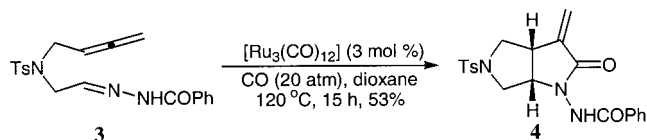


fused α -methylene- γ -butyrolactam, we explored the cyclocarbonylation of δ -allenyl imine **3** and examined the stereochemistry of the resulting products (Scheme 4). We observed only the *cis*-fused α -methylene- γ -butyrolactam **4** as the sole product, which supports a [2 + 2 + 1] cycloaddition. The *cis* stereochemistry of **4** was clearly determined by NOE interactions in NOESY experiments (see Supporting Information).



Scheme 4. The cyclocarbonylation of δ -allenyl imine **3** gave *cis*-fused α -methylene- γ -butyrolactam **4** as the sole product.

In summary, the results presented above show that ruthenium-catalyzed cycloaddition reactions of allenyl aldehydes and ketones with carbon monoxide efficiently afford α -methylene- γ -butyrolactone products. This methodology should find wide applications in the synthesis of natural products that contain the *exo*-methylene- γ -butyrolactone functionality, and further investigations are underway in our laboratory.

Experimental Section

Typical procedure: A stainless-steel autoclave was charged with the allenyl aldehyde **1a** (80 mg, 0.30 mmol), 1,4-dioxane (4 mL), and $[\text{Ru}_3(\text{CO})_{12}]$ (2 mg, 1 mol %). The system was flushed three times with CO (20 atm). The autoclave was then pressurized to 20 atm, and the mixture was stirred at 120 °C for 12 h. The solution was then cooled and concentrated in vacuo to give a residue, which was subjected to silica-gel column chromatography (EtOAc/hexane 1:2) to yield the cyclized product **2a** (66 mg, 75%) as a white solid. M.p. 115 °C; R_f = 0.48 (EtOAc/hexanes 1:1); ^1H NMR (500 MHz, CDCl_3): δ = 2.45 (s, 3H), 3.07 (dd, 1H, J = 5.3, 11.7 Hz), 3.22 (dd, 1H, J = 10.0, 7.6 Hz), 3.37 (dd, 1H, J = 10.0, 2.9 Hz), 3.55 (m, 1H), 3.63 (dd, 1H, J = 0.6, 11.7 Hz), 4.97 (m, 1H), 5.77 (d, 1H, J = 2.4 Hz), 6.35 (d, 1H, J = 2.4 Hz), 7.36 (d, 2H, J = 8.2 Hz), 7.68 (d, 2H, J = 8.2 Hz); ^{13}C NMR (125 MHz, CDCl_3): δ = 169.6, 145.2, 137.4, 132.1, 130.6, 128.7, 125.8, 79.7, 55.2, 54.7, 42.6, 22.3; HR-MS: calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: 293.0776, found: 293.0705.

Typical experimental procedures for the preparation of **1a**, **1c–j**, **2a**, and **3**, as well as spectroscopic and analytical data for **1a–j**, **2a**, **2c–f**, **2i–j**, and **4** can be found in the Supporting Information.

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- [9] Preparation of allenyl aldehyde **1a**: a) propargyl *p*-tosylamide, $\text{BrCH}_2\text{CH}_2(\text{OMe})_2$, K_2CO_3 , DMF, 100 °C, 10 h, 85%; b) Crabbe reaction: HCHO , CuBr , $i\text{Pr}_3\text{NH}$, dioxane, reflux, 68% (see: F. Crabbe, B. Nassim, M.-T. Robert-Lopes, *Org. Synth. Coll. Vol. 7* (Ed.: J. P. Freeman), **1990**, pp 276–277); c) trifluoroacetic acid/ $\text{CHCl}_3/\text{H}_2\text{O}$ (1:2:1), 0 °C, 1.5 h, 78% (see Supporting Information).

Novel Ene-Like Cycloisomerization Reaction of Nitrile Oxides with a Tethered Allyltrimethylsilyl Group**

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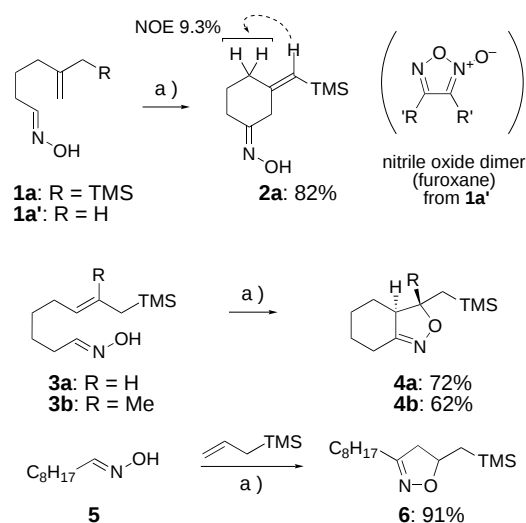
The nitrile oxide functional group is a well-known 1,3-dipole and highly useful owing to its high reactivity toward unsaturated C–C bonds to furnish [3+2] cycloadducts.^[1] In addition to such a traditional role, we have found that it also functions as an enophile^[2] in an intramolecular reaction with an allyltrimethylsilyl group.^[3] 5-Methylene-6-(trimethylsilyl)-hexanal oxime (**1a**) was treated with sodium hypochlorite^[4] in dichloromethane at 0 °C for 2 h to give the product of an ene-like reaction (**2a**) in 82% yield as a single diastereomer; no

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[3+2] cycloadducts, fused or bridged, were detected (Scheme 1). In NMR experiments a distinct nuclear Overhauser enhancement (NOE) observed between the exocyclic olefinic proton and C(4) protons indicates their close proximity.



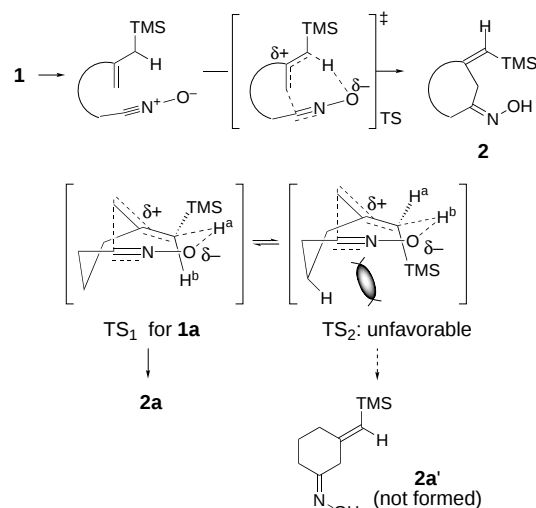
Scheme 1. Cycloisomerization reactions of **1** and [3+2] cycloaddition reactions of **3** and **5**. Conditions: a) NaOCl, CH₂Cl₂, 0 °C, 2 h. TMS = trimethylsilyl.

To our surprise, this novel reaction did not occur with substrates of similar structure such as **1a'**, **3a**, and **3b**, which instead underwent dimerization of nitrile oxide and expected [3+2] cycloaddition to give furoxane and isoxazolines (**4a** and **4b**), respectively (Scheme 1). Furthermore, no ene-like process was effected at all for the intermolecular version: the reaction of nonanal oxime **5** and allyltrimethylsilane afforded cycloadduct **6** almost quantitatively (Scheme 1).^[5]

This ene-like reaction is unprecedented^[6,7] and highly profitable because it features very mild reaction conditions (0 °C, 2 h), the formation of C–C bonds through a cycloisomerization process, and the retention of oxime and vinyltrimethylsilyl functions in the products, which would be suitable for further manipulations.

The selection of reaction pathways—the ene-like reaction or [3+2] cycloaddition—depends on whether the allyltrimethylsilyl unit is tethered to the oxime at the β -position (**1a**) or γ -position (**3a**, **3b**). Closely inspecting molecular models led us to speculate that **1a** is much more flexible than **3a** (or **3b**), which after deprotonation would lead to effective overlap of the π orbitals of the allyl sp² carbon atom and the nitrile oxide sp carbon atom. If this orbital overlap progresses at the transition state (Scheme 2, TS₁ for **1a**), proton delivery from the allylic position (H^a) to the negatively charged oxygen atom would be enhanced in a concerted manner and give rise to the cyclic oxime **2a** as a single isomer. The transition state leading to **2a'** (TS₂) is unfavorable because of inevitable steric interactions.

Although positive charge develops on the carbon β to the TMS group as the orbital overlap progresses at the transition state, it can be stabilized by the β -effect of the silicon atom.^[8] This is the reason why the allyltrimethylsilyl group is required



Scheme 2. Possible reaction mechanism of the novel cycloisomerization reaction.

for the ene-like reaction, and a simple allylic substrate **1a'** lacking the TMS group gave the nitrile oxide dimer (Scheme 1).

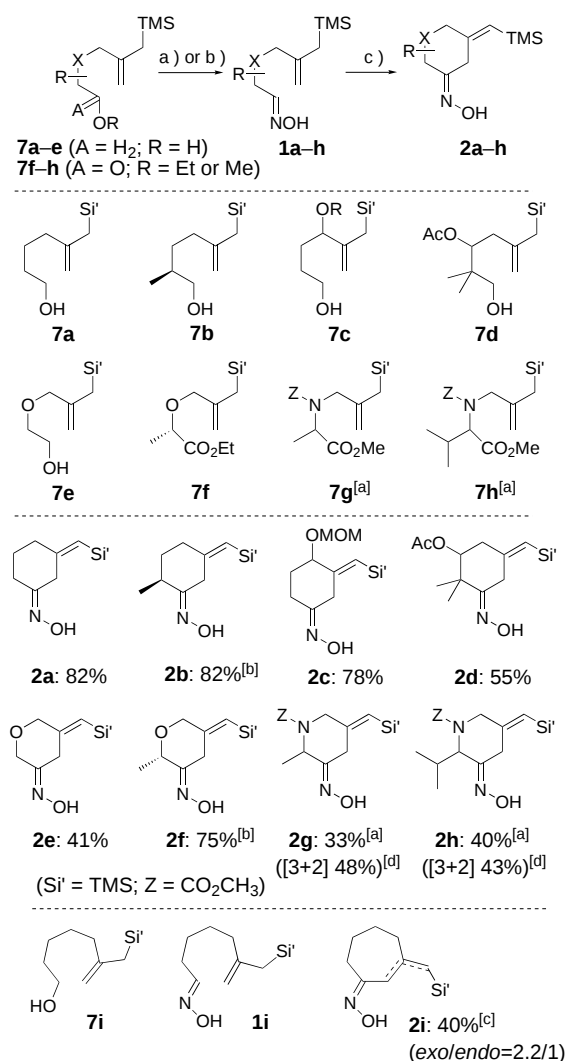
For this new C–C bond-forming process to be accepted as a general protocol in organic synthesis, simple and versatile methods for preparing **1** must be available. We have developed methods leading to key intermediate alcohols **7a–e** and esters **7f–h**,^[9] which are direct precursors for oximes **1a–h**, through oxidation and reduction, respectively, followed by condensation with hydroxylamine. These oximes underwent cycloisomerization under standard conditions to give the expected products **2a–h** (Scheme 3).

In every case a single geometrical isomer was obtained in moderate to high yields.^[10] NOE experiments revealed their geometries, which were additionally supported by the regio-specific Beckmann rearrangements of **2a** and **2b** to **8** and **9**, respectively (Scheme 4).^[11] Competitive ene-like reactions and intramolecular [3+2] cycloaddition reactions were observed for the aza versions **1g** and **1h** to give a mixture of cyclic oximes **2g** and **2h**, respectively, and isoxazolines (Scheme 3). Heptanal oxime **1i** proved to be amenable to the ene-like reaction to give cycloheptanone oxime **2i** in 40 % yield as a mixture of *exo* and *endo* isomers (bottom in Scheme 3).^[12]

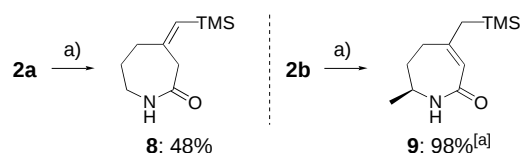
Although further studies are needed to completely understand the mechanism shown in Scheme 2, the potential intermediates **10** and **11** can be ruled out. Bredt's rule^[13] does not support the formation of the bridged [3+2] cycloadduct **10**. In addition, **10** and the cationic intermediate **11**, if produced, should afford possible geometrical isomer **2a'** and 3-(methylene)cyclohexanone oxime (**12**), which, in fact, were not detected at all (Scheme 5).

Experimental Section

General procedure for ene-like cyclizations: To a solution of oxime **1a** (70 mg, 0.36 mmol) in CH₂Cl₂ (7 mL) was slowly added an aqueous solution of NaOCl (available chlorine 5 %, 1.0 mL) at 0 °C over 1 h. The mixture was stirred vigorously and allowed to warm to room temperature for 1 h. The reaction mixture was diluted with water and extracted with several portions of EtOAc. The combined extracts were dried over Na₂SO₄

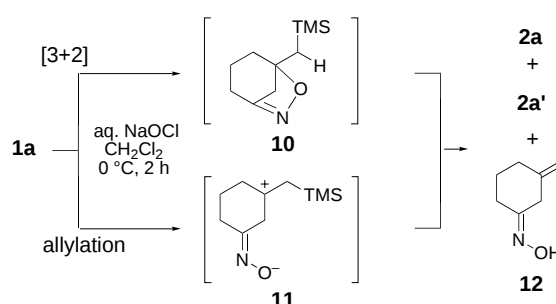


Scheme 3. Cycloisomerization reactions of various allylsilyl oximes. Yields are for products isolated by SiO₂ column chromatography in step c. Conditions: a) 1. SO₃ · pyridine, Et₃N/DMSO, 2. NH₂OH, Et₃N/EtOH; b) 1. DIBALH, THF, −78 °C, 1 h, 2. NH₂OH, Et₃N/EtOH; c) NaOCl/CH₂Cl₂, 0 °C → RT, 2 h. [a] Racemic product was obtained under the given conditions (see Supporting Information) though optically active amino acid esters were employed. [b] Optical purity, not determined. [c] Combined yield of *exo* and *endo* isomers, which could be separated by SiO₂ column chromatography. [d] For structures, see Supporting Information. DIBALH = diisobutylaluminum hydride, MOM = methoxymethyl.



Scheme 4. Synthesis of functionalized seven-membered lactams by the regioselective Beckmann rearrangement. Conditions: a) MsCl, pyridine/CH₂Cl₂, 0 °C, 2 h. [a] Optical purity, not determined. Ms = methane sulfonyl.

and concentrated to give an oil, which was purified by column chromatography on silica gel to afford the cyclic oxime **2a** (58 mg, 82 %).



Scheme 5. Hypothetical products via intermediates **10** and **11**.

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- [8] The silicon atom has been attributed a similar effect in the intramolecular ene reaction of an allenyltrimethylsilyl–imine system, see ref. [3].
- [9] See the Supporting Information for the syntheses of **7a–h**.
- [10] Two sets of NMR signals (¹H and ¹³C, at 23 °C) were observed for **2h**. Variable-temperature ¹H NMR experiments showed that the signal intensity for each set changed at 40 °C and the two signals for each set fused and became broad at 50 °C; upon cooling, the original spectrum was restored. An isopropyl substituent in **2h** would probably raise the barrier for inversion at the nitrogen atom at room temperature for steric reasons. In marked contrast this inversion seems to be quite facile in the corresponding methyl version **2g** (see Supporting Information pp. S21–S23). Thus, **2h** would exist as a mixture of conformers probably due to inversion at the nitrogen atom.
- [11] We do not yet know why the initial product of the Beckmann rearrangement product of **2b**, a γ -trimethylsilyl- β,γ -unsaturated lactam, efficiently isomerized to **9**. Achiral **2a** simply rearranged to **8** (48 % yield) without subsequent isomerization.
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