phenylcyclopropyl]-*N*-benzylaldonitrone (**1**), stereoselectively gave the *anti*-product **3**, in which the stereoselectivity was particularly high when $MgBr_2$ was the additive. In this study, the reaction pathway was investigated in detail. The stereoselective addition was initially thought to occur via either a 1,5-chelation-controlled or a bisected *s-trans* conformation-controlled pathway. However, Grignard addition to a nonchelating silyl ether-type substrate, *C*-[*cis*-2-(*tert*-butyldiphenylsilyloxymethyl)-*trans*-2-phenylcyclopropyl]-*N*-benzylaldonitrone (**7**), also gave the *anti*-product **9** with high stereoselectivity suggesting that chelation is not important in the reaction. Theoretical calculations of *C*-cyclopropylaldonitrones showed that the coordination of Mg^{2+} at the nitrone oxygen significantly stabilizes the bisected *s-trans* conformer due to the effective hyperconjugation between the π^* of the nitrone C=N bond and the electron-donating cyclopropane orbitals. This kind of orbital interaction is able to stabilize the transition state of the nucleophilic addition and is maximized in the bisected conformation, in which the orbitals of the forming bond and the cyclopropane C−C bond are in an almost planar arrangement. Thus, the high stereoselectivity can be explained by nucleophilic attack on the less hindered side of the C=N bond of the substrates in the Mg^{2+}−coordinated bisected *s-trans* conformation.

Introduction

Cyclopropanes are important in synthetic and medicinal chemical studies, and therefore, considerable effort has been devoted to developing efficient methods for preparing cyclopropane-related compounds.[1−6] Cyclopropanes attached to an unsaturated bond, such as vinylcyclopropanes, cyclopropyl ketones, or cyclopropanecarbaldehydes, preferentially exist in the bisected *s-trans* and *s-cis* conformations, as shown in Figure 1a, due to the hyperconjugation between the unsaturated bond orbital and the strong electron-donating orbitals of the cyclopropane ring.[1,7] Nucleophilic additions, such as hydride reductions, to cyclopropyl ketones often occur highly stereoselectively probably via the stable bisected conformation-controlled pathway.[8,9] In this paper, we demonstrate that Lewis acid coordination to *C*-cyclopropylaldonitrones effectively stabilizes the bisected *s-trans* conformation to realize highly stereoselective Grignard additions.

In recent years, increasing attention has been focused on the stereoselective reactions of nitrones with carbon nucleophilic reagents, which are used in the preparation of a variety of asymmetric amines.[10] We speculated that *C*-cyclopropylaldonitrones should also prefer the bisected conformations, as shown in Figure 1b, which could be stabilized by the characteristic electron-donating effect

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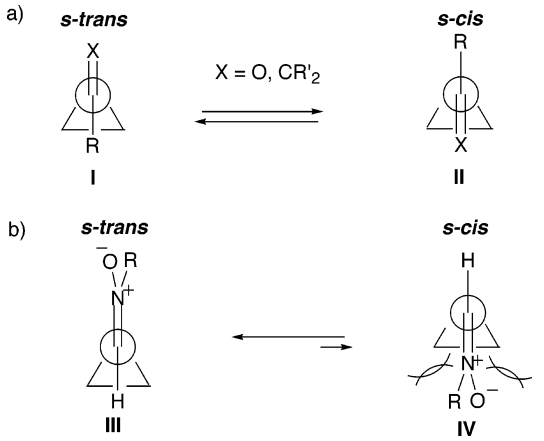

FIGURE 1. Bisected *s-cis* and *s-trans* conformations of α,β-unsaturated cyclopropanes.

of the cyclopropane ring, as in vinylcyclopropanes, cyclopropyl ketones, and cyclopropanecarbaldehydes.[11] The *s-trans* conformer seems to be more stable than the *s-cis*, due to the steric repulsion between the nitrone moiety and the cyclopropane ring in the *s-cis* conformer. Based on these considerations, we investigated the conformation and Grignard reaction of a *C*-cyclopropylaldonitrone, *C*-[*cis*-2-(*N*,*N*-diethylcarbamoyl)-*trans*-2-phenylcyclopropyl]-*N*-benzylaldonitrone (**1**) (Scheme 1).[11] The X-ray crystallographic and NOE analyses of **1** showed that it was stable in the bisected *s-trans* conformation both in solid state and in solution. Grignard addition to the nitrone **1** occurred stereoselectively to give the *anti*-product **3**, where the stereoselectivity was particularly high when $MgBr_2$ was used as the additive, as summarized in Table 1.[11b] The stereochemical results could be explained by the attack of the nucleophile from the less-hindered face on the bisected *s-trans*-conformer **A** (Scheme 1).[11]

SCHEME 1

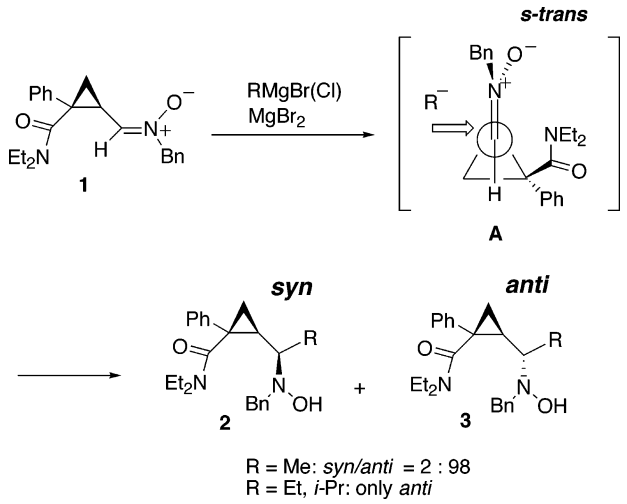

TABLE 1. Addition Reactions of Grignard Reagents to *C*-Cyclopropylaldonitrone 1[a]

entry	reagent (equiv)	additive (equiv)	yield (**2** + **3**)	*syn*/*anti*[b]
1	MeMgBr (3)		63	10:90
2	MeMgBr (3)	HMPA (5)	32	17:83
3	MeMgBr (3)	TMSCl (2)	88	14:86
4	MeMgBr (3)	$ZnBr_2$ (2)	62	13:87
5	MeMgBr (3)	$MgBr_2$ (2)	81	2:98
6	EtMgBr (3)	$MgBr_2$ (2)	80	only *anti*
7	*i*-PrMgCl (5)	$MgBr_2$ (2)	77	only *anti*

[a] The reaction was performed in Et_2O/THF (2:1) at −78 °C for 8 h. [b] Determined by ^1H NMR.

We also found that the Grignard additions to the cyclopropanecarbaldehyde **4** proceeded highly stereoselectively to form the *anti*-product **5** (Scheme 2).[6a,c] Moreover, the stereochemical outcome could be understood by attack of the nucleophile on the less hindered face of the stereoelectronically stabilized bisected *s-trans* conformer **B** of the substrate. Like the nitrone **1**, the aldehyde **4** was shown to be in the bisected *s-trans* conformation in the solid state by X-ray crystallographic analysis.[6c] However, recent experimental studies and calculations using **4** and the related substrates **6a**−**c** have shown that the stereoselective nucleophilic addition does not occur via the bisected *s-trans* conformation-controlled pathway (**B**) but rather via an unusual seven-membered 1,4-chelation-controlled pathway (**C**).[12]

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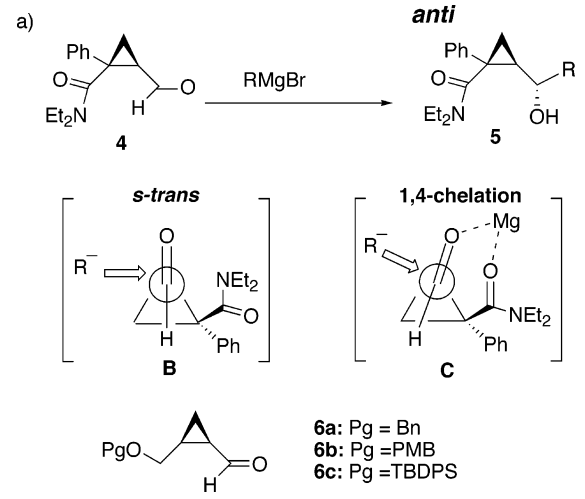
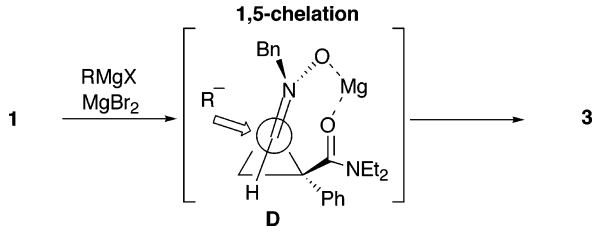
SCHEME 2



SCHEME 3



These results suggested that the above stereoselective addition to the nitrone **1** might also occur via a chelation-controlled pathway (**D**), as shown in Scheme 3, although such a 1,5-chelation-controlled addition seemed unusual.[10,13] Thus, we planned to clarify the actual reaction pathway of the stereoselective addition to *C*-cyclopropylaldonitrones.

Results and Discussion

Conformational Analysis by Calculations. Although a number of theoretical and experimental studies on the conformation of vinylcyclopropanes, cyclopropanecarbaldehydes, and cyclopropyl ketones have been carried out,[1,6a,c,7,9,12] our previous study[11] may be the only one to investigate the conformation of a *C*-cyclopropylaldonitrone. It would be important to confirm whether the bisected *s-trans* and/or *s-cis* conformations generally predominate in *C*-cyclopropylaldonitrones. In particular, a quantitative study on the conformation would be useful for discussing and understanding the reaction pathway.

We investigated the conformational stability of *C*-cyclopropylaldonitrones by ab initio calculations using structurally simplified model compounds, i.e., *C*-cyclopropyl-*N*-methylaldonitrone (**i**) and *C*-(*cis*-2-methylcyclopropyl)-*N*-methylaldonitrone (**ii**) (Figure 2). The rotational barrier energy around the $N_1-C_1-C_2-H_2$ dihedral angle on the model compounds was calculated on the

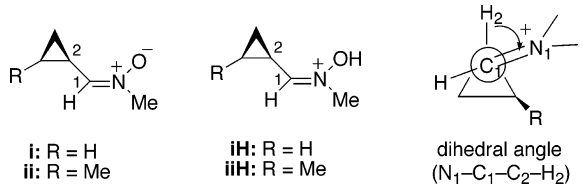


FIGURE 2. Model *C*-cyclopropylaldonitrones for ab initio calculations.

basis of DFT (density functional theory) using the Gaussian 98 program.[14] The dihedral angle was rotated from 0° to 360° at intervals of 20°, and each conformation was optimized at RHF/3-21G(d). The single point energies of the optimized conformers were calculated at RB3LYP/6-31G(d), and the obtained energy profiles are shown in Figure 3. For the *C*-cyclopropylaldonitrone **i**, the minimum energy values were observed at an angle of 0° (360°) and 180° (Figure 3a), where it assumes the bisected *s-trans* and *s-cis* conformations, respectively, and the two conformers have almost the same stability. It is interesting that the energy was not at a maximum in the perpendicular conformers at 90° (Figure 4a) and 270° (Figure 4b) but rather at 120° (Figure 4c) and 240° (Figure 4d). The energetically minimum bisected conformers at 0° and 180° were about 3.2 kcal/mol more stable than the maximum energy conformers at 120° and 240°. The bisected *s-cis* and *trans* conformers of **i** were fully optimized by a higher level of theory at RB3LYP/6-31G(d), in which the *s-trans* conformer is only 0.05 kcal/mol more stable than the *s-cis*. When a methyl group was introduced into the cyclopropane ring at the position *cis* to the nitrone moiety of **i**, namely **ii**, the energy profile became asymmetric, as shown in Figure 3b. The energy was quite high at a 160° angle, due to the steric effect of the methyl group. The minimum energy values were observed in an *s-trans*-like conformer at 20° and also in an *s-cis*-like conformer at 200°, while the *s-trans*-like conformer was slightly (about 0.8 kcal/mol) more stable than the *s-cis*-like. These calculations demonstrate that only the two energy minimum conformers exist, the *s-cis* and *s-trans* for **i** and the *s-cis*-like and *s-trans*-like for **ii**, and that the energy differences between the minimum energy conformers might be insignificant.

We next investigated the conformation of the two model compounds in their nitrone *O*-protonated forms, i.e., **iH** and **iiH** (Figure 2), which could be simplified models of a Lewis acidic metal ion-coordinated structure. Interestingly, as shown in Figure 3a,b, the protonation drastically changed the energy profiles. The energy of the protonated **iH** is at a minimum in the bisected *s-trans* conformer at 0° (360°) and in the *s-cis* conformer at 180°

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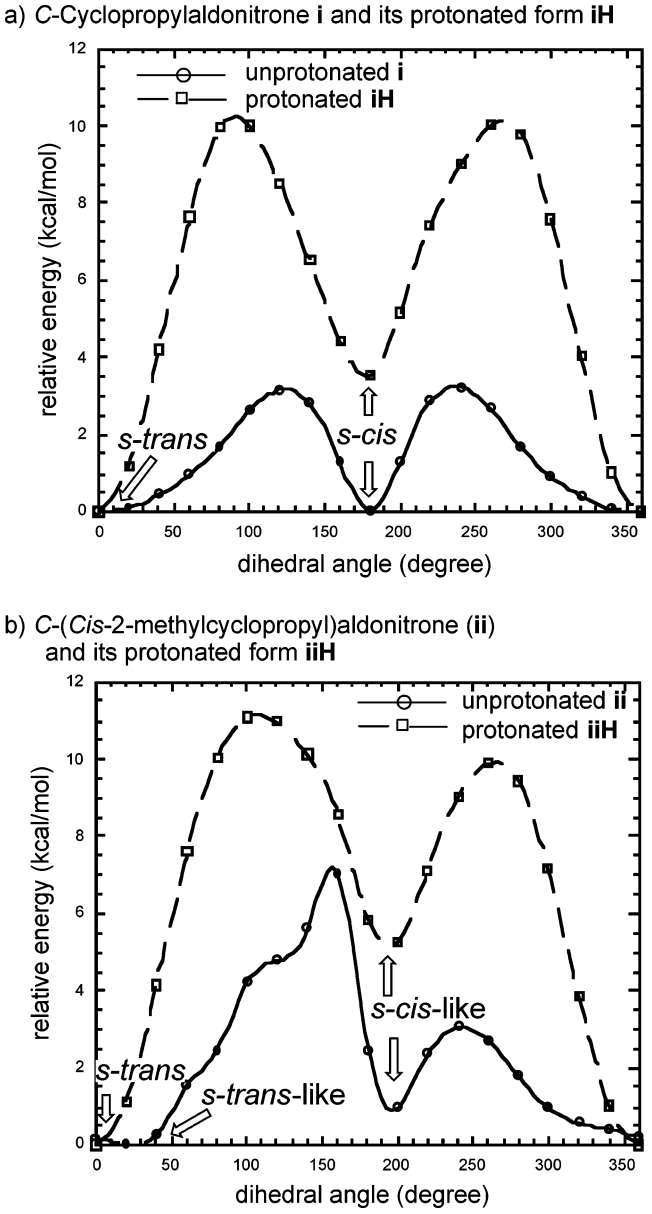


FIGURE 3. Rotational barrier energies around the $N_1-C_1-C_2-H_2$ dihedral angle of the model compounds **i** and its protonated form **iH** (a) and **ii** and its protonated form **iiH** (b).

(Figure 3a) and is at a maximum in the exactly perpendicular conformers at 90° (Figure 4a) and at 270° (Figure 4b). It should be noted that the *s-trans* conformer is not only significantly more stable than the perpendicular conformers ($\Delta E = 10$ kcal/mol), but also, importantly, it is more stable than the *s-cis*-conformer ($\Delta E = 3.5$ kcal/mol). The energy profile of the protonated **iiH** bearing a *cis*-methyl substituent is similar to that of **iH** (Figure 3b). However, in **iiH**, the bisected *s-trans* conformer is relatively more stable than that in **iH**, due probably to the steric demand of the methyl substituent.

The bisected *s-cis* and *s-trans* conformers of **iH** and **iiH** were fully optimized by a higher level theory at RB3LYP/6-31G(d), and the stable conformations obtained and their relative energies are shown in Figure 5. The *s-trans* conformer was 3.41 kcal/mol more stable than the *s-cis* conformer for **iH** (Figure 5a). The energy difference between the *s-trans* and the *s-cis* conformers for **iiH** is

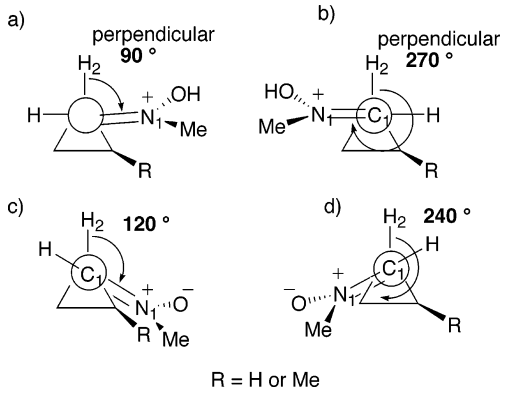


FIGURE 4. Newman projection of the maximum energy conformers of **i** (a and b) and its protonated form **iH** (c and d).

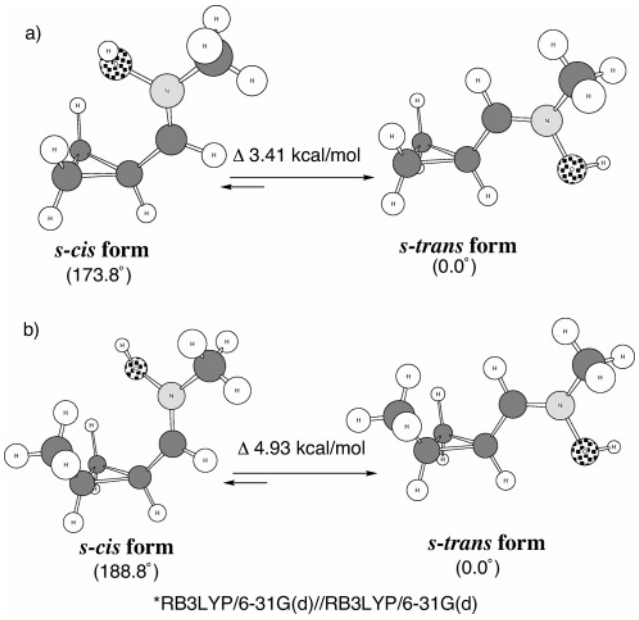
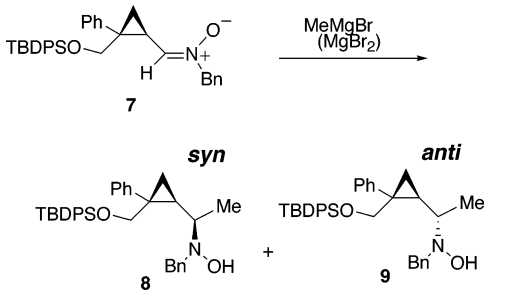


FIGURE 5. Minimum energy *s-cis*- and *s-trans* conformers and their relative energies obtained by the ab initio calculations of the model compounds in their protonated forms **iH** (a) and **iiH** (b).

4.93 kcal/mol (Figure 5b), which suggests that the *s-trans* is almost the only conformer occurring in the protonated **iiH**. These calculations clearly demonstrate that *C*-cyclopropylaldonitrones can be significantly stabilized in the bisected *s-trans* conformation when a Lewis acidic metal coordinates to the nitrone oxygen.

Grignard Addition with a Nonchelating Substrate. With the calculation results suggesting that the *s-trans* conformer is very stable under the Lewis acidic conditions in mind, we next examined the Grignard reaction of a *C*-cyclopropylaldonitrone **7** (Scheme 4), in which the carbamoyl group of **1** at the position *cis* to the nitrone moiety on the cyclopropane ring was replaced with a *tert*-butyldiphenylsilyl (TBDPS) oxymethyl group. Substrate **7** was designed to determine whether chelation is important in the Grignard addition to *C*-cyclopropylaldonitrones, since the nonchelating nature of the silyl ether oxygen is well-known.[13] Treatment of the known aldehyde **10**[12] with *N*-BnNHOH·HCl formed the desired nitrone **7** quantitatively (Scheme 5), and the conformation was investigated by NOE experiments. When the

SCHEME 4



SCHEME 5

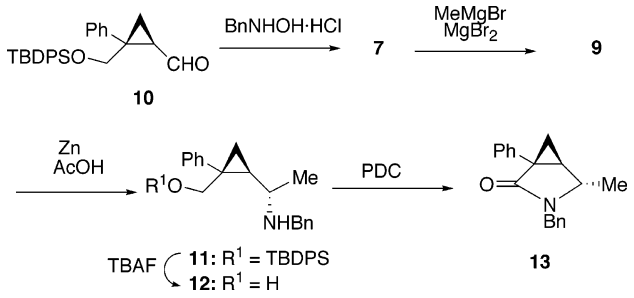


TABLE 2. Addition Reactions of MeMgBr to *C*-Cyclopropylaldonitrone 7[a]

entry	reagent (equiv)	additive (equiv)	yield (**8** + **9**)[b]	*syn*/*anti*[c]
1	MeMgBr (3)	none	25 (70)	6:94
2	MeMgBr (3)	$MgBr_2$ (2)	50 (39)	only *anti*

[a] The reaction was performed in Et_2O/THF (2:1) at −78 °C for 8 h. [b] The substrate **7** was recovered in 70% (entry 1) and 39% (entry 2) yields. [c] Determined by ^1H NMR.

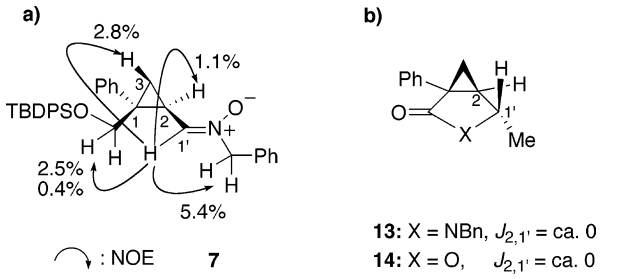


FIGURE 6. NOE experiments of the *C*-cyclopropylaldonitrone **7** (a) and coupling constants of the 3-oxa- and 3-azabicyclo-[3.1.0]hexane derivatives **13** and **14** (b).

1′-H was irradiated, NOEs were observed at the 3-H, which is in the position *cis* to the nitrone moiety, of the cyclopropane ring (2.8%), and at the benzyl methylene proton (5.4%), and silyloxymethylene protons (2.5%, 0.4%), as shown in Figure 6a. Thus, the compound is a *Z*-nitrone restricted in the bisected *s-trans*-like conformation in solution.

The reaction of **7** with MeMgBr was first carried out at −78 °C in Et_2O/THF. The reaction conditions were the same as those previously employed for **1** (entry 1 in Table 1). The reaction of the silyl ether substrate **7** gave highly stereoselectively the *anti*-product **9** (*syn*/*anti* = 6:94, entry 1 in Table 2), despite its nonchelating silyl ether structure. The *syn*/*anti*-ratio in the reaction was higher than that of the corresponding carbamoyl-type substrate **1** (entry 1 in Table 1, *syn*/*anti* = 10:90), which might

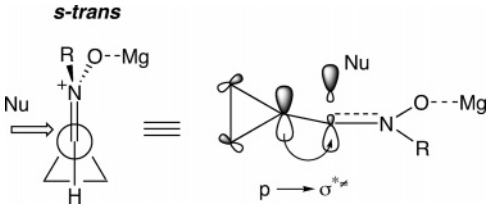


FIGURE 7. Transition-state model for nucleophilic attack on the Mg^{2+}-coordinated *C*-cyclopropylaldonitrone.

have formed a chelate under the reaction conditions. When $MgBr_2$ was used as an additive in the Grignard reaction, *the anti*-product **9** was formed exclusively and the yield was also improved (entry 2 in Table 2).

The stereochemistry of the *anti*-product **9** was determined by chemical transformations. We previously reported that the configuration of compounds with a bicyclo[3.1.0]hexane system, such as the 3-oxabicyclo-[3.1.0]hexane derivative **14** (Figure 6b), can be determined by the *J* values in the ^1H NMR.[6c] Thus, **9** was converted into the 3-azabicyclo[3.1.0]hexane derivative **13**, via reduction of the *N*-oxide moiety, de-*O*-silylation, and PDC oxidation, as shown in Scheme 5. The $J_{2,1'}$ value of **13** was about 0 Hz, similar to that of **14**, indicating its 1′*S*-configuration (Figure 6b).

These results using the nonchelating silyl ether-type substrate **7** confirmed that the highly *anti*-selective Grignard addition reaction on the *cis*-substituted *C*-cyclopropylaldonitrones occurs via the bisected *s-trans* conformation-controlled pathway.

Discussion. It has been recognized that the conformation of the transition state and the intermediate can be strongly influenced by conformational effects which stabilize the ground-state conformation.[15] In nucleophilic addition to *C*-cyclopropylaldonitrones, the conformations of the transition state and the ground state would be similar because of the characteristic stereoelectronic feature of *C*-cyclopropylaldonitrones.

The Walsh model[16] is useful in understanding the conjugating ability of the cyclopropane ring, by which the bisected conformational stability is explained through interaction of the p-orbitals on the cyclopropyl carbons and the adjacent π^* orbital (C=N in the case of *C*-cyclopropylaldonitrones) because of their planar arrangement.[1a,b,7h] Such orbital interaction should also effectively stabilize the transition state of the nucleophilic attack. In the course of the attack, the p-orbital of the cyclopropane ring, which can be characterized as a strong electron-donor,[1a] interacts with the antibonding orbital ($\sigma^{*\neq}$) of the electron-deficient incipient bond between the nucleophile and the nitrone carbon. This p−$\sigma^{*\neq}$ orbital interaction is maximized in the bisected conformation, in which the orbitals of the newly forming bond and the cyclopropane C−C bond are in an almost planar arrangement, as shown in Figure 7. This kind of stabilization of

(15) For examples, see: (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim Acta* **1992**, *75*, 604−620. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169. (c) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870−11882. (d) Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021−1023.

(16) Walsh, A. D. *Nature (London)* **1947**, *159*, 712−713.

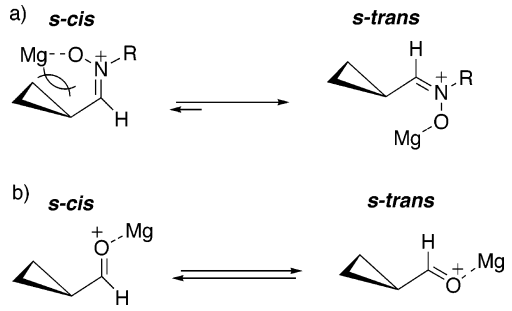


FIGURE 8. Mg^{2+}-coordinated bisected *s-cis* and *s-trans* conformers of *C*-cyclopropylaldonitrone (a) and cyclopropanecarbaldehyde (b).

the transition states of nucleophilic attack due to the orbital interaction of $\sigma^{*\neq}$ has been explained by Cieplak.[17]

The ab initio calculations on *C*-cyclopropyl-*N*-methylaldonitrone (**i**) showed that although its energy is at a minimum in the bisected *s-cis* and *s-trans* conformations, the energy is not at a maximum in their perpendicular conformations. The maximum energy was observed at the angle of 120° (Figure 4c) and 240° (Figure 4d), where the cyclopropane ring and the nitrone C=N bond are almost eclipsed. The results suggest that the torsional strain between the cyclopropane ring and the C=N bond may significantly affect the nitrone conformation. The results of the calculations on the protonated nitrones as models of the Mg^{2+}-coordinated reactive intermediates are vitally important in understanding the reaction pathway of the Grignard reactions of *C*-cyclopropylaldonitrones, since, during the course of the reaction, the coordination of Mg^{2+} to the oxygen atom makes the nitrone C=N bond reactive to nucleophiles, which is essential for nucleophilic attack to occur. The protonation of the oxygen atom lowers the energy of the π^* of the C=N bond, where the p$-\pi^*$ interaction is able to lower the energy of the bisected conformers more effectively than that of the unprotonated nitrone. This was supported by the results of calculations on **i** and its protonated form **iH**, namely that the rotational energy barrier, i.e., the energy difference between the energetically minimum bisected conformer and the maximum conformer, tripled when the nitrone oxygen was protonated (about 3.2 kcal/mol for the unprotonated **i** and more than 10 kcal/mol for the protonated **iH**). In the protonated form **iH** the calculated energy is at a maximum at the exactly perpendicular conformers (Figure 4a,b), where the p$-\pi^*$ orbital interaction should be at a minimum. These calculations suggest that when the nitrone oxygen is coordinated with Mg^{2+}, the dominant factor determining the conformation of the molecule is the orbital interaction. Although the bisected *s-cis* and *s-trans* conformers should be similarly stabilized by the orbital interaction in their coordinated (protonated) form, the calculations proved that the *s-trans* conformer is significantly more stable than the *s-cis*. In the coordinated bisected *s-cis*-conformer, steric repulsion between the O$-$Mg (O$-$H in the calculations) moiety and cyclopropane moiety would occur, as shown in Figure 8a, resulting in a net stabilization of the *s-trans* conformer.

(17) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−8462. (c) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265−1336.

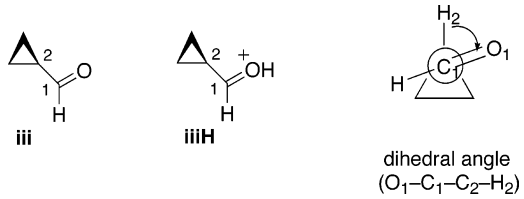


FIGURE 9. Cyclopropanecarbaldehyde (**iii**) and its protonated form (**iiiH**).

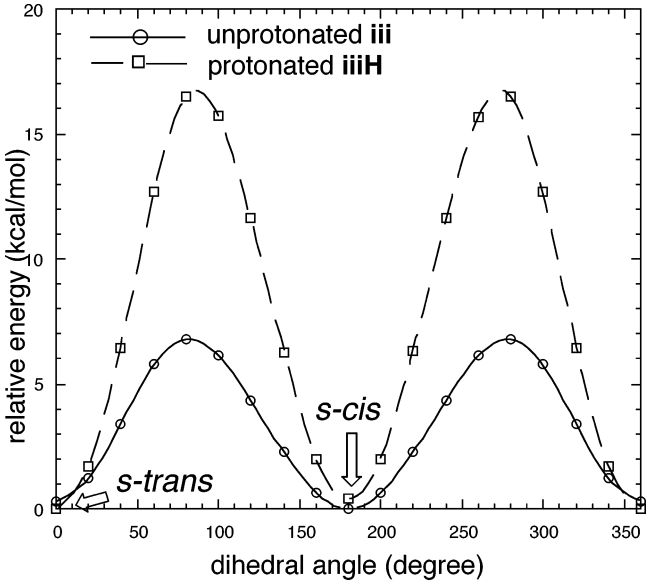


FIGURE 10. Rotational barrier energies around the $O_1-C_1-C_2-H_2$ dihedral angle of the model compound **iii** and its protonated form **iiiH**.

Thus, the high stereoselectivity is explained by nucleophilic attack on the less hindered side of the C=N bond of the Mg^{2+}-coordinated bisected *s-trans* conformation, which is significantly stabilized by the p$-\pi^*$ orbital interaction.

A question might arise from the above results, to wit, why does the Grignard addition to *cis*-substituted cyclopropanecarbaldehydes, which seem to have structural and stereoelectronic features similar to the corresponding *C*-cyclopropylaldonitrones, not proceed stereoselectively via the bisected transition state pathway?[11] For example, Grignard addition of MeMgBr to the cyclopropanecarbaldehyde **10** (structure shown in Scheme 5), which bears the *cis*-TBDPSOCH$_2$ substituent on the cyclopropane ring as in the nitrone **7**, gave a mixture of the *syn*/*anti*-products almost nonstereoselectively (e.g., at −78 °C in THF, *syn*/*anti* = 2.8:1; at −78 °C in CH_2Cl_2, *syn*/*anti* = 1.3:1).[12]

Conformations of cyclopropanecarbaldehyde (**iii**) and its formyl *O*-protonated form **iiiH** (Figure 9) were analyzed by ab initio methods similar to those described above, and the results are shown in Figure 10. The energy profile of **iii** shows that the bisected *s-cis* and the *s-trans*-conformers are significantly stabilized compared with the other conformers, similar to the profile of the corresponding nitrone **i**. However, the profile of the protonated **iiiH** demonstrates that the *s-trans* and the *s-cis* conformers have almost the same energy, which is in contrast to the results on the protonated nitrone **iH**

which show that the *s-trans* conformer is considerably more stable than the *s-cis* conformer (Figure 3a). As shown in Figure 8b, steric repulsion in both the *s-cis* and the *s-trans* conformers of the aldehyde is inconsequential; therefore, these conformers would have almost the same stability. Accordingly, the Grignard additions to the *cis*-substituted cyclopropanecarbaldehydes are likely to proceed via both the bisected *s-cis* and the *s-trans* reaction pathways to result in an almost nonstereoselective outcome.

Conclusion. Theoretical calculations of *C*-cyclopropylaldonitrones clarified that the coordination of Mg^{2+} at the nitrone oxygen significantly stabilizes the bisected *s-trans* conformer due to the effective hyperconjugation between the π^* of the nitrone C=N bond and the electron-donating cyclopropane orbitals. In nucleophilic addition to *C*-cyclopropylaldonitrones, the bisected transition state can be stabilized by a similar orbital interaction between the p-orbital of the cyclopropane ring and the antibonding orbital of the electron-deficient incipient bond. Thus, a highly stereoselective Grignard addition was realized by nucleophilic attack on the less hindered side of the C=N bond of the substrates in the Mg^{2+}-coordinated bisected *s-trans* conformation.

Experimental Section

***(Z)-N*-[(1*S*,2*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-2-phenylcyclopropylmethylene]benzylamine *N*-Oxide (7).** A mixture of **10**[12] (415 mg, 1.00 mmol) and *N*-benzylhydroxylamine hydrochloride (192 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated in vacuo (for removing CH_2Cl_2), 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 1:1, then MeOH/$CHCl_3$ 1:49) to give **7** as white crystals (519 mg, 100%): mp (hexane−AcOEt) 99−100 °C; $[\alpha]^{23}_D$ +71.39 (*c* 1.190, $CHCl_3$); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.99 (9 H, s, −C(*CH*$_3$)$_3$), 1.27 (1 H, dd, H-3a, J = 4.8, 5.4 Hz), 1.44 (1 H, dd, H-3b, J = 4.8, 8.9 Hz), 2.63 (1 H, ddd, H-2, J = 5.4, 7.7, 8.9 Hz), 3.69 (1 H, d, −*CH*$_2$OSi, J = 11.0 Hz), 3.91 (1 H, d, −*CH*$_2$-OSi, J = 11.0 Hz), 4.86 (1 H, d, −*CH*$_2$Ph, J = 13.4 Hz), 4.82 (1 H, d, −*CH*$_2$Ph, J = 13.4 Hz), 6.71 (1 H, d, H-1′ (CH=N), J = 7.7 Hz), 7.21−7.51 (20 H, m, aromatic); NOE (400 MHz, CD_2Cl_2, 24 °C) 2.8 (H-1′ → H-3a), 2.5 (H-1′ → -*CH*$_2$OSi), 0.9 (H-1′ → -*CH*$_2$OSi), 5.4 (H-1′ → -*CH*$_2$Ph); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 17.8 (C-3), 19.3 (−*C*(CH$_3$)$_3$), 21.7 (C-2), 26.9 (−C(*CH*$_3$)$_3$), 36.9 (C-1), 68.0 (C-1′), 69.4 (−*C*H$_2$Ph), 126.3, 127.94, 128.0, 128.5, 128.9, 129.0, 129.4, 129.9, 130.0, 130.2, 133.4, 133.4, 134.0, 135.8, 135.8, 137.43, 142.77; LR-MS (FAB) *m/z* 520 ((M + H)$^+$, 100). Anal. Calcd for $C_{34}H_{37}NO_2Si$: C, 78.57; H, 7.18; N, 2.69. Found: C, 78.33; H, 7.24; N, 2.88.

General Procedure for the Addition of Grignard Reagent to Nitrone 7. A mixture of nitrone **7** (52 mg, 0.10 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) in a solvent (3 mL) was stirred at room temperature for 30 min and then cooled to −78 °C. To the mixture was added a solution of MeMgBr [0.14 mL, 0.20 mmol, 1.4 M in toluene/THF (3:1)], and the resulting mixture was stirred for 8 h at the same temperature. After addition of sarturated aqueous NH_4Cl, 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 a mixture of **8** and **9** or pure **9**. The mixture of **8** and **9**: ^{1}H NMR (500 MHz, $CDCl_3$) for **8** δ 0.85 (1 H, dd, H-3a, J = 4.7, 5.5 Hz), 0.95 (9 H, s, −C(*CH*$_3$)$_3$), 1.09 (1 H, dd, H-3b, J = 4.7, 8.6 Hz), 1.44 (1 H, m, H-2), 1.60 (3 H, d, Me, J = 6.4 Hz), 2.75 (1 H, m, CH−N), 3.64 (1 H, d, −*CH*$_2$OSi, J = 10.9 Hz), 3.83 (1 H, d, −*CH*$_2$Ph, J = 13.3 Hz), 3.90 (1 H, d, −*CH*$_2$OSi, J = 10.9 Hz), 4.02 (1 H, d, −*CH*$_2$Ph, J = 13.3 Hz), 4.62 (1 H, br s, −OH), 7.22−7.40 (20 H, m, aromatic). **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (1 H, dd, H-3a, J = 4.8, 5.6 Hz), 0.95 (9 H, s, −C(*CH*$_3$)$_3$), 1.07 (1 H, dd, H-3b, J = 4.8, 9.2 Hz), 1.28 (3 H, d, Me, J = 5.4 Hz), 1.44 (1 H, ddd, H-2, J = 5.6, 9.2, 9.2 Hz), 2.74 (1 H, m, CH−N), 3.86 (1 H, d, −*CH*$_2$Ph, J = 13.4 Hz), 3.87 (1 H, d, −*CH*$_2$OSi, J = 10.9 Hz), 3.98−4.00 (2 H, m, −*CH*$_2$OSi and −*CH*$_2$Ph), 4.95 (1 H, br s, −OH), 7.19−7.50 (20 H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8 (C-3), 19.2 (C-2″), 19.2 (−*C*(CH$_3$)$_3$), 26.8 (−C(*CH*$_3$)$_3$), 28.8 (C-1), 33.1 (C-2), 61.1 (C-1″), 62.4 (C-1′), 68.00 (−*C*H$_2$Ph), 126.3, 127.0, 127.5, 127.6, 128.0, 128.3, 129.3, 129.5, 129.5, 129.7, 133.3, 133.5, 135.6, 135.7, 138.7, 144.7; HR-MS (FAB) calcd $C_{35}H_{42}NO_2Si$ 536.2985, found 536.2961 ((M + H)$^+$).

(1*S*,2*R*)-2-[(*S*)-1-(Benzylamino)ethyl]-1-*tert*-butyldiphenylsilyloxymethyl-1-phenylcyclopropane (11). A mixture of **9** (27 mg, 50 μmol) and Zn powder (33 mg, 0.50 mmol) in AcOH/CH_2Cl_2 (1:5, 1.2 mL) was stirred at room temperature for 3 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:1, $CHCl_3$/AcOEt 1:1, then MeOH/$CHCl_3$ 1:10) to give **11** (20 mg, 77%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47 (1 H, dd, J = 4.8, 6.0 Hz), 0.86 (9 H, s), 0.91 (1 H, dd, J = 4.8, 8.8 Hz), 1.22 (3 H, d, J = 6.2 Hz), 1.43 (1 H, ddd, J = 6.0, 8.8, 8.8 Hz), 2.22 (1 H, br s), 2.51 (1 H, dq, J = 6.0, 8.8 Hz), 3.65 (1 H, d, J = 11.0 Hz), 3.81 (1 H, d, J = 13.6 Hz), 3.96 (1 H, d, J = 13.6 Hz), 3.99 (1 H, d, J = 11.0 Hz), 7.04−7.06 (2 H, m), 7.12−7.16 (5 H, m), 7.23−7.43 (11 H, m), 7.49−7.51 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 19.0, 19.6, 26.8, 31.9, 33.4, 51.0, 53.3, 68.1, 126.5, 126.6, 127.4, 127.7, 128.0, 128.1, 128.27, 129.3, 129.5, 130.7, 132.8, 133.8, 135.5, 135.7, 144.5; HR-MS (FAB) calcd $C_{35}H_{42}NOSi$ 520.3036, found 520.3041 ((M + H)$^+$).

(1*S*,2*R*)-2-[(*S*)-1-(Benzylamino)ethyl]-1-hydroxymethyl-1-phenylcyclopropane (12). A mixture of **11** (10 mg, 20 μmol) and TBAF (1.0 M in THF, 40 μL, 40 μmol) in THF (1 mL) was stirred at room temperature for 12 h. The mixture was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/AcOEt 1:1 then, MeOH/$CHCl_3$ 1:10) to give **12** (5.6 mg, 100%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (1 H, dd, J = 4.7, 5.4 Hz), 1.17 (1 H, dd, J = 4.7, 8.6 Hz), 1.27 (1 H, ddd, J = 5.4, 8.6, 8.6 Hz), 1.42 (3 H, d, J = 6.2 Hz), 2.65 (1 H, dq, J = 6.2, 8.6 Hz), 3.55 (1 H, d, J = 12.2 Hz), 3.73 (1 H, d, J = 12.2 Hz), 3.98 (1 H, d, J = 12.2 Hz), 4.18 (1 H, d, J = 12.2 Hz), 7.16−7.38 (10 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.5, 32.3, 32.8, 50.0, 54.5, 68.5, 126.1, 127.4, 128.1, 128.2, 128.6, 128.7, 138.7, 144.7; HR-MS (FAB) calcd $C_{19}H_{24}NO$ 282.1858, found 282.1871 ((M + H)$^+$).

(1*S*,4*S*,5*R*)-4-Methyl-2-oxo-1-phenyl-3-benzyl-3-azabicyclo[3.1.0]hexane (13). A mixture of **12** (5.6 mg, 20 μmol) and PDC (15 mg, 40 μmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 12 h. The resulting mixture was filtered through a pad of Florisil and celite, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:4) to give **13** (5.2 mg, 94%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (1 H, dd, H-6a, $J_{6a,6b}$ = 4.4, $J_{6a,5}$ = 4.8 Hz), 1.31 (3 H, d, 4-Me, J = 6.4 Hz), 1.43 (1 H, dd, H-6b, $J_{6b,6a}$ = 4.4, $J_{6b,5}$ = 7.6 Hz), 1.84 (1 H, dd, H-5, $J_{5,6a}$ = 4.8, $J_{5,6b}$ = 7.6 Hz), 3.40 (1 H, q, H-4, J = 6.4 Hz), 3.95 (1 H, d, −*CH*$_2$Ph, J = 14.9 Hz), 4.95 (1 H, d, −*CH*$_2$-Ph, J = 14.9 Hz), 7.21−7.45 (10 H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 20.7, 26.7, 33.8, 44.1, 53.2, 127.1, 127.5, 128.2, 128.4, 128.6, 128.7, 136.5, 137.4, 173.7; HR-MS (FAB) calcd $C_{19}H_{20}NO$ 278.1545, found 278.1530 ((M + H)$^+$).

Calculations. All ab initio and DFT calculations were performed using the Gaussian 98 program[14] on an SGI O2 workstation. The $N_1(O_1)-C_1-C_2-H_2$ dihedral angle of the compounds was rotated from 0° to 360° at the intervals of 20°,

and the conformations were optimized at RHF/3-21G(d). Finally, single-point energies were calculated at RB3LYP/6-31G(d) (Figures 3 and 10). The bisected *s-cis* and *s-trans* conformers were fully optimized at RB3LYP/6-31G(d), and their single point energies were calculated by RB3LYP/6-31G-(d) (Figure 5).

Acknowledgment. This investigation was supported by a Grant-in-Aid for Creative Scientific Research (13NP0401) (A.M.), a Grant-in-Aid for Scientific Research (S.S.), and Research Fellowships for Young Scientists (H.A.) from the Japan Society for the Promotion of Science. We are grateful to Ms. H. Matsumoto, A. Maeda, and S. Oka (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analyses and to Daiso Co., Ltd., for the gift of chiral epichlorohydrins.

Supporting Information Available: General experimental methods, ^{1}H NMR charts of **9**, **11**, **12**, and **13**, absolute energies, and atomic coordination of the calculated structures for the model compounds **i**, **ii**, and **iii** and their protonated forms **iH**, **iiH**, and **iiiH**. This material is available free of charge via the Internet at http://pubs.acs.org.

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