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Five-Membered Cyclic Nitronates in C–C Coupling with 1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethylene

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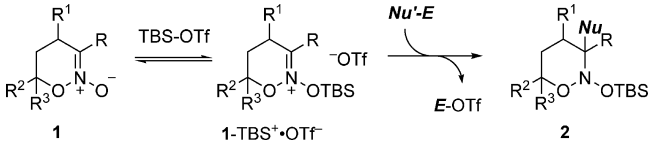
Five-membered cyclic nitronates **3** undergo TBSOTf-catalysed C–C coupling reactions with silyl ketene acetal **4** to give good to excellent yields of 3,3-disubstituted *N*-(OTBS)-isoxazolidines **5**, which could not be obtained by previously known procedures. The problems of diastereoselectivity of the C–C coupling reactions are discussed. The transformations of the nitroso acetals **5** upon action of Ac_FOH/methanol or some reducing agents (H_2/Ni_{Ra}, LAH, Al/Hg) have been examined.

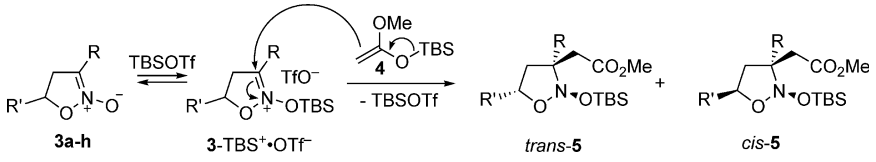
Introduction

Recently, we reported on a radically new reaction of covalent nitronates, their C–C coupling reactions with π nucleophiles. This process was performed on six-membered cyclic nitronates **1** (Scheme 1).[1,2] The reaction proceeds with the electrophilic assistance of trialkylsilyl triflates (usually TBSOTf) via the cationic intermediate **1**-TBS$^+$·OTf$^-$. The formation of the new C–C bond is accompanied by a reorganization of the π system of the nucleophile Nu′-E. If the electrofuge E is a TBS group, it is appropriate to use only a catalytic amount of TBSOTf (10–20 mol-%) in this reaction.

The nitroso acetals **2** are mainly formed with high diastereoselectivity.[1,2] The stereochemical outcome of the reactions can be explained by distal-to-C-6 attack of the nucleophile on the dominant conformer of the cationic intermediate **1**-TBS$^+$·OTf$^-$. In addition, in the transition state, the Nu fragment and the lone electron pair (LEP) on the nitrogen atom are antiperiplanar. This leads to a *trans* arrangement of the nitrogen LEP and Nu in the formed nitroso acetals **2**.



Scheme 1. C–C coupling reactions of six-membered cyclic nitroso acetals. R = H, alkyl; R^1, R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, alkoxyl; TBS = $SiMe_2tBu$; Nu′-E = π nucleophile; E = electrofuge (trialkylsilyl or trialkylstannyl).



Scheme 2. C–C coupling reactions of five-membered cyclic nitronates **3a**–**h** with silyl ketene acetal **4** under TBSOTf catalysis.

Cationic intermediates similar to **1**-TBS$^+$·OTf$^-$ were also observed with other types of nitronates.[2] Therefore one could expect that C–C coupling reactions with π nucleophiles would be a common reaction for covalent nitronates. In this connection, we report in this paper the C–C coupling reactions of five-membered cyclic nitronates **3** with silyl ketene acetal **4** (Scheme 2).

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Results and Discussion

Addition of Silyl Ketene Acetal 4 to Nitronates 3a–h

The cation **3**-TBS$^+$ (R = Me, R′ = Ph, Scheme 2), which is formed upon the action of TBSOTf on nitronate **3a**, was studied by low-temperature NMR spectroscopy in CD_2Cl_2.[2] This prompted us to examine the reactions of other five-membered cyclic nitronates **3** in the above-mentioned C–C coupling reactions with silyl ketene acetal **4**.

The starting nitronates **3a**–**h** (see Table 1) were obtained from primary aliphatic nitro compounds (ANCs) of general formula RCH_2NO_2 and terminal olefins $R'CH{=}CH_2$ according to a previously reported procedure.[3] Silyl ketene acetal **4** was chosen as the test π nucleophile for the C–C coupling reactions with nitronates **3** because it has been shown to possess appropriate reactivity in coupling reactions with nitronates **1**, including C-3-substituted representatives.[2] In addition, a peculiarity of the structure of the putative adducts **5** also provoked us to use ketene acetal **4**. Indeed, at the moment, no common approach is known for the preparation of *N*-siloxyisoxazolidines with a flexible α proton in the substituent at C-3, such as the MeO_2CCH_2 group. The classic strategy, [3+2] cycloaddition of nitrone esters with terminal olefins,[4] is inefficient for the preparation of isoxazolidines similar to products **5**[5] (Scheme 3). Therefore, successful realization of the reaction between **3** and **4** could extend the list of available *N*-siloxyisoxazolidines. The main results of the coupling reactions between **3** and **4** are listed in Table 1.

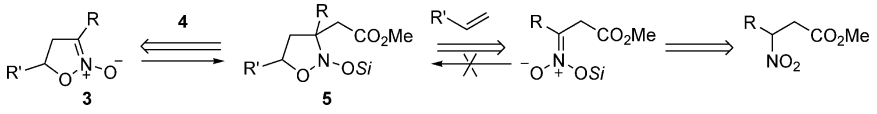
Optimization of the reaction conditions was performed on nitronate **3a**. It was found that the workup procedure previously used for six-membered nitronates[1,2] (procedure A in Table 1) is inappropriate for the isolation of **5a**. Under these conditions, only traces of adduct **5a** were detected by TLC in a complex mixture of unidentified products (see Table 1, Entry 1). However, the addition of triethylamine and methanol prior to aqueous workup allowed the isolation of adduct **5a** in good yield (see procedure B, Table 1, Entry 2). Nevertheless, elevation of the reaction temperature from –94 °C to the more convenient –78 °C led to a significant decrease in the yield of the target derivative **5a** (see Table 1, Entry 3). This obstacle could be overcome by the addition of 2,6-lutidine to the reaction mixture prior to the addition of the silyl triflate (see procedure C, Table 1, Entry 4). Under these conditions the yield of **5a** was even higher than that obtained by procedure B. We believe that the need for such modifications arises from a higher sensitivity of **5a** compared with **2** towards traces of TfOH. The latter may be present as an impurity in moisture-sensitive TBSOTf or as a byproduct of some unidentified side-reaction. Note that the overall yield decreased owing to a decrease in the yield of only the *trans* isomer (see Table 1, Entries 2–4). Thus, the *cis* isomer can be considered as more stable than the *trans* isomer under the reaction and workup conditions.

Procedure C, which appears to be the most efficient and convenient method of workup for the C–C coupling reaction of five-membered cyclic nitronate **3a**, was applied to the C–C coupling reactions of silyl ketene acetal **4** with other nitronates **3b**–**h**. The corresponding adducts **5b**–**h** were isolated in good-to-excellent yields (Table 1). Only two adducts (**5b**,**h**) were isolated as single *trans* diastereoisomers. In the other cases, mixtures of *cis* and *trans* isomers of the adducts **5** were obtained. In two cases (**5c**,**g**), these mixtures

Table 1. C–C coupling reactions of five-membered cyclic nitronates **3** with silyl ketene acetal **4**.

Entry	**3** and **5**	R	R′	*T* [°C]/*t* [h] (workup method)[a,b]	Isolated yields of adducts **5** [%]		
					trans-**5**	*cis*-**5**	Total yield of **5** (*trans*/*cis*)
1	**a**	Me	Ph	–94/1.5 (A)	–	–	–
2	**a**	*Me*	*Ph*	*–94/1.5 (B)*	*54*	*16*	*70 (3.4:1)*
3	**a**	Me	Ph	–78/1.0 (B)	28	15	43 (1.9:1)
4	**a**	*Me*	*Ph*	*–78/1.0 (C)*	*61*	*16*	*77 (3.8:1)*
5	**b**	Me	OEt	–78/2.0 (C)	90	–	90 (*trans* only)
6	**c**	Me	CO_2Me	–78/2.0 (C)	66	6	72 (11:1)
7	**d**	Et	Ph	–78/1.5 (C)	[c]		77 (3.5:1)
8	**e**	*n*-C_6H_{13}	Ph	–78/1.5 (C)	[c]		91 (4.3:1)[d]
9	**f**	Bn	Ph	–78/1.25 (C)	[c]		71 (5.5:1)
10	**g**	$(CH_2)_2CO_2Me$	Ph	–78/3.5 (C)	68	22	90 (3:1)[e]
11	**h**	Bn	OEt	–94/2.0 (B)	89	–	89 (*trans* only)

[a] Optimal conditions for the preparation of **5a** are marked in italic font. [b] A: workup with a saturated aqueous solution of $NaHCO_3$ (at –94 °C); B: successive addition of Et_3N (0.3 equiv.) and MeOH (0.25 equiv.) prior to workup with a saturated aqueous solution of $NaHCO_3$ (at –94 °C); C: C–C coupling reactions at –78 °C in the presence of 2,6-lutidine (0.25 equiv.), addition of MeOH (0.25 equiv.) prior to workup with a saturated aqueous solution of $NaHCO_3$ (at –78 °C). [c] Inseparable mixture of *cis*/*trans* isomers (see Scheme 2). [d] The isolated total yield is 64% at 70% conversion of nitronate **3e** (starting **3e** was recovered in 30% yield). [e] The isolated total yield is 45% at 50% conversion of nitronate **3g** (starting **3e** was recovered in 50% yield).



Scheme 3. C–C coupling reactions of **3** and **4** as the only approach to *N*-siloxyisoxazolidines **5**.

could be separated by column chromatography. In the other cases (**5d**–**f**), the *cis* and *trans* isomers were characterized in their mixtures.

Comparison of the Reactivity of Five- and Six-Membered Cyclic Nitronates

To estimate the scope of the process depicted in Scheme 2, the reactivities of five- and six-membered nitronates in C–C coupling reactions with π nucleophiles were compared. To this end, a competitive reaction of the model nitronates **1a** and **3a** with silyl ketene acetal **4** was carried out (Scheme 4).

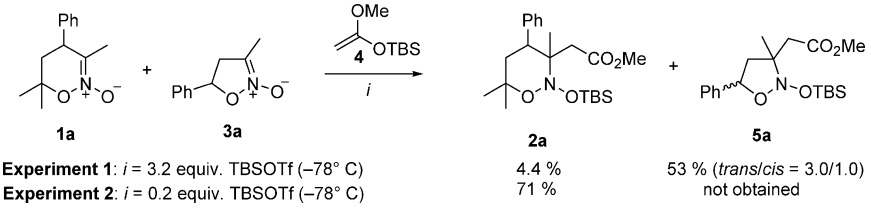
It is evident that the ratio of TBSOTf/(**1a** + **3a**) significantly affects the outcome of this competitive reaction, which can be readily explained by a more detailed analysis of various equilibrium processes in the reaction mixture (see Scheme 5).

The equilibration of **1a**, **3a** and TBSOTf can be described by the following three processes: (a) the formation of the six-membered cation **1a**-TBS$^+$·OTf$^-$ from nitronate **1a** and the silyl triflate, (b) the formation of the five-membered cation **3a**-TBS$^+$·OTf$^-$ from nitronate **3a** and the silyl triflate and (c) silyl exchange between the cation and nitronate of different ring sizes, that is, **1a**-TBS$^+$·OTf$^-$ + **3a** ⇌ **1a** + **3a**-TBS$^+$·OTf$^-$.

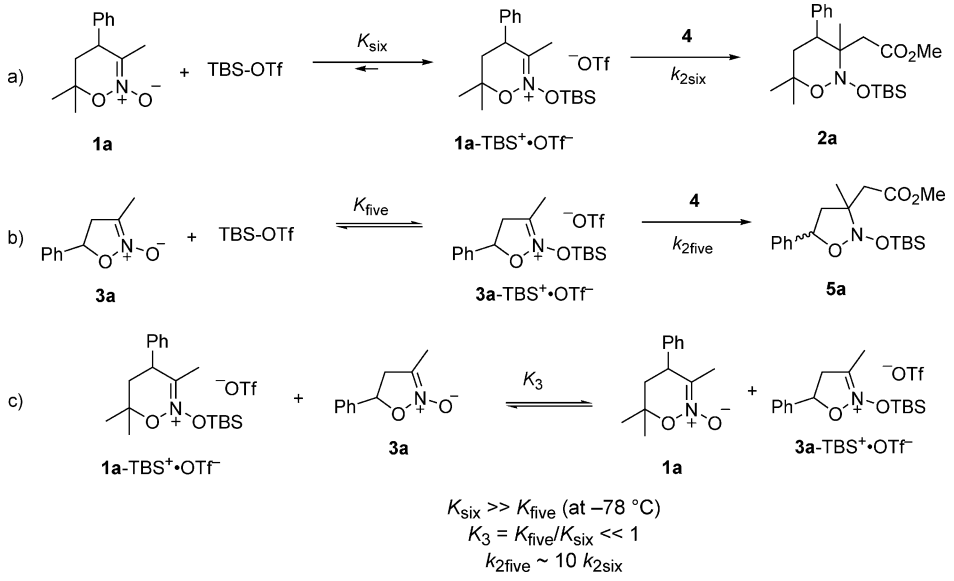
Clearly, the third process could be described as a superposition of the first and the second process reversed. Processes (a) and (b) have been studied previously[2] and allow the third process to be described.

It was found that nitronate **1a** at –78 °C in the concentration range of 0.2–0.03 M is converted completely into the ionic pair **1a**-TBS$^+$·OTf$^-$, even upon treatment with a minimal excess of TBSOTf. At the same time, for the system of **3a** and TBSOTf, a flexible equilibrium with the ionic pair **3a**-TBS$^+$·OTf$^-$ forms. The thermodynamic parameters of this equilibrium were established as $\Delta H° = -29.0 \pm 1.3$ kJ/mol and $\Delta S° = -104.8 \pm 6.7$ J/mol K.[2] According to these data, at –78 °C the equilibrium constant $K_{five} = 197$ L/mol. Correspondingly, for a 0.1 M solution of **3a**, the conversion into **3a**-TBS$^+$·OTf$^-$ is equal to 80% in the presence of 1.0 equiv. of TBSOTf and to 95% in the presence of 2.0 equiv. of TBSOTf. These data reveal that at lower temperatures $K_{six} >> K_{five}$.

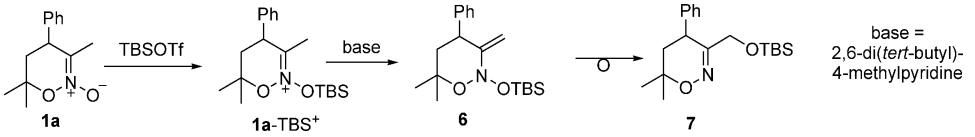
Under the conditions of the first experiment (Scheme 4), in the presence of a large excess of the silyl triflate, the conversion of the two starting nitronates into the corresponding cations is almost complete. Therefore the ratio of the C–C coupling products **5a**/**2a** corresponds to the ratio of the rate constants k_{2five}/k_{2six}. Consequently, the cation **3a**-TBS$^+$ derived from the five-membered nitronate **3a** in the reaction with ketene acetal **4** is more reactive than the cat-



Scheme 4. Competitive reaction of nitronates **1a** and **3a** with silyl ketene acetal **4**.



Scheme 5. Equilibrium processes in **1a**/**3a**/TBSOTf system and irreversible C–C coupling.



Scheme 6. Formation of the dihydrooxazine **7** in the competitive reaction of **1a** and **3a** with **4** and an excess of TBSOTf.

ion **1a**-TBS$^+$ derived from the six-membered cyclic nitronate **1a** by one order of magnitude. The difference in the ring substitution pattern does not allow one to make general conclusions about the relative reactivities of the cations of the five-membered nitronates. However, the above result is one reason to expect that for C–C coupling reactions with π nucleophiles no drastic changes in reactivity will take place by switching from six- to five-membered nitronates, and thus the scope of C–C coupling reactions of five-membered nitronates with π nucleophiles will be the same as that for six-membered nitronates.[1]

The second experiment in Scheme 4 can be explained by assuming that the rate of silyl transfer is much higher than the rate of C–C coupling. In this context, direct silylation of the cyclic nitronates with cationic intermediates, that is, process (c), should also be discussed [see Equation (c) in Scheme 5]. In this process the equilibrium constant K_3 is equal to K_{five}/K_{six} or, in other words, $K_3 << 1$. With this consideration, in the case of a deficiency of the silyl triflate, the ionic pair **1a**-TBS$^+$·OTf$^-$ acts as the only reactive species in the competitive C–C coupling reaction with ketene acetal **4**.

In the first experiment of Scheme 4, the reaction mixture contained the dihydro-oxazine **7** as well the nitroso acetals **2a** and **5a** (Scheme 6, 36% yield based on **1a**). Its structure was confirmed by full agreement of its spectra with the spectra of a sample prepared independently according to a known procedure.[6]

Both experiments in Scheme 4 were conducted in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a proton trap, according to the conditions of previously described kinetic investigations.[2] Evidently, compound **7** forms after deprotonation of the cationic intermediate **1a**-TBS$^+$ with base followed by rearrangement of the enamine **6**.[6] At the same time, the formation of oxazine **7** was not observed in the kinetic investigation of the reaction of **1a**-TBS$^+$ with a moderate excess of silyl ketene acetal **4**.[2] Therefore one can conclude that dihydrooxazine **7** is formed from nitronate **1a** only after full consumption of the nucleophile **4**. Thus, the formation of **7** does not affect the **5a**/**2a** ratio and should not be taken into account in the analysis of the above-mentioned competitive experiments.

Structure Elucidation of the Isoxazolidines 5a–h

The structures of the isoxazolidines **5a**–**h** were unambiguously confirmed by elemental analysis as well as by ^{1}H, ^{13}C, ^{29}Si NMR and 2D NMR spectroscopy (COSY, HSQC and NOESY). The isoxazolidines **5a**–**c**,**g**,**h** were characterized as individual diastereomers, whereas the nitroso acetals **5d**–**f** were analysed as mixtures of diastereomers (see Table 1).

It is well known that the nitrogen inversion of *N*-alkoxy- and *N*-silyloxyisoxazolidines is very slow at room temperature.[7] Thus, to determine the structures of the isoxazolidines **5** the relative configurations of the three stereocentres, namely the N, C-3 and C-5 atoms, had to be identified. From the literature data,[8] an envelope conformation with the nitrogen atom in the envelope flap and the OTBS substituent in a pseudo-axial position was assumed for the isoxazolidines **5**. The NOESY technique was used to determine the arrangement of the substituents. The most informative spatial interactions are shown in Figure 1.

The characteristic 2-H/OTBS interaction reflects a *cis* orientation of the pseudo-axial OTBS group and the pseudo-equatorial CH_2CO_2Me moiety for all adducts **5a**–**h** (Figure 1). (Previously, *cis* configurations of the CH_2CO_2Me and OTBS moieties were also noted for the adducts of six-membered cyclic nitronates **1** with silyl ketene acetal **4** and other π nucleophiles.[1,2]) The relative configurations of the R′ and CH_2CO_2Me substituents (or R′ and OTBS) were determined by the presence of a 1-H/5-H interaction in the *cis* isomers and the 5-H/OTBS interaction in the *trans* isomers (see Figure 1).

Thus, all the diastereomers of the adducts **5a**–**h** have an identical relative configuration of the N atom and C-3, but the diastereomeric pairs differ in each case by the relative configuration of the stereocentres at C-3 and C-5.

Stereochemistry of the C–C Coupling Reactions of the Cations 3-TBS$^+$ with π Nucleophiles

It appears that the mechanistic considerations used to explain the stereochemical outcomes of the C–C coupling reactions of six-membered cyclic nitronates **1** with π nucleo-

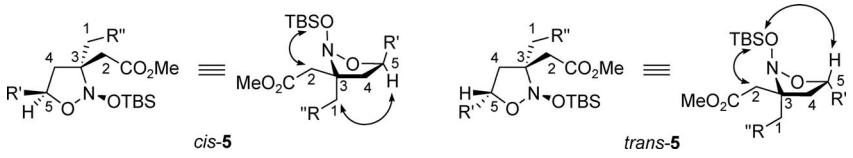


Figure 1. Key NOESY correlations for the *trans* and *cis* isomers of the nitroso acetals **5**.

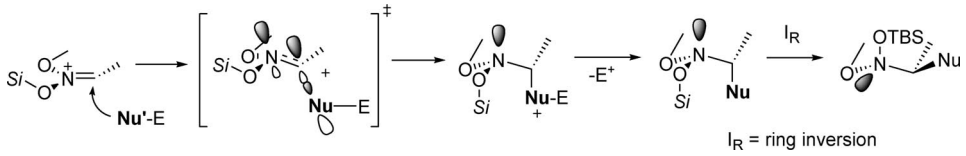


Figure 2. Proposed course of C–C coupling reactions of **3** and **4**.

philes[2] are also applicable to five-membered cyclic nitronates **3**. According to the mechanistic scheme described above, the relative configurations of the C-3 and N stereocentres in the nitroso acetals **5** will be defined by the spatial arrangement of the nascent LEP of the N atom and the new C–C bond in the transition state (TS), and the relative configurations of the C-3 and C-5 stereocentres of the nitroso acetals **5** will depend on the preference of the facial approach of the nucleophile **4** to the plane of the reactive conformation of the cation **3**-TBS$^+$, that is, distal or proximal nucleophilic attack with respect to the prominent C-5 atom.

The *trans* configuration of the nucleophile moiety and the nitrogen LEP in all the diastereomers of the adducts **5** (see the discussion in the former section) reflects the fact that the nascent nitrogen LEP and the forming C–C bond are antiperiplanar in the TS (see Figure 2).

Inasmuch that the relative configurations of the CH_2CO_2Me and OTBS substituents are the same in all adducts **5**, the structure of the TS should be governed by a fundamental factor. We believe this fundamental is the stabilization of the TS by the n–σ* interaction of the nascent nitrogen LEP and the C(3)–CH_2CO_2Me bond, which is most effective in the case of an antiperiplanar orientation (anomeric effect). It is known that an antiperiplanar orientation of the orbitals of forming/breaking bonds is inherent to a number of addition and elimination reactions.[9] Note that the hampered nitrogen inversion in the nitroso acetals **5** allows this feature to be observed in the nucleophilic addition to the C=N double bond (that is, **3** + **4** C–C coupling).

With regard to the C-3/C-5 relative configuration, the mechanism is more complex. An experimental study has shown that the stereochemical outcomes of the C–C coupling reactions of the cations **1**-TBS$^+$ with π nucleophiles result from a distal approach of the π nucleophile to the dominant conformation of the cationic intermediate.[1,2] This mechanistic description is possible only as a result of hampered inversion in the cations **1**-TBS$^+$. As a rule, the dominant conformations of the cation **1**-TBS$^+$ and the initial nitronate **1** are the same.[2] Therefore the stereochemical outcomes of the C–C coupling reactions of six-membered nitronates **1** with π nucleophiles can be predicted confidently from a conformational analysis of the ^{1}H NMR spectra of the initial nitronates **1**.[2]

However, from the stereochemical results of the **3** + **4** coupling reactions we could not derive a clear mechanistic picture in a similarly simple way. Indeed, there is no evidence of hampered inversion in the cations **3**-TBS$^+$, and in the case of a low interconversion barrier both conformers could be the reactive conformers. Therefore the same stereochemical outcome can be obtained from alternative approaches of **4** to alternative conformations of the cation **3**-TBS$^+$ (see Figure 3). The *cis* isomers of adducts **5** could be a result of a distal approach of Nu′ (attack A) on the conformer *exo*-**3**-TBS$^+$ as well as a result of a proximal approach of Nu′ (attack C) on the other invertomer *endo*-**3**-TBS$^+$. A similar analysis could also be performed for the generation of the nitroso acetals *trans*-**5**. Therefore the reacting conformers of the cationic intermediates **3**-TBS$^+$ cannot be defined from the stereochemical outcomes of the reactions between **3** and **4**.

The preference of any approach of the nucleophile towards the cation **3**-TBS$^+$ should be governed by the minimization of steric hindrances (see Figure 3). It is reasonable to assume that steric hindrances from the plane O–N=C(3)–C(4) are equal for "upper" and "lower" approaches of the nucleophile **4**. In this situation, approach D seems the most preferable because in this case hindrance from the prominent C-5 atom and the substituent R′ is absent. Approach B is hampered by the prominent C-5 atom, and approach A could be hampered by substituent R′. Finally, approach C is clearly the least preferable because it is hampered by both the C-5 atom and the pseudo-axial substituent R′.

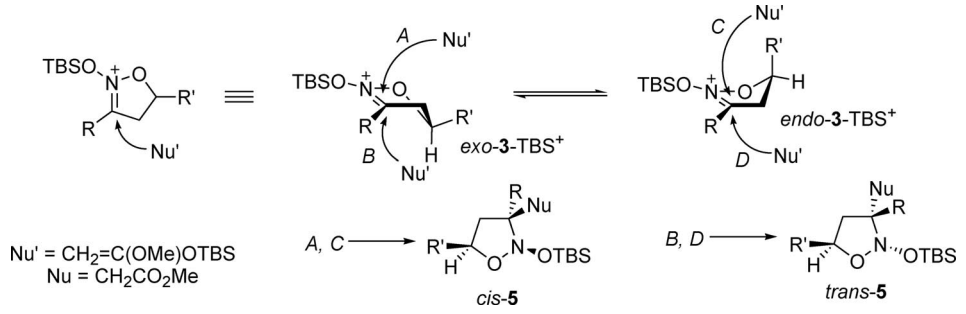


Figure 3. Stereochemical outcomes of the C–C coupling reactions of **3** and **4**.

In fact, the C–C coupling reactions of five-membered nitronates **3a**,**c**–**g** are of low diastereoselectivity with some predominance of the *trans* isomer (see Table 1). However, the 5-ethoxy-substituted nitronates **3b**,**h** give *trans* isomers exclusively. For the cationic intermediates derived from these nitronates the conformation of *endo*-**3**-TBS$^+$ (Figure 3) seems to be strongly preferred due to the presence of an anomeric centre at C-5.[10] In this case approach D leading to adducts *trans*-**5** clearly is strongly preferred for the above-mentioned conformation.

Selected Transformations of the Isoxazolidines 5

The chemical properties of 3-monosubstituted *N*-siloxyisoxazolidines are well studied.[11] The principal feature of the reactivity of these compounds is an easy cleavage of one of two weak N–O single bonds, which leads to β-hydroxy-substituted oximes (by endocyclic N–O bond cleavage) or to the corresponding isoxazolines (by exocyclic N–O bond cleavage). Reduction of the nitroso acetal moiety of *N*-siloxyisoxazolidines is also known.[11,12] At the same time, 3,3-disubstituted *N*-siloxyisoxazolidines have not been investigated experimentally although several examples of their transformations can be found.[4,13]

Furthermore, various *N*-alkoxyisoxazolidines with a three-carbon tether between C-3 and the exocyclic oxygen atoms have been well explored. The main synthetic application of these bicyclic nitroso acetals, easily available by [3+2] cycloaddition reactions of six-membered cyclic nitronates, is the hydrogenation of the nitroso acetal moiety, which proceeds with retention of the carbon stereocentres of the isoxazolidine ring.[14–17]

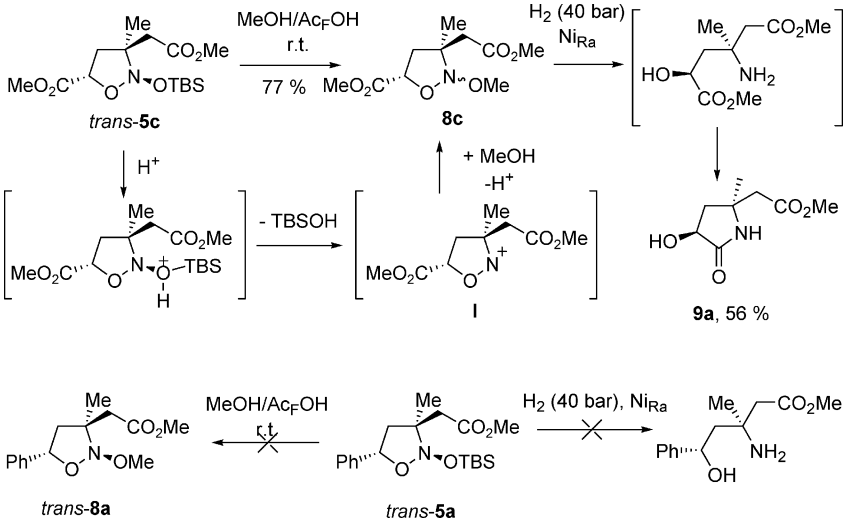
In addition, isoxazolidines **5a**–**h**, bearing a CH_2CO_2Me moiety at the C-3 atom, could be considered as prospective precursors of unnatural β-amino acids.

Some examples of useful transformations of the isoxazolidines **5** are briefly illustrated below. Reduction of the weak single N–O bond appears to be a thermodynamically favourable process that could be hampered by steric hindrance at the reaction centre.[16,17] To examine the possibility of the catalytic hydrogenation of the adducts **5**, we attempted to reduce the adducts *trans*-**5a** and *trans*-**5c** with hydrogen gas on Raney nickel (Scheme 7). In both cases, hydrogenation under mild conditions (40 bar, room temperature) failed, presumably due to the bulkiness of the TBSO group. Nevertheless, product **9a** was obtained from *trans*-**5c** indirectly by exchange of the bulky TBSO group in *trans*-**5c** for the sterically less hindered MeO group in **8c** after *trans*-**5c** solvolysis in dilute methanolic trifluoroacetic acid. Isoxazolidine **8c** formed as a mixture of diastereoisomers that differ in the configuration of the stereocentre at the nitrogen atom with retention of the configurations at the other stereocentres (Scheme 7). This confirms that the siloxy fragment is exchanged via the nitrenic cation **I**.

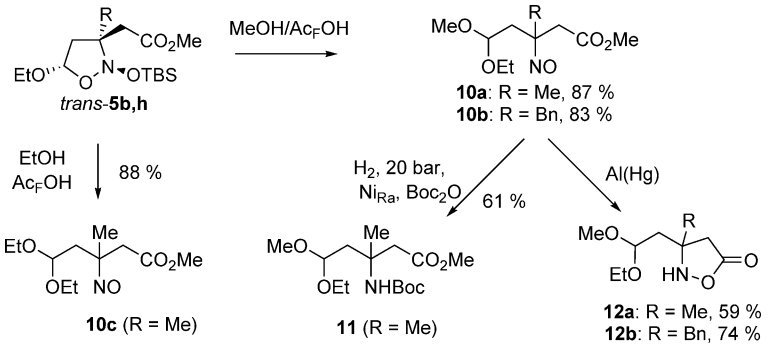
Isoxazolidine **8c**, unlike *trans*-**5c**, was readily hydrogenated on Raney nickel to give the substituted pyrrolidine **9a** with retention of the carbon stereocentres (C-3 and C-5) of *N*-methoxyisoxazolidine **8c** and, consequently, the carbon stereocentres of *trans*-**5c**. However, the exchange reaction discussed above is not common; under identical conditions, the nitroso acetal *trans*-**5a** gives a complex mixture of unidentified compounds instead of the target product **8a**.

N-Siloxyisoxazolidines with an alkoxy group at C-5 have not been described previously, probably due to the poor reactivity of the silyl nitronates of secondary aliphatic nitro compounds in the [3+2] cycloaddition reactions with electron-rich olefins. Therefore the reactivities of the adducts **5b** and **5h** are of special interest. The isoxazolidines *trans*-**5b** and *trans*-**5h** react with dilute alcoholic trifluoroacetic acid in a different way to *trans*-**5c** (Scheme 8).

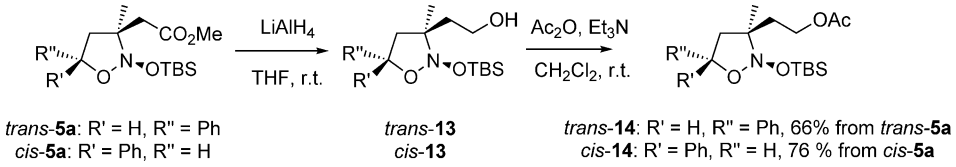
Under the action of methanolic trifluoroacetic acid, the isoxazolidine rings of *trans*-**5b**,**h** cleave to give the sky-blue nitroso compounds **10a**,**b**, respectively. With ethanolic trifluoroacetic acid, symmetrical acetal **10c** was formed from the nitroso acetal *trans*-**5b**. Remarkably, the nitroso acetal moiety in **5** is more sensitive towards acid than the acetal



Scheme 7. Some transformations of the nitroso acetal *trans*-**5c**.



Scheme 8. Some reactions of the 5-ethoxy-substituted isoxazolidines *trans*-**5b**,**h**.



Scheme 9. Selective reduction of the ester moiety in the nitroso acetals **5** with $LiAlH_4$.

moiety at the C-5 centre. According to the NMR data, the nitroso compounds **10a**,**b** form as single diastereomers with unassigned relative configurations at the stereocentres.

Hydrogenation of the nitroso compound **10a** on Raney nickel and reduction of **10a**,**b** with aluminium amalgam proceeded diastereoselectively to give **11** and **12a**,**b**, respectively, which can be considered as direct precursors of unnatural β-amino acids.

It was shown that the ester moiety of the adduct **5a** could be selectively reduced. Treatment of *cis*- or *trans*-**5a** with $LiAlH_4$ in tetrahydrofuran resulted in reduction of the ester functionality to the CH_2OH group with retention of all the stereocentres, including the stereocentre at the nitrogen atom (Scheme 9). Crystalline *trans*-**13** was purified by crystallization from hexane and was characterized as such and as the acetate *trans*-**14**, whereas the non-crystalline *cis*-**13** decomposes in the course of purification by column chromatography on silica gel and was purified and characterized as the acetate derivative *cis*-**14**.

Conclusions

Five-membered cyclic nitronates **3** react smoothly with silyl ketene acetal **4** in the presence of TBSOTf as catalyst to give 3-(methoxycarbonylmethyl)-substituted *N*-siloxyisoxazolidines **5**. This type of products could not be obtained by conventional procedures based on the [3+2] cycloaddition of the corresponding silyl nitronates with olefins. The reactivities of the five-membered cyclic nitronates in C–C coupling reactions with silyl ketene acetal **4** are similar to those of their six-membered analogues studied previously. The adducts **5** were formed with low diastereoselectivity. In general, isomers with a *trans* configuration of the R′ substituent at C-5 and the CH_2CO_2Me moiety slightly dominate. However, the presence of the alkoxy group at C-5 of the nitronate **3** ensures exclusive *trans* diastereoselectivity of the C–C coupling. For all the adducts **5** obtained, the LEP of the nitrogen atom and the CH_2CO_2Me moiety have a *trans* configuration.

The reactions of the *N*-siloxyisoxazolidines **5** with dilute alcoholic trifluoroacetic acid as well as with some reducing systems (hydrogen/Raney nickel, Al/Hg, $LiAlH_4$) have been briefly examined. As a rule, the transformations are characterized by high diastereoselectivity. The nitroso acetals **5** can be considered as direct precursors of unnatural β-amino acids and related substances.

Experimental Section

General Remarks: 1D and 2D NMR spectra were recorded at room temperature with a Bruker AM-300 NMR spectrometer for 0.1–0.2 M solutions in $CDCl_3$ [^{1}H: 300.13 MHz; ^{13}C: 75.13 MHz; ^{29}Si: 59.58 MHz (with INEPT), COSY, HSQC, NOESY]. The chemical shifts (^{1}H, ^{13}C and ^{29}Si) are given in ppm (δ scale) relative to the residual solvent signals;[18] coupling constants are given in Hz. All 1D and 2D NMR experiments were performed by using standard techniques and Bruker NMR software. The ratios of the stereoisomers were derived from the relative integral intensities of the characteristic signals in the ^{1}H NMR spectra. Elemental analyses were performed by the Analytical Laboratory of the Institute of Organic Chemistry. Melting points (uncorrected) were determined with a Kofler apparatus. Reactions with TBSOTf were conducted under dry Ar. CH_2Cl_2 and THF were distilled prior to use from CaH_2 and benzophenone ketyl, respectively. Triethylamine and 2,6-dimethylpyridine were distilled from KOH under Ar. Solvents for column chromatography and extractions (ethyl acetate, hexane) were distilled without additional agents. The following reagents were prepared according to known procedures: nitronates **1a**,[1] **3a**–**h**,[3] *tert*-butyl(1-methoxyvinyloxy)dimethylsilane (**4**)[19] and TBSOTf.[20] Merck silica gel 60 (0.040–0.063 mm) was used for column chromatography. For the successful isolation of some products, silica gel was deactivated with triethylamine.[21] Aluminium TLC plates precoated with silica gel QF_{254} (Merck) were used for analytical thin-layer chromatography; the eluents used for analyti-

cal TLC are specified in parentheses after the R_f values. Visualization for analytical TLC: UV (254 nm) and treatment with 4-$MeOC_6H_4CHO$ (for **5**, **8**, **10** and **12**–**14**) or ninhydrin (for **9** and **11**).

Procedures for the Preparation of Isoxazolidines 5 (see Table 1): Procedure A is the General Procedure published in ref.[1]

Procedure B: The silyl ketene acetal **4** (1.1 equiv.) was added to a solution of nitronate **3** (0.8–4.0 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL per mmol of **3**), and the solution was chilled to –94 °C (acetone/liquid nitrogen). TBSOTf (0.2 equiv.) was added at –94 °C with stirring, which was continued at –94 °C for the time indicated in Table 1. Then the reaction mixture was quenched at –94 °C by the successive addition of Et_3N (0.3 equiv.) and methanol (0.25 equiv.). After additional stirring at –94 °C for 2 min, hexane (6 mL per mmol of **3**) and water (3 mL per mmol of **3**) were added, and the reaction mixture was allowed to warm to room temperature. The aqueous layer was separated and washed with hexane (2 × 6 mL per mmol of **3**), and the combined organic layers were washed with brine (one-third of the combined organic layers volume), dried with anhydrous sodium sulfate and the solvents evaporated. Crude products were purified by gradient column chromatography with ethyl acetate/hexane as eluent (from 1:30 to 1:10 by volume); unreacted nitronate **3** (if remained) was eluted with pure ethyl acetate.

Procedure C: The silyl ketene acetal **4** (1.1 equiv.) and 2,6-dimethylpyridine (0.25 equiv.) were added to a solution of nitronate **3** (0.8–5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL per mmol of **3**), and the mixture was chilled to –78 °C (acetone/dry ice). TBSOTf (0.2 equiv.) was added at –78 °C with stirring, which was continued at –78 °C for the time indicated in Table 1. Then the mixture was quenched at –78 °C by the addition of methanol (0.25 equiv.). After additional stirring at –78 °C for 2 min, hexane (6 mL per mmol of **3**) and water (3 mL per mmol of **3**) were added, and the reaction mixture was allowed to warm to room temperature. Further operations are the same as in Procedure B. For the exact amounts of nitronates **3** and other reagents, as well as detailed characterizations of the isoxazolidines **5a**–**h**, see the Supporting Information.

Competitive Reactions of Nitronates 1a and 3a with Silyl Ketene Acetal 4

Experiment 1: TBSOTf (0.17 mL, 0.74 mmol) was added to a stirred solution of nitronates **1a** (51 mg, 0.23 mmol) and **3a** (43 mg, 0.24 mmol), silyl ketene acetal **4** (45 mg, 0.24 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (205 mg, 1.0 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C, and the reaction mixture was stirred at –78 °C for 1.5 h. Then the reaction mixture was quenched at –78 °C by the successive addition of Et_3N (0.21 mL, 1.5 mmol) and MeOH (0.048 mL, 1.19 mmol). Further operations are the same as in procedure B after quenching of the reaction mixture. After column chromatography, an inseparable mixture (75 mg) of isoxazolidine **5a** (yield 53% based on **3a**, with a *trans*-**5a**/*cis*-**5a** ratio of ca. 3.0:1.0), nitroso acetal **2a** and dihydrooxazine **7** (in 4.4 and 36% yields, respectively, based on **1a**) was obtained as a colourless oil. Yields were derived from the NMR molar ratio of the mixture of components and total weight of the mixture.

Experiment 2: TBSOTf (0.012 mL, 0.05 mmol) was added to a stirred solution of nitronates **1a** (54 mg, 0.25 mmol) and **3a** (44 mg, 0.25 mmol), silyl ketene acetal **4** (45 mg, 0.24 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (21 mg, 0.1 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C and the reaction mixture was stirred at –78 °C for 18 h. Then the reaction mixture was quenched at –78 °C by the successive addition of Et_3N (0.05 mL, 0.36 mmol) and MeOH (0.005 mL, 0.12 mmol). Further operations are the same as for procedure B after quenching of the reaction mixture. After column chromatography, nitroso acetal **2a** (73 mg, 71%) was obtained as a white crystalline. Adduct **5a** was not detected in the NMR spectra.

Transformations of Isoxazolidines 5

Transformations of 5c: CF_3CO_2H (0.0044 mL, 0.1 equiv.) was added to a solution of *trans*-**5c** (200 mg, 0.58 mmol) in methanol (3.0 mL) at room temp. After 1.5 h at room temp., triethylamine (0.016 mL, 0.2 equiv.) was added, and the resulting mixture was concentrated in vacuo and the residue purified by gradient column chromatography (ethyl acetate/hexane as eluent, from 1:3 to 1:1, v/v). Isoxazolidine **8c** (110 mg, 77% yield, colourless oil) was obtained as an inseparable mixture of isomers (ca. 5:4 ratio), which differ in the configuration of the nitrogen stereocentre. Isoxazolidine **8c** (154 mg, 0.62 mmol) was hydrogenated in the presence of Raney nickel in methanol (3.0 mL, room temp., 40 bar, 24 h, stirring). Then the catalyst was removed by filtration, washed with methanol (2 × 3.0 mL) and the combined filtrates were concentrated in vacuo. The residue was purified by gradient column chromatography (ethyl acetate/methanol as eluent, from 1:0 to 10:1, v/v) to give lactam **9a** (66 mg, 56% yield) as a colourless viscous oil.

Alcoholysis of Isoxazolidines 5b,h: A solution of CF_3CO_2H in the corresponding alcohol was added to a stirred solution of isoxazolidine in methanol or ethanol at room temp. in a quantity to obtain a 0.001–0.006 M solution of CF_3CO_2H. The reaction mixture was stirred at room temp. for 1–6 h and then quenched with triethylamine, concentated and purified by column chromatography or by short-path distillation. For details of the reaction conditions and characterization of the products, see the Supporting Information

Transformations of Nitroso Compounds 10a,b

Hydrogenation of 10a in the Presence of Raney Nickel: The nitroso compound **10a** (105 mg, 0.45 mmol) was hydrogenated in the presence of Raney nickel in methanol (2.5 mL) and Boc_2O (0.17 mL, 0.8 mmol) (room temp., 20 bar, 1 h, stirring). Then the catalyst was removed by filtration, washed with methanol (2 × 3.0 mL), and the combined filtrates were concentrated in vacuo. Additional Boc_2O (0.2 mL) was added to the residue, and the resulting mixture was kept at room temp. for 48 h. The residue was purified by gradient column chromatography (ethyl acetate/hexane mixture as an eluent, from 1:10 to 1:1, v/v) to give the protected amine **11** (87 mg, 61% yield) as a colourless oil.

Reduction of Nitroso Compounds 10a,b with Aluminium Amalgam:[22] Aluminium foil, cut into small pieces (0.8–1.0 mmol), was added to a solution of the nitroso compounds **10a**,**b** (0.3–0.5 mmol) in THF/H_2O (10:1, v/v) at room temp. with stirring. Then $HgCl_2$ at the tip of a spatula was added (exothermic reaction has an inductive period from one to several minutes!). The reaction mixture was stirred at room temp. until the blue colour disappeared and the silvery pieces of foil had turned into a grey powder. The inorganic residue was filtered through Celite 545 and washed with THF (twice with same volume as the reaction mixture). The combined filtrate and washings were concentrated, and the residue was purified by gradient column chromatography (ethyl acetate/hexane as eluent, from 1:5 to 2:1, v/v). For details, see the Supporting Information.

Reduction of 5a with $LiAlH_4$: A solution of *trans*-**5a** (150 mg, 0.41 mmol) in THF (1.0 mL) was added to a stirred solution $LiAlH_4$ (15.6 mg, 0.41 mmol) in THF (1.0 mL) under argon at –30 °C, and the reaction mixture was allowed to warm to ambient temperature. After 1 h at room temp., $Na_2SO_4 \cdot 10H_2O$ (0.5 g, 1.55 mmol) was added to the reaction mixture, and stirring was

continued for an additional 30 min. Then the solids were filtered and washed with THF (2 × 5 mL). The combined filtrate and washings were concentrated. The residue was dissolved in hexane (10 mL), filtered through Celite 545 to remove the residual inorganic haze, concentrated and recrystallized from hexane to give *trans*-**13** (92 mg, 66% yield) as white needle crystals. Triethylamine (0.062 mL, 3.0 equiv.) and Ac_2O (0.021 mL, 1.5 equiv.) were added to a solution of *trans*-**13** (50 mg, 0.148 mmol) in CH_2Cl_2 (1.0 mL) at room temp. After 48 h at room temp., *n*-butylamine (0.017 mL) was added to quench excessive acetic anhydride, and, after 5 min, the reaction mixture was concentrated. The residue was purified by column chromatography with ethyl acetate/hexane/triethylamine as eluent (25:75:2 by volume) to give acetate *trans*-**14** (56 mg, quantitative yield) as a colourless oil, which crystallized on standing. Acetate *cis*-**14** (110 mg, 76% yield) was obtained analogously from *cis*-**5a** (140 mg, 0.38 mmol) without intermediate purification of alcohol *cis*-**13**. As some *cis*-**5a** (28 mg, 20%) was recovered, the yield of *cis*-**14** based on converted *cis*-**5a** is 95%.

Supporting Information (see footnote on the first page of this article): Details of experiments as well as spectral characterizations of the products prepared.

Acknowledgments

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