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New C−C Coupling Reaction of Cyclic Nitronates with Carbon Nucleophiles. Umpolung of the Conventional Reactivity of Nitronates

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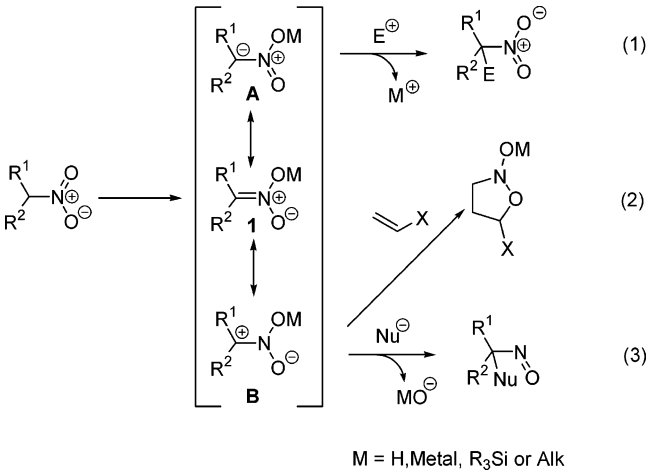
Abstract: Cyclic six-membered nitronates **1** are involved in diastereoselective C−C coupling reactions with various nucleophiles in the presence of either catalytic or stoichiometric amounts of TBDMSOTf to give the previously unknown *N*-siloxytetrahydrooxazines. The intermediacy of *N*,*N*-bis(oxy)iminium cations was proven by NMR data.

Nitronate functionality is normally associated with α-C-nucleophilic[1,2] or 1,3-dipolar reactivity[1] (Scheme 1, eqs 1 and 2), in which both reactivities constitute the basis of the numerous synthetic transformations of aliphatic nitro compounds (ANC).[1,2] However, as it is reflected in the canonical form B, the electronic structure of nitronates **1** can also provoke an α-C-electrophilic activity of these species if appropriate reaction partners are employed (eq 3).

Due to the feebly marked electrophilic reactivity of nitronates **1**, reactions similar to eq 3 are very rare, and all cases of C−C coupling of nitronates found in the literature imply the activation of the nitronate functionality with strong acids in harsh conditions (Scheme 2, e.g., M = H; A−X = a mixture of H−OTf and H−O_2CCF_3, 20−70 °C).[3,4]

Although iminium cations **2**, tentatively proposed as intermediates of these processes, should possess a high reactivity, the incompatibility of strong Brønsted acids with the majority of nucleophilic reagents narrows the scope of the application of this protocol for the selective organic transformations.

SCHEME 1. Reactivity of Nitronates



We suggest that the activation of nitronates **1** by means of silylation instead of protonation should improve the possibilities of this strategy. In the course of our systematic study of silylation of ANC, we have encountered a number of extraordinary processes, which proceed under very mild conditions and could be accounted for with an intermediacy of silylated cations **2** (M = A = SiR_3).[5] However, it is still an open issue whether cationic intermediates of this type can be generated as kinetically stable species and can be involved in the intermolecular C−C bond-forming reactions with carbon nucleophiles.[6] The investigation of this problem is the subject of the present paper.

In line with the above-mentioned facts, silyl (M = SiR_3) and alkyl (M = alkyl) nitronates **1** are considered possible precursors of target cations **2**. However, the protolytic lability of silyl nitronates and the thermal instability of acyclic alkyl nitronates[1] can hamper the systematic study of cations **2**. This circumstance prompted us to choose the generally more-stable and readily available six-

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(1) (a) Ono, N. *The Nitro Group in Organic Synthesis*; John Wiley & Sons-VCH: New York, 2001; pp 249−301. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.

(2) For employment of silyl nitronates in classical reactions of ANC. For modification of the Henry reaction, see: (a) Seebach, D.; Beck, A. K.; Lehr, F.; Webler, T.; Colwin, E. W. *Angew. Chem., Int. Ed. Engl.* **1981**, 20 and references therein. For modification of the Mannich reaction, see: (b) Kalinin, A. V.; Apasov, E. T.; Ioffe, S. L.; Kozjukov, V. P.; Kozjukov, V. P. *Bull. Acad. Sci. Div. Chem. Sci.* **1985**, *34*, 2442 (Russian translation, **1985**, 2635). For modification of the Michael reaction, see: (c) Marti, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann.* **1995**, 1193. (d) Tartakovsky, V. A.; Ioffe, S. L.; Dilman, A. D.; Tishkov, A. A. *Russ. Chem. Bull.* **2001**, *50*, 1936.

(3) Prakash, S.; Schleyer, P. V. R. *Stable Carbocation Chemistry*; John Wiley & Sons: New York, 1997; pp 525−539 and references therein.

(4) *N*,*N*-Bis(hydroxy)iminium cations are widely discussed as intermediates of the Nef reaction: Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc*. **1965**, *87*, 1742.

(5) For the suggested generation of **2** by silylation of silylnitronates, see: (a) ref 2d. For the suggested generation of **2** by interaction of *N*,*N*-bissiloxyenamines with certain electrophiles, see: (b) Dilman, A. D.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *J. Org. Chem*. **2000**, *65*, 8826. (c) Dilman, A. D.; Ioffe, S. L.; Mayr, H. *J. Org. Chem*. **2001**, *66*, 3196. (d) Ustinov, A. V.; Dilman, A. D.; Ioffe, S. L.; Strelenko, Yu. A.; Smit, W. A.; Tartakovsky, V. A. *Mendeleev Commun*. **2003**, 74.

(6) (a) It is likely that the bistrimethylsilyl derivative of methazonic acid, obtained 40 years ago by silylation of nitromethane, is formed as a result of the analogue's C−C coupling between cation $[CH_2{=}N(OSiMe_3)_2]^+$ and silyl nitronate $CH_2{=}N(O)OSiMe_3$: Klebe, J. F. *J. Am. Chem. Soc*. **1964**, *86*, 3399. For intramolecular trapping of *N*,*N*-bis(siloxy)iminium cations, see: (b) Tishkov, A. A.; Kozintsev, A. V.; Lyapkalo, I. M.; Ioffe, S. L.; Kachala, V. V.; Strelenko, Yu. A.; Tartakovsky, V. A. *Tetrahedron Lett.* **1999**, 5075. (c) Smirnov, V. O.; Tishkov, A. A.; Kozintsev, A. V.; Lyapkalo, I. M.; Ioffe, S. L.; Kachala, V. V.; Strelenko, Yu. A.; Tartakovsky, V. A. *Russ. Chem. Bull*. **2000**, *49*, 874.

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SCHEME 2. Strategy for Nucleophilic Addition to Nitronates

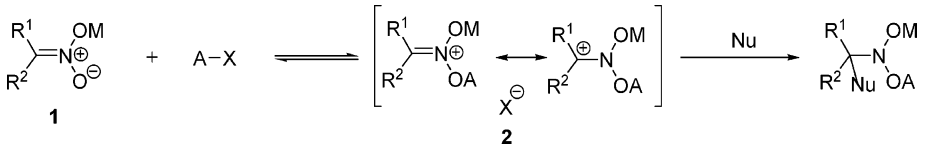


TABLE 1. C−C Coupling of Nitronates 1 with Silyl Ketene Acetal 3

entry	1	R^1	R^2	R^3	R^4	oxazine 4	yield (%)	ratio[a]
1	**1a**	H	Ph	Me	Me	**4a**	91	
2	**1b**	H	Me	Me	Me	**4b**	88	
3	**1c**	H	Ph	OMe	Me	**4c**	91	
4	**1d**	H	An	H	OEt	**4d**	93	
5	**1e**	H	An	OEt	H	**4e**:**4e′**	88	1.5:1
6	**1f**	H	OBz	Me	Me	**4f**:**4f′**:**4f″**	88	19:1:2[b]
7	**1g**	H	OCO−C_6H_4−NO_2-*p*	Me	Me	**4g**:**4g′**: **4g″**	92	20:1.5:1[c]
8	**1h**	Me	H	H	H	**4h**	95	
9	**1i**	Me	H	Me	Me	**4i**	90	
10	**1j**	Me	Ph	Me	Me	**4j**	92	

[a] Determined by integration of the ^{1}H NMR spectra of the crude product. [b] The column chromatography allowed us to isolate pure **4f** (77%) and a mixture of its invertomer **4f″** and diastereomer **4f′** (2:1; 11%). **4f** transforms slowly into **4f″** during storage in $CDCl_3$ solution at rt (see Supporting Information). [c] The column chromatography allowed us to isolate pure **4g** (82%) and a mixture of its invertomer **4g″** and diastereomer **4g′** (2:3; 10%). **4g** transforms slowly into **4g″** during storage in $CDCl_3$ solution at rt (see Supporting Information).

membered cyclic nitronates **1a**−**j** (Table 1) as the objects of silylation for this preliminary study.[7]

The generation of iminium cations **2** from nitronates **1** and TBDMSOTf has been studied by NMR with the example of **1a** (Scheme 3).

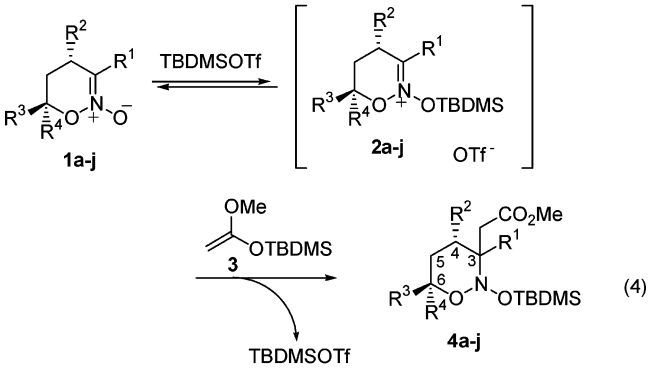
The addition of an equimolecular amount of TBDMSOTf to a solution of **1a** in $CDCl_3$ in an NMR tube leads to the generation of cation **2a** (with significant downfield shifts of both ^{1}H and ^{13}C NMR signals of the CH-3 and CH-4 fragments[8]). The characteristic ^{29}Si signal of **2a** (δ = 50.1 ppm) was also observed in the ^{29}Si NMR spectrum.

The presence of a large $^3J_{H,H}$ value for the CH-4 proton in cation **2a** and its precursor **1a** shows that both species exist predominantly in a half-chair conformation with the pseudoequatorial arrangement of the Ph group.

The study of the correlation of ^{1}H NMR spectra with temperature has shown an exchange between **1a**, **2a**, and TBDMSOTf to be slow at −50 °C and rapid at −20 °C (see Supporting Information, page S26). The reversibility of the observed changes indicated that **2a** is stable up to 0 °C for at least 15 min.[9]

The introduction of two electronegative oxygen atoms to the nitrogen center of the iminium moiety should bring about a noticeable increase in its electrophilicity, and one could expect then species **2** to react smoothly with the silyl-capped nucleophiles.[10]

An efficient C−C coupling of nitronates **1a**−**j** with the model ketene acetal **3** was indeed achieved in the presence of a catalytic amount of TBDMSOTf under very mild conditions (eq 4 and Table 1).[11] As a result, a representative set of functionalized *N*-siloxytetrahydro-[4*H*]-oxazines (**4a**−**j**) have been prepared in excellent yields.



The presence of a substituent (R^1 = Me) at C-3 significantly retards the reaction, and an increase in the reaction time and amount of catalyst is needed to achieve the complete conversion (see Table 1, entries 8−10).

The formation of compounds **4** proceeds mostly with a high diastereoselectivity. In fact, products **4a**−**d**,**h**−**j** were isolated as individual diastereomers in almost quantitative yields.[12] For adducts **4f**,**g**, minor diastereoisomers **4f′**,**g′** were also obtained in ≤6% yields (entries 6 and 7). Practically no diastereoselectivity was observed for the formation of a mixture of **4e** and **4e′** (entry 5).

To evaluate the scope and limitations of this new C−C coupling reaction, the reactivity of model nitronate **1a** toward some other nucleophiles was investigated (Scheme 4).

Thus, nitronate **1a** reacts with silyl enol ether **5** to give the expected ketone **6**. The same diastereomer of product **6** was also obtained upon the interaction of **1a** with enamine **7** followed by the hydrolysis of salt **8** that formed initially.

In contrast to enamine **7**, its silylated analogue **9** underwent an exclusive N−C coupling with **1a** to give enamine **10** in good yield.[13] At the same time, *N*-siloxyenamine **11** turned out to be unreactive toward **1a**.

Methallylstannane **12** reacts with **1a** to give the corresponding oxazine **13**.

(7) Compounds **1a**−**j** were prepared from nitromethane or nitroethane using the modified procedures of the following: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Kanemasa, S.; Yoshimiya, T.; Wada, E. *Tetrahedron Lett.* **1998**, 8869.

(8) Similar changes in NMR spectra upon the silylation of nitrones have been attributed to the generation of *N*-siloxy-*N*-alkyliminium cations: Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallee, Y. *Tetrahedron* **2000**, *56*, 791.

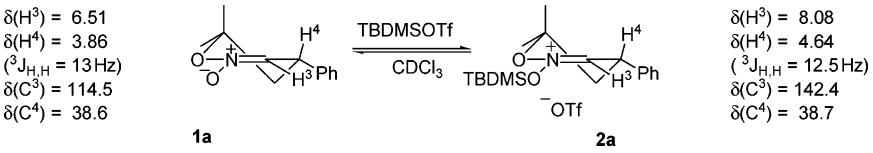
(9) The NMR investigation of the *N*,*N*-bis(oxy)iminium cations formed upon the interaction of TBDMSOTf with other nitronates will be published in due course.

(10) The electrophilicity parameter (*E*) for *N*,*N*-dialkyliminium cations is ca. −5: Mayr, H.; Ofial, A. R. *Tetrahedron Lett.* **1997**, 3503. It might be expected that the *E* parameter for cations **2** is higher.

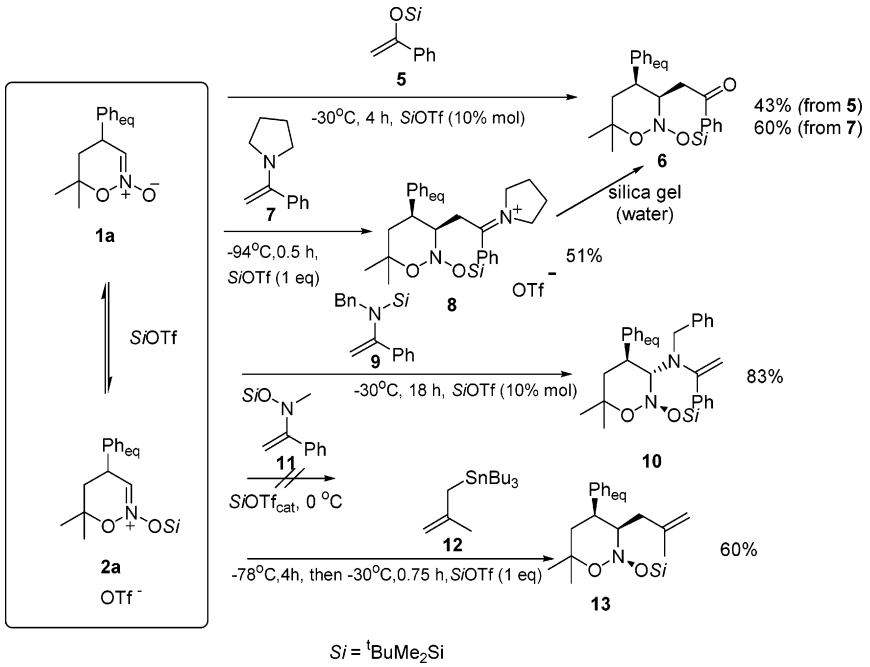
(11) For catalytic activation of electrophilic reagents with silicon Lewis acids, see: Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733.

(12) The ^{1}H NMR data of crude reaction mixtures did not reveal the presence of the diastereomers, except those shown in Table 2.

SCHEME 3. Interaction of Nitronate 1a with TBDMSOTf (δ in parts per million relative to TMS)



SCHEME 4. Interaction of Nitronate 1a with Various Nucleophiles Promoted by TBDMSOTf



Reactions **1a** + **7** and **1a** + **12** require no less than a stoichiometric amount of TBDMSOTf. All adducts shown in Scheme 4 were obtained as individual diastereomers.[12]

The configurations of nitronates **1** and the target products were determined by means of NMR (analysis of the $^3J_{H,H}$ coupling constants[14] and NOE experiments) and X-ray analysis (see Table 2).[15] For nitronates **1a**−**j** and cations **2a**−**j**, a half-chair conformation was assumed. The X-ray analysis revealed that tetrahydrooxazines **4c**,**d**,**f**,**g**″,**j** and **10** exist in a chair conformation in a solid state.[15,16]

It should be mentioned that X-ray data secured an unambiguous determination of the configuration of the endocyclic nitrogen atom in these adducts.[17] NMR and X-ray data show that all of the studied compounds adopt

TABLE 2. Stereochemical Outcome of Reaction in Eq (5)

entry	1	R2 (position)[a]	product	R1 relative to R2 (position of R1)[a]	OSi relative to R1 (position of OSi)
1	**1a**	Ph (eq)	**4a**	trans (eq)	trans (eq)[b]
2	**1b**	Me (eq)	**4b**	trans (eq)	trans (eq)[b]
3	**1c**	Ph (eq)	**4c**	trans (eq)	trans (eq)[c]
4	**1d**	An (ax)	**4d**	cis (ax)	trans (ax)[c]
5	**1e**	An (eq)	**4e**	cis (eq)	trans (eq)[b]
			4e′	trans (eq)	trans (eq)[b]
6	**1f**	OBz (ax)	**4f**	cis (eq)[c]	cis (eq)[c]
			4f′	trans (eq)	trans (eq)[b]
			4f″	cis (ax)[d]	trans (eq)[d]
7	**1g**	OCO−C_6H_4−NO_2-*p* (ax)	**4g**	cis (eq)[d]	cis (eq)[d]
			4g′	trans (eq)	trans (eq)[b]
			4g″	cis (ax)[c]	trans (eq)[c]
8	**1h**	H	**4h**		trans (eq)[b]
9	**1i**	H	**4i**		trans (eq)[b]
10	**1j**	Ph (eq)	**4j**	trans (eq)[c]	trans (eq)[c]
11	**1a**	Ph (eq)	**6**	trans (eq)	trans (eq)[b]
12	**1a**	Ph (eq)	**8**	trans (eq)	trans (eq)[b]
13	**1a**	Ph (eq)	**10**	trans (eq)[c]	cis (ax)[c]
14	**1a**	Ph (eq)	**13**	trans (eq)	trans (eq)[b]

[a] Established by NMR. [b] Established by comparison with NMR data for **4c**. [c] Established by X-ray data. [d] Stereochemical assignments for **4f**″ and **4g** were based on the similarity of their NMR spectra with those of **4g**″ and **4f**, respectively.

(13) The N-attack of carbenium cations on enamines can be characterized by a rate higher than that of the C-attack (for the discussion, see ref 10 and references therein). Normally, *N*-vinylammonium cations are thermodynamically less stable than the isomeric iminium ions (i.e., the products resulted from C-attack). Therefore, N-alkylated enamine **9** could be formed as a kinetic product, which cannot rearrange to the iminium cation like **8** due to the fast irreversible loss of the silyl group.

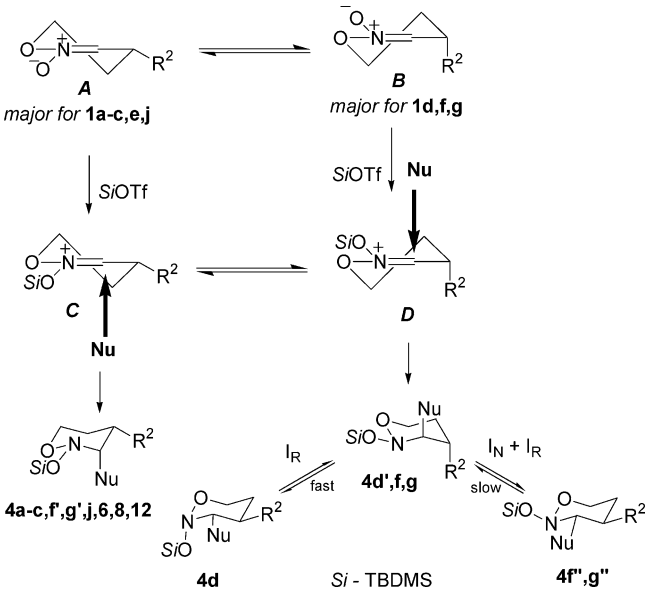
(14) (a) Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*; Thieme, G., Ed.; Verlag: Berlin, 1995; p 108. (b) Lambert, J. B.; Takeuchi, Y. *Cyclic Organonitrogen Stereodynamics*; VCH: New York, 1992; Chapters 7.1.1 and 7.2.1 and references therein.

(15) CCDC 230273 (**4d**), CCDC 230274 (**4c**), CCDC 230275 (**4f**), CCDC 230276 (**10**), CCDC 230277 (**4g**″), and CCDC 230278 (**4j**) contain the supplementary crystallographic data for this paper. These data can be obtained online (http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi) free of charge.

(16) For conformational analysis of some *N*-oxides, 5,6-dihydro-[4*H*]-oxazines, and tetrahydro-[4*H*]-oxazines, see ref 14b and the following: Tishkov, A. A.; Lesiv, A. V.; Khomutova, Yu. A.; Strelenko, Yu. A.; Nesterov, I. D.; Antipin, M. Yu.; Ioffe, S. L.; Denmark, S. E. *J. Org. Chem*. **2003**, *68*, 9477.

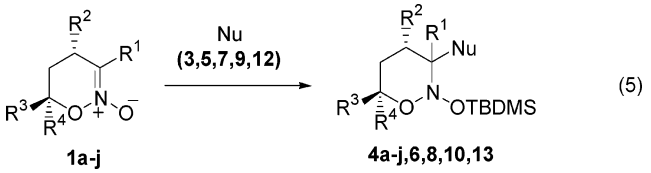
(17) For data on the hindered inversion of the nitrogen atom in the systems bearing the O−N−O fragment, see: Rudchenko, V. F. *Chem. Rev*. **1993**, *93*, 725.

SCHEME 5. Stereoselectivity of the C−C Coupling Reaction of Cations 2 with Nucleophiles



the same conformations in a solution and in a crystal state.

The stereochemical course of the reaction **1a**−**j** + Nu (eq 5) is described in Table 2 and Scheme 5. The general feature of this reaction is the formation of cis-functionalized tetrahydrooxazines (*e*-R^2 and *a*-Nu) from nitronates with *e*-R^2 and trans-functionalized tetrahydrooxazines (*a*-R^2 and *a*-Nu) from nitronates with *a*-R^2.



(5)

Nitronates **1** should exist as a mixture of conformers A and B with a low barrier of interconversion.[18] It seems reasonable to suggest that the same factors could determine the relative stability of nitronates **1** and silylated cations **2** derived thereof. The next suggestion is that only a major conformation of cation **2** reacts, in general, with nucleophiles.

The attack of a nucleophile on an oxazinium ion should proceed from the side opposite to the C-6 atom of the oxazine ring (bold arrows in Scheme 5).[19] Commonly, the most-stable conformer of a target product is generated initially. However, tetrahydrooxazine **4d**, obtained in the reaction of **1d** + **3**, is likely a product of the ring inversion (I_R) of the initially formed unstable **4d′**.

The slow transformation of products **4f** and **4g** into **4f″** and **4g″**, respectively, is most likely a result of a sequence of the I_N and I_R stereodynamic processes (cf. refs 14b and 17).

The formation of diastereomers **4e′**−**g′**, along with **4e**−**g**, in reactions of **1e**−**g** with ketene acetal **3** can be observed due to the competitive attack of **3** on both conformers C and D of cations **2e**−**g**.[20]

In conclusion, the described stereoselective C−C coupling reaction of the cyclic six-membered alkyl nitronates with nucleophiles creates an opportunity for the preparation of various tetrahydro-[4*H*]-*N*-siloxyoxazines, bearing the functionalized substituents at C-3.[21] The search for applications of this new class of compounds in organic synthesis, as well as further studies of the masked electrophilic reactivity of various nitronates, will soon be the subject of our research.

Experimental Section

General Procedure for Addition of 3 to Cyclic Nitronates 1a−j. To a stirred solution of nitronate **1** (1 mmol) and ketene acetal **3** (0.24 mL, 205 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added TBDMSOTf [0.023 mL, 0.1 mmol, if R^1 = H (**1a**−**g**) or 0.046 mL, 0.2 mmol, if R^1 = Me (**1h**−**j**)]. The reaction mixture was stirred for 1 h at −78 °C (R^1 = H) or for 18 h at −78 °C (R^1 = Me) (TLC monitoring) and was quenched at −78 °C by the successive addition of hexane (5 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL). The temperature was allowed to reach 20 °C; the organic layer was separated, and the aqueous layer was back-extracted with hexane (2 × 5 mL). Combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (silica gel, EtOAc/hexane, 1:20 → 1:3) to give **4** (88−95%).

Similar procedures were used for the preparation of compounds **6**, **8**, **10**, and **13** (for details, see the Supporting Information).

Acknowledgment. This work was performed with the financial support of the Russian Basic Research Foundation (Grants 02-03-33350, 03-03-32777, 03-03-04001, and 03-03-06149) Deutsche Forschungsgemeinschaft MA 673/19 and Federal Program "Integration" (Project B0062). We thank Drs. I. M. Lyapkalo and A. D. Dilman for helpful discussions.

Supporting Information Available: Full experimental procedures, analytical data for all compounds, CIF files for **4c**,**d**,**f**,**g″**,**j** and **10**, and NMR data for cationic intermediate **2a** and for some initial and target products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For the discussion of I_R and I_N processes in oxazine derivatives, see ref 14b.

(19) For the discussion of stereochemistry of the reduction of 5,6-[4*H*]-dihydrooxazines, see: Zimmer, R.; Arnold, Th.; Homann, K.; Reissig, H.-U. *Synthesis* **1994**, 1050.

(20) Alternatively, the generation of **4e′**−**g′**, along with **4e**−**g**, could be explained as a result of the competition between syn and anti approaches of **3** relative to C-6 of the cationic intermediate **2** (cf. ref 19).

(21) The prepared tetrahydrooxazine derivatives **4a**−**j**, **6**, **8**, **10**, and **13** could be considered structural analogues to the well-known *N*-trialkylsiloxyisoxazolidines. (For preparation of natural and biologically active compounds from *N*-trialkylsiloxyisoxazolidines, see ref 1b.)