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Stereocontrolled intramolecular nitrile oxide cycloaddition reaction using a gauche–gauche interaction

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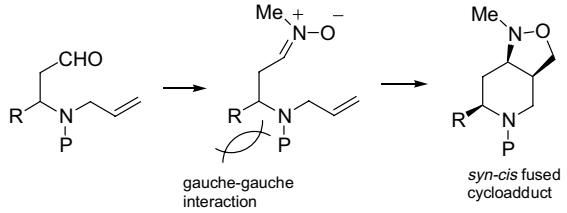
Abstract—A gauche–gauche interaction is proposed as a powerful controlling factor for the stereochemistry in the intramolecular nitrile oxide cycloaddition reaction derived from N-protected 3-(*N*-allylamino)propionaldehyde and 2-(*N*-homoallylamino)acetaldehyde oximes. High levels of stereoselectivity (76% de to perfect) were obtained from the reaction involving nitrile oxides with substituents at the adjacent carbon atom to the tether nitrogen.

Intramolecular cycloaddition reaction of nitrones and nitrile oxides has been widely recognized as a very powerful method for stereoselective construction of oxygen and nitrogen-containing 5-membered frameworks,[1] which are important motifs used as key building blocks for total synthesis and medicinal compounds. Although many strategies have been developed for the stereocontrolled intramolecular nitrone cycloaddition reaction, limited ones are known for the intramolecular nitrile oxides cycloaddition reaction. Especially, few examples have been found in literatures based on the systems with simple and acyclic tethers linking by sp^3-units between the nitrile oxide and dipolarophiles.[2] In a recent paper, we reported a regio- and diastereoselective cycloaddition reaction of *N*-methyl nitrone derived from N-protected 3-(*N*-allylamino)propionaldehyde system.[3] Therein, the gauche–gauche interaction[4] between the protective group (P) on the amino nitrogen and the substituent (R) at the adjacent carbon atom to the nitrogen would effectively govern the cycloaddition transition state to afford syn–cis fused perhydroisoxazolo[4,3-*c*]pyridine derivatives selectively (Scheme 1).

If this gauche–gauche interaction is generally operational for intramolecular reactions, we believed that stereocontrol in the cycloaddition reactions having similar transition state geometries could be attained using this interaction. Our next concern was directed toward the cycloaddition reaction of nitrile oxide in the same system, expecting that more facile stereocontrol than nitrone one taking account for the more rigid geometry of nitrile oxide.



Scheme 1. Stereocontrolled nitrone cycloaddition reaction using gauche–gauche interaction.

Oximization of aldehyde **1**[5] in an ordinary method afford efficiently oximes **2** as *E*/*Z* mixtures (*E*/*Z* ratio: 3:2–2:3). We used oximes **2** without further purification in the next reaction which is the oxidation of oximes **2**. When the treatment of oxime **2a** (R = Me; P = Ts) with sodium hyphochlorite solution (2.5 equiv) in dichloromethane at room temperature for 1 h, nitrile oxide cycloadduct **4a**[6] was obtained in 86% yield as a sole product after a short-column chromatography on silica gel. Similar treatment of **2b–e** gave also cycloadducts **4b–e** in

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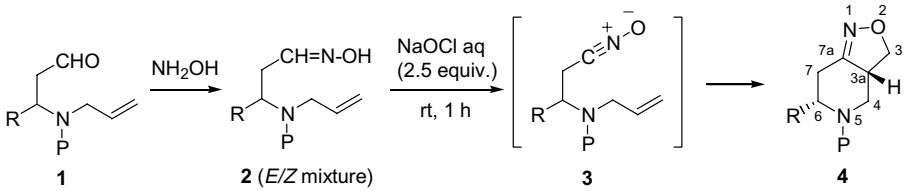
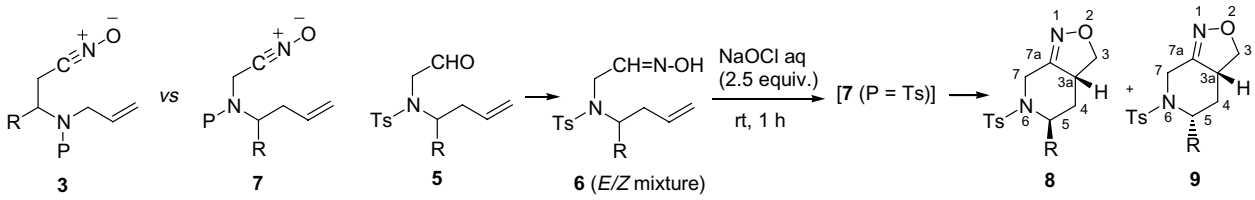
Table 1. Stereoselective cycloaddition reaction of nitrile oxides **3** leading to **4**



Entry	Oxime	R	P	Product/yield[a] (%)
1	**2a**	Me	Ts	**4a**/86
2	**2b**	Me	Ms	**4b**/98
3	**2c**	Me	CO_2Et	**4c**/91
4	**2d**	Me	Boc	**4d**/91
5	**2e**	Ph	Ts	**4e**/82

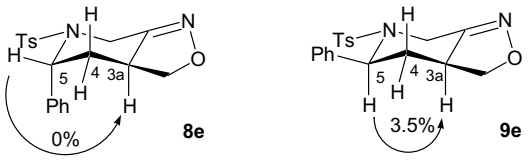
[a] Isolated yield.



Scheme 2. Cycloaddition reaction of nitrile oxides.

good yields nevertheless the kind of the protecting groups (P) (Table 1).[7] The structure of cycloadducts **4** were deduced to be *syn*-adduct on the basis of the signal patterns of 3-H_2, 3a-H and 4-H_2 and 6-H and 7-H_2 in their ^{1}H NMR spectra: two large coupling constants were observed among 3-H (ax), 3a-H (pseudo ax) and 4-H (ax) together with the geminal coupling constants due to 3-H_2 and 4-H_2 each other, while none of large coupling were observed between 6-H (eq) and 7-H_2. Fortunately, recrystallization of **4b** from benzene/hexane afforded good single crystals for the X-ray structure analysis[8] and the structure of **4b** was confirmed to be (3a*R**,6*R**)-(±)-3,3a,4,5,6,7-hexahydro-5-mesyl-6-methylisoxazolo[4,3-*c*]pyridine (see Schemes 2, 3).

Stimulated by these findings, we investigated the stereocontrol of nitrile oxides **7** from 2-(*N*-homoallylamino)acetaldehydes **5**,[9] in which the NP and CR in the nitrile oxides **3** are interchanged. Therein, the protecting group was fixed to tosyl group (Ts) and the R was varied from methyl (Me) to more bulkier phenyl and alkyl groups. Similar treatment of oximes **6** with sodium hyphochlorite gave also *anti*-nitrile oxide cycloadducts **8** along with small amounts of *syn*-isomers **9** in good to excellent total yields and highly stereoselectively (Table 2).[10] The structure of cycloadducts **8** and **9** was assigned also on the basis of the signal patterns of 4-H_2 and 5-H in their ^{1}H NMR spectra. In major **8**, one proton at a higher field (4-H_{ax}) of the methylene protons 4-H_2 was observed as ddd with two large (ax–ax and geminal) and one small (ax–eq) coupling constants and another (4-H_{eq}) was observed as br dd with one large (geminal) and two small (eq–eq) coupling constants. The 5-H_{eq} in **8b** and **8d** was observed as multiplets with four small to medium (without ax–ax) coupling constants. This means that the 5-H is occupied at the equatorial position. On the other hand, in minor **9e** isolated, 4-H_{ax} was observed as ddd with three large (two ax–ax and geminal) coupling constants and another 4-H_{eq} was observed as ddd with one large (geminal) and two medium (two ax–eq) coupling constants. While the irradiation of 5-H in **8e** did not cause any apparent NOE

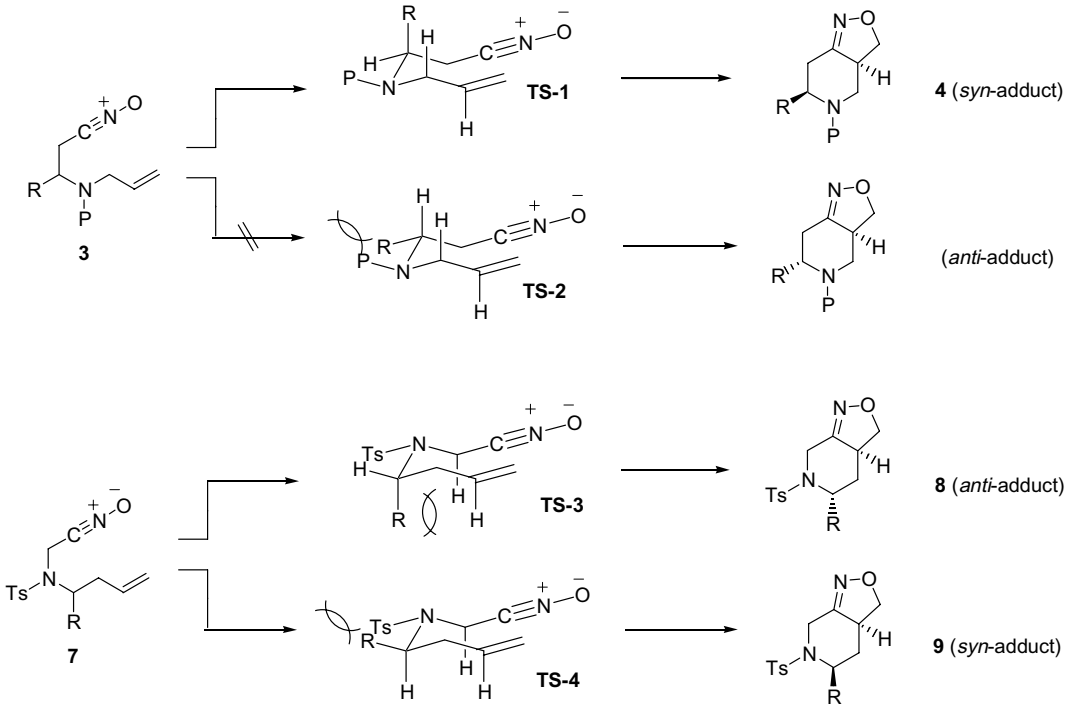


Scheme 3. NOE measurements of *anti*-**8e** and *syn*-adduct **9e**.

Table 2. Cycloaddition reaction of nitrile oxide **7** leading to hexahydroisoxazolo[3,4-*c*]pyridine **8** and **9**

Entry	Oxime	R	Yield[a] (%)	Products/ratio[b]
1	**6a**	Me	80	**8a**/97 **9a**/3
2	**6b**	*n*-Pr	90	**8b**/91 **9b**/9
3	**6c**	*i*-Pr	93	**8c**/92 **9c**/8
4	**6d**	*n*-Hexyl	98	**8d**/91 **9d**/9
5	**6e**	Ph	96	**8e**/91 **9e**/9
6	**6f**	Bn	73	**8f**/88 **9f**/12

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectra of the crude mixtures.



Scheme 4. Transition state geometries for the cycloaddition reaction of nitrile oxides **3** and **7**.

enhancement of 3a-H, that in **9e** caused an NOE enhancement of 3a-H (3.5%) (Scheme 4). This suggests a 1,3-diaxial relationship between 3a-H and 5-H in **9e** and we deduced that 5-H occupies the axial position. Finally, the structure of major **8d** was confirmed unambiguously to be (3a*R**,5*R**)-(±)-5-hexyl-6-tosyl-3,3a,4,5,6,7-hexahydroisoxazolo[3,4-*c*]pyridine by X-ray single crystal structure analysis.[8]

The outcome of the stereoselectivities in the intramolecular cycloaddtion reaction of nitrile oxides **3** and **7** could be explained by transition state geometry: in the transition states the acyclic tethers linking the nitrile oxide and alkenyl moiety in **3** and **7** should be held in a chair-like piperidine ring conformation. When protecting group P occupies the equatorial position in the transition state of the cycloaddition of nitrile oxide **3**, the substituent R is expected to occupy the axial position in order to avoid the gauche–gauche interaction between the P and R moiety. Consequently, the exclusive formation of *syn*-cycloadduct **4** results via **TS-1** (Scheme 4). On the other hand, a somewhat different situation was found in the transition state **TS-3** of the cycloaddition of nitrile oxide **7**; additional 1,3-diaxial interactions with the R substituent, similarly in an axial position avoids any gauche–gauche interaction with one of the methylene protons adjacent to the amino nitrogen and the inner vinylic proton of the dipolarophile moiety, should be taken into account (Scheme 4). As shown in Table 2, the intramolecular cycloaddition reaction of nitrile oxide **7** afforded mixtures of *anti*-**8** and *syn*-cycloadducts **9** and the highest stereoselection (**8**:**9** = 97:3) was accomplished in the reaction of **7a**, which bears methyl group as a substituent (R = Me), the least sterically bulky group.

In conclusion, we have demonstrated the usefulness of the gauche–gauche interaction as a stereocontrolling factor in the intramolecular cycloaddition reaction of nitrile oxides. We believe that this methodology could be applied to an efficient stereoselective preparation of simple bicyclic heterocyclic systems through the deprotection. Extension of the present strategy to other intramolecular reactions is currently under progress.

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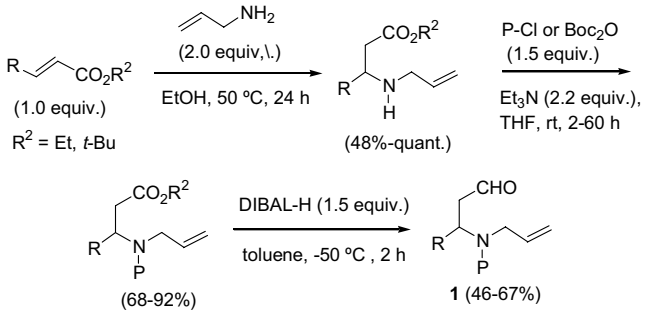
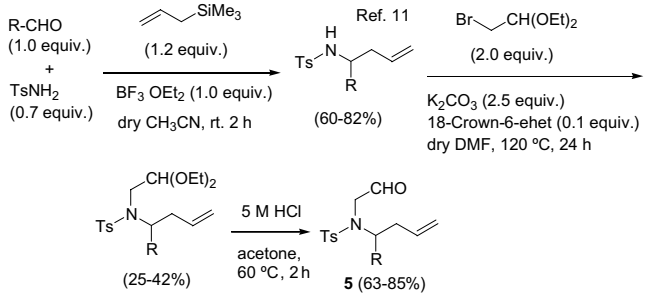
3. Tanaka, M.; Hikata, J.; Yamamoto, H.; Noguchi, M. *Heterocycles* **2001**, *55*, 223–226.
4. We used the term of $A^{1,3}$-strain for this interaction. However, in order to obtain a better understanding for this chemistry, we prefer the term of gauche–gauche interaction correctly.
5. Aldehydes **1** were prepared according to the following scheme:



6. To a solution of oxime **2a** (0.148 g, 0.50 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added dropwise a 5% aqueous sodium hyphochlorite (1.5 mL, 2.5 equiv) for 30 min. After completing the addition the reaction mixture was allowed to warm to room temperature and to stir for additional 1 h. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was subjected to a flash column chromatography on silica gel to afford **4a** (86%) as an eluent of hexane/ethyl acetate (3/1). Compound **4a**: Colorless prisms from 2-propanol; mp 125 °C; IR (KBr) 1340, 1280 (SO_2); ^{1}H NMR ($CDCl_3$; 270 MHz) 0.98 (3H, d, $J = 6.9$ Hz, 6-CH_3), 2.43 (3H, s, Ts-CH_3), 2.46–2.59 (2H, m, 7-H_2), 2.90 (1H, dd, $J = 11.2$, 13.2 Hz, 4-H), 3.32 (1H, m, 3-H), 3.77 (1H, dd, $J = 8.6$, 9.9 Hz, 3-H), 4.23 (1H, dd, $J = 6.9$, 13.2 Hz, 4-H), 4.48 (1H, dd, $J = 8.6$, 10.6 Hz, 3-H), 4.59 (1H, m, 6-H), 7.32, 7.70 (each 2H, each br d, $J = 8.3$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$; 67.8 MHz) 16.2 (6-CH_3), 21.5 (Ts-CH_3), 31.0 (7-C), 44.2 (4-C), 46.9 (3a-C), 48.9 (6-C), 70.6 (3-C), 126.9, 130.0, 137.4, 143.8 (Ar-C), 155.1 (7a-C).
7. During the preparation of this manuscript, a communication on the intramolecular nitrile oxide cycloaddition stereocontrolled based on the same as our strategy was found; Kadowaki, A.; Nagata, Y.; Uno, H.; Kamimura, A. *Teterahedron Lett.* **2007**, *48*, 1823–1825.
8. Structures of hexahydroisoxazolo[4,3-*c*]pyridine **4a** and hexahydroisoxazolo[3,4-*c*]pyridine **8d** were confirmed by single crystal X-ray structure analysis and their crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 621689 for **4a** and CCDC 621692 for **8d**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
9. Aldehydes **5** were prepared according to the following scheme:[11]



10. To a solution of oxime **6b** (0.93 g, 0.40 mmol) in CH_2Cl_2 (4 mL) cooled at 0 °C was added dropwise a 5% aqueous sodium hyphochlorite (1.5 mL, 2.5 equiv) for 12 min. After completing the addition, the reaction mixture was allowed to warm to room temperature and to stir for additional 1 h. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was subjected to a flash column chromatography on silica gel to afford **9b** (8%) as an eluent of hexane/ethyl acetate (5/1) and **8b** (82%) as an eluent of hexane/ethyl acetate (3/1). Compound **8b**: Colorless plates from hexane/benzene; mp 70 °C; ^{1}H NMR ($CDCl_3$; 270 MHz) 0.97 (3H, t, $J = 6.9$ Hz, 5-$CH_2CH_2CH_3$), 1.12 (1H, ddd, $J = 5.0$, 11.5, 13.2 Hz, 4-H), 1.36–1.49 (3H, m, 5-CH*H*CH_2CH$_3$), 1.74 (1H, m, 5-C*H*HCH$_2$CH$_3$), 1.84 (1H, ddd, $J = 1.3$, 5.9, 13.2 Hz, 4-H), 2.42 (3H, s, Ts-CH_3), 3.27 (1H, dd, $J = 6.9$, 11.6 Hz, 3-H), 3.37 (1H, m, 3a-H), 3.86 (1H, dd, $J = 1.0$, 16.2 Hz, 7-H), 4.10 (1H, m, 5-H), 4.45 (1H, dd, $J = 6.9$, 9.2 Hz, 3-H), 4.85 (1H, d, $J = 16.2$ Hz, 7-H), 7.30 (2H, br d, $J = 8.3$ Hz, Ar-H), 7.70 (2H, br d, $J = 8.3$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$; 67.8 MHz) 13.6 (5-$CH_2CH_2CH_3$), 19.3 (5-$CH_2CH_2CH_3$), 21.5 (Ts-CH_3), 32.1 (5-$CH_2CH_2CH_3$), 32.6 (4-C), 38.6 (7-C), 41.7 (3a-C), 52.2 (5-C), 73.7 (3-C), 127.2, 129.7, 137.2, 143.7 (Ts-C), 153.0 (7a-C). Compound **9b**: Colorless paste; ^{1}H NMR ($CDCl_3$; 270 MHz) 0.90 (3H, t, $J = 7.2$ Hz, 5-$CH_2CH_2CH_3$), 1.18–1.34 (4H, m, 5-$CH_2CH_2CH_3$), 1.45 (1H, ddd, $J = 8.9$, 10.6 Hz, 4-H), 2.33 (1H, td, $J = 7.6$, 13.2 Hz, 4-H), 2.44 (3H, s, Ts-CH_3), 2.69 (1H, m, 3a-H), 3.63 (1H, dd, $J = 8.3$, 11.5 Hz, 3-H), 3.97 (1H, m, 5-H), 4.08 (1H, dd, $J = 2.0$, 18.2 Hz, 7-H), 4.40 (1H, dd, $J = 8.3$, 9.9 Hz, 3-H), 4.67 (1H, d, $J = 18.2$ Hz, 7-H), 7.31 (2H, br d, $J = 8.3$ Hz, Ar-H), 7.69 (2H, br d, $J = 8.3$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$; 67.8 MHz) 13.8 (5-$CH_2CH_2CH_3$), 19.3 (5-$CH_2CH_2CH_3$), 21.4 (Ts-CH_3), 21.6 (5-$CH_2CH_2CH_3$), 32.3 (4-C), 40.1 (7-C), 44.0 (3a-C), 53.1 (5-C), 73.9(3-C), 127.3, 129.9, 137.2, 143.9 (Ts-C), 157.8 (7a-C).
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