# Nucleophilic 5-*endo-trig* cyclizations of *N*-homoallylic sulfonamides: a facile method for the construction of pyrrolidine rings†

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**Normally disfavored 5-*endo-trig* cyclizations proceed in *N*-homoallylsulfonamides bearing a $CF_3$, $CCl_3$, $CO_2Et$ or CN group at the C-3 position, *via* an intramolecular $S_N2'$-type or addition reaction to construct pyrrolidine rings, even though the system allows a more favorable 5-*exo-trig* pathway.**

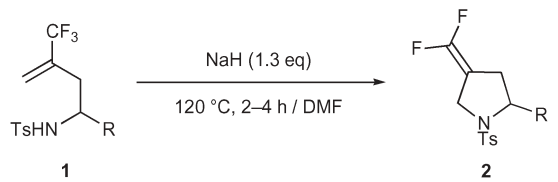
It has long been considered, following Baldwin's rules,[1] that the 5-*endo-trig* cyclization is a geometrically disfavored process. These ring closures can be classified into three categories: nucleophile-driven,[2] electrophile-driven,[3] and radical-initiated[4] cyclizations. Among them, the nucleophile-driven 5-*endo-trig* cyclization has rarely been observed in synthetic chemistry and is still a challenge in organic synthesis.

Recently, we have accomplished the disfavored 5-*endo-trig* cyclization in 2-trifluoromethyl-1-alkenes **1** bearing a 4-methylbenzenesulfonamide (tosylamide: TsNH–) moiety as an intramolecular nucleophile (Scheme 1).[5] The nitrogen anion attacked the alkene in an $S_N2'$ fashion with elimination of a fluoride ion to afford difluoromethylene-substituted pyrrolidines **2**. In this cyclization, the 5-*endo-trig* products were obtained without any products of the favored 5-*exo-tet* ring closure. These results show that (i) the trifluoromethyl group activates the C–C double bond in **1** to allow the normally disfavored 5-*endo-trig* cyclization and (ii) this reaction has a high potential in the synthesis of substituted pyrrolidines.[6]

To expand the scope of this synthetic method for functionalized pyrrolidines, the reactions of other types of electrophilic moieties with intramolecular *N*-nucleophiles have been investigated. Herein, we wish to report the nucleophilic 5-*endo-trig* cyclization of *N*-homoallylic sulfonamides containing an electron-withdrawing group at the C-3 position.

We first set our goal on 3-halomethyl-substituted analogs of *N*-homoallylsulfonamides (Table 1). Such substrates were expected to possess an $S_N2'$-type reactivity similar to that of 2-trifluoromethyl-1-alkenes. Their reaction with nucleophiles would occur at the terminal vinylic carbon, followed by elimination. Before investigating other 2-halomethyl-1-alkene systems, we confirmed that the substituent (R) at the homoallylic position did not affect the course of the reaction, because substrate **1b** gave the 5-*endo-trig* product, pyrrolidine **2b**, albeit in diminished yield (entry 2). When trichloromethyl-substituted alkene **1c** was treated with NaH in DMF (*N*,*N*-dimethylformamide), cyclization readily proceeded in a 5-*endo-trig* fashion at 80 °C, a lower temperature than that of the trifluoromethyl counterpart, affording dichloromethylene-substituted pyrrolidine **2c** in 89% yield (entry 3). To evaluate the advantage of trihalomethyl ($CX_3$) groups in the 5-*endo-trig* process, we employed alkene substrates with a 2-monohalomethyl (CHDX) group, whose deuterium atom was introduced to differentiate between the 5-*endo-trig* and the 5-*exo-tet* products. In contrast to the trihalomethylated substrates, fluoromethyl-, chloromethyl- and bromomethyl-1-alkenes **1d–f** underwent direct substitution without allylic rearrangement, leading to the 5-*exo-tet* product **3d** exclusively (Table 1, entries 4–6).

The preference in **1a–c** for the 5-*endo-trig* cyclization over the normally favored 5-*exo-tet* cyclization can be explained as follows. The sulfonamidate, in the 5-*exo-tet* approach, meets severe electrostatic and steric repulsions from the halogens present on the trihalomethyl group, which consequently retards the normally favored 5-*exo-trig* process. On the other hand, the 5-*endo-trig* approach, while geometrically disfavored, has no such repulsions. Because the steric and electrostatic repulsions dominate over the geometric distortion, only the 5-*endo-trig* cyclization proceeds in the trihalomethyl substrates.




**Scheme 1** Nucleophilic 5-*endo-trig* cyclization of *N*-(3-trifluoromethyl-homoallyl)sulfonamides **1**.

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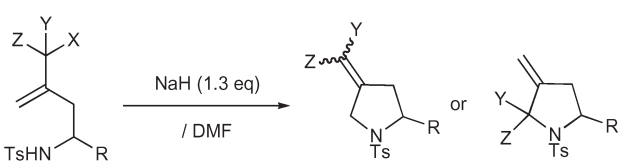
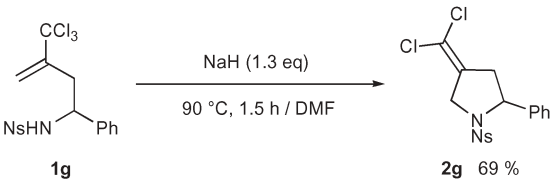
**Table 1** Nucleophilic cyclization of *N*-(3-halomethylhomoallyl)-sulfonamides **1**




| Entry | 1 | CYZ | X | R | Conditions | 2 (%) | 3 (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $CF_2$ | F | Ph | 130 °C, 3 h | 91 | — |
| 2 | **1b** | $CF_2$ | F | H | 130 °C, 4 h | 67 | — |
| 3 | **1c** | $CCl_2$ | Cl | Ph | 80 °C, 1 h | 89 | — |
| 4 | **1d** | CHD | F | Ph | 110 °C, 2 h | — | 91 |
| 5 | **1e** | CHD | Cl | Ph | 50 °C, 1 h | — | 86 |
| 6 | **1f** | CHD | Br | Ph | rt, 0.25 h | — | 89 |

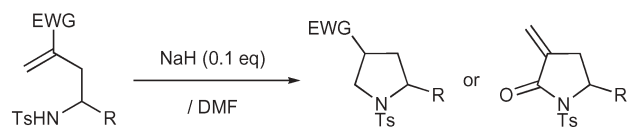



**Scheme 2** Nucleophilic 5-*endo-trig* cyclization of *N*-(3-trichlororomethylhomoallyl)sulfonamide **1g**.

(Trichloromethyl)alkene **1g** bearing a nosyl group (Ns: *o*-$NO_2C_6H_4SO_2$–)[7] on the nitrogen instead of a tosyl group also underwent the 5-*endo-trig* cyclization to afford pyrrolidine **2g** (Scheme 2). However, other examined (trichloromethyl)alkenes with an intramolecular nitrogen nucleophile failed to cyclize. The substrates with a free amine ($NH_2$–) or a benzylamine ($PhCH_2NH$–) moiety resulted in decomposition upon heating, probably due to the strongly basic conditions. The cyclization of the substrates with a benzamide (PhCONH–) or a carbamate (*t*-BuOCONH–) moiety gave poor results. This fact might be due to the partial pyramidalization of the sulfonamidate in the transition state,[8] which could help the geometrically unfavorable cyclization, when compared with the planar amide and carbamate nitrogen anions. The relative stability of the *N*-sulfonamide nitrogen anions may also prevent decomposition prior to the cyclization.

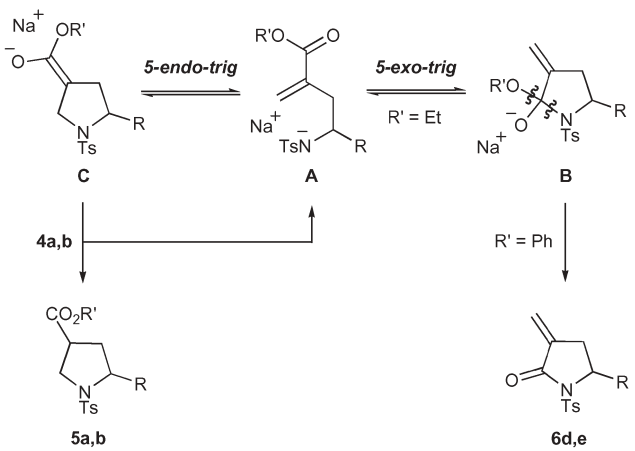
Then, taking into account the relative electrophilicity of the trihalomethyl-substituted alkene moiety, we examined different electrophiles, such as α,β-unsaturated esters and nitriles (Table 2). Baldwin *et al*. previously reported that the 5-*exo-trig* cyclization proceeded more favorably than the 5-*endo-trig* pathway in an α,β-unsaturated ester bearing an amino group.[1] Pursuing the goal of 5-*endo-trig* cyclization, we adopted the aforementioned sulfonamide moiety as an *N*-nucleophile. Whereas treatment of ethyl ester **4a** with 1 equiv. of NaH gave the expected 5-*endo-trig* product **5a** only in 12% yield (entry 1), a catalytic amount (0.1 equiv.) of NaH[2d] raised the yield to 87% (entry 2).‡ When ethyl ester **4b** and nitrile **4c** were subjected to similar reaction conditions, the 5-*endo-trig* products **5b** and **5c** were obtained in high yield (entries 3 and 4). In contrast to ethyl esters, phenyl esters **4d** and **4e** afforded the 5-*exo-trig* cyclization products **6d** and **6e** exclusively (entries 5 and 6).§

**Table 2** Nucleophilic cyclization of 2-functionalized 1-alkenes **4**




| Entry | 4 | EWG | R | Conditions | 5 (%) (*anti*:*syn*)[b] | 6 (%) |
|---|---|---|---|---|---|---|
| 1[a] | **4a** | $CO_2Et$ | Ph | 110 °C, 3 h | 12 | — |
| 2 | **4a** | $CO_2Et$ | Ph | 110 °C, 3 h | 87 (59 : 41)[c] | — |
| 3 | **4b** | $CO_2Et$ | H | 110 °C, 4 h | 72 | — |
| 4 | **4c** | CN | Ph | 50 °C, 4 h | 88 (37 : 63)[c] | — |
| 5 | **4d** | $CO_2Ph$ | Ph | 100 °C, 1 h | — | 90 |
| 6 | **4e** | $CO_2Ph$ | H | 100 °C, 1 h | — | 76 |

[a] NaH (1.0 eq.) was used. [b] Determined by $^1H$ NMR. [c] See footnote.¶




**Scheme 3** Nucleophilic 5-*endo-trig* and 5-*exo-trig* cyclizations of α,β-unsaturated esters **4**.

Thus, not only trihalomethyl groups ($CF_3$ and $CCl_3$) but other electron-withdrawing groups ($CO_2Et$ and CN) also promote the 5-*endo-trig* cyclization. Moreover, both 5-*endo-trig* and 5-*exo-trig* cyclization products can be obtained by choosing an appropriate alkoxy group in the starting esters ($CO_2Et$ or $CO_2Ph$).

In the α,β-unsaturated ester system, both preferences can be interpreted as follows (Scheme 3). The 5-*exo-trig* cyclization of **A** preferentially proceeds up to intermediate **B**, which has two leaving groups, a sulfonamidate and an alkoxide. Because 4-methylbenzenesulfonamidate is a better leaving group than ethoxide, the reaction of ethyl esters **4a** and **4b** (R′ = Et) goes back to intermediate **A**. Once the disfavored 5-*endo-trig* cyclization proceeds, further protonation of intermediate **C** with the starting sulfonamide **4** occurs to give pyrrolidines **5**. On the other hand, phenyl esters **4d** and **4e** (R′ = Ph) undergo elimination of phenoxide, a better leaving group than sulfonamidate, *via* intermediate **B** to give lactams **6**, the 5-*exo-trig* products.

In conclusion, we have shown that sulfonamides are good intramolecular nucleophiles for the nucleophilic 5-*endo-trig* cyclization of electron-deficient alkenes. The normally disfavored 5-*endo-trig* cyclization is effected in *N*-homoallylsulfonamides bearing a $CF_3$, $CCl_3$, $CO_2Et$ or CN group at the C-3 position, which provides an easy access to functionalized pyrrolidines. Thus, the nucleophilic 5-*endo-trig* cyclization can be achieved by choosing the right combination of nucleophile, electrophile, and reaction conditions.

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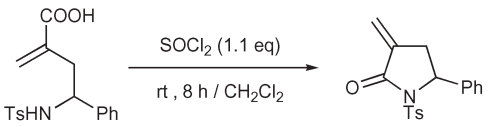
## Notes and references

‡ *Representative procedure*: To a solution of *N*-(1-phenyl-3-ethoxycarbonyl-3-buten-1-yl)-4-methylbenzenesulfonamide (**4a**, 234 mg, 0.62 mmol) in DMF (6 mL) was added NaH (1.5 mg, 0.06 mmol) under argon. After the reaction mixture was stirred at 110 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was then extracted twice with AcOEt and the combined organic extracts were washed with water twice, brine and dried over $Na_2SO_4$. The solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt–hexane–$Et_3N$ 20 : 79 : 1), affording **5a** (203 mg, 87%, *anti* : *syn* = 59 : 41) as a white solid. $^1H$ NMR (500 MHz, $CDCl_3$): ***anti* isomer**: $\delta$ 1.18 (3H, t, $J$ = 7.1 Hz), 2.06 (1H, ddd, $J$ = 12.5, 6.7, 3.0 Hz),

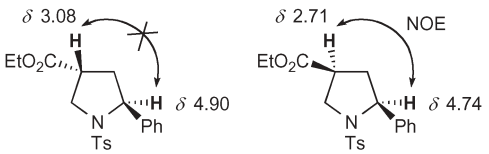
2.13–2.20 (1H, m), 2.41 (3H, s), 3.08 (1H, dddd, $J$ = 6.3, 6.3, 6.3, 6.3 Hz), 3.57 (1H, dd, $J$ = 10.1, 8.7 Hz), 3.89 (1H, dd, $J$ = 10.1, 7.9 Hz), 4.00–4.05 (2H, m), 4.90 (1H, dd, $J$ = 8.1, 3.0 Hz), 7.20–7.31 (7H, m), 7.69 (2H, d, $J$ = 8.4 Hz); ***syn* isomer**: $\delta$ 1.15 (3H, t, $J$ = 7.1 Hz), 2.13–2.20 (1H, m), 2.43 (3H, s), 2.49 (1H, ddd, $J$ = 13.0, 7.7, 7.7 Hz), 2.71 (1H, dddd, $J$ = 6.0, 6.0, 6.0, 6.0 Hz), 3.77 (1H, dd, $J$ = 11.3, 8.9 Hz), 3.91 (1H, dd, $J$ = 11.3, 8.0 Hz), 4.00–4.05 (2H, m), 4.74 (1H, dd, $J$ = 7.7, 7.7 Hz), 7.22–7.31 (7H, m), 7.60 (2H, d, $J$ = 8.4 Hz). $^{13}$C NMR (126 MHz, $CDCl_3$): ***anti* isomer**: $\delta$ 14.0, 21.5, 38.3, 41.3, 50.8, 61.0, 62.8, 125.9, 126.4, 127.4, 127.5, 128.4, 134.5, 142.0, 143.5, 171.8; ***syn* isomer**: $\delta$ 14.0, 21.5, 39.4, 42.6, 51.1, 61.0, 63.6, 125.9, 126.3, 127.3, 127.5, 128.3, 135.1, 141.5, 143.5, 171.4. IR (neat) 3032, 2920, 2850, 1732, 1348, 1219, 1161, 914 cm$^{-1}$. Anal. Calcd. for $C_{20}H_{23}NO_4S$; C, 64.32; H, 6.21; N, 3.75. Found: C, 64.07; H, 6.17; N, 3.55%.

§ The *5-exo-trig* cyclization was easily effected also in other active carboxylic acid derivatives, such as acyl chlorides and mixed anhydrides.




**4f** **6d** 95 %

¶ The 2,4-*anti*/*syn* stereochemistry of pyrrolidine **5a** was determined by NOESY experiment. A cross peak between the 2- and 4-protons was not observed in the major product, but in the minor product. The signals of the 2- and 4-protons in the *anti*-isomer were observed at lower field ($\delta$ 4.90 and 3.08) than those in the *syn*-isomer ($\delta$ 4.74 and 2.71). The configuration of **5c** was determined by analogy with **5a** by comparing the C2- and C4-proton chemical shifts of each isomer.




***anti*-5a** (major) ***syn*-5a** (minor)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