N-(β,β-Difluorovinyl)oxazolidin-2-ones: First Synthesis and Application in [3+2]- and [4+2]-Cycloaddition-Type Reactions

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Abstract: *N*-(β,β-Difluorovinyl)oxazolidin-2-ones were conveniently prepared in good yields in two steps from the parent oxazolidin-2-ones. The [3+2]- and [4+2]-cycloaddition-type reactions with electron-deficient partners were investigated as first application of these new enamides. TMSOTf was efficient in promoting these two reactions, and the corresponding heterocyclic difluoro adducts were obtained in high yields.

Key words: *N*-(β,β-difluorovinyl)oxazolidin-2-ones, trimethylsilyl trifluoromethanesulfonate, 1,3-dipolar cycloaddition, Diels–Alder reaction, dipolarophile, nitrone, heterodiene

The incorporation of at least one fluorine atom into organic molecules often enhances or modifies biological and therapeutic activities. Consequently, 20% of drugs now commercialized are fluorinated compounds.[1] A myriad of procedures allows the selective introduction of fluorine atom and fluoroalkyl groups into organic molecules.[2] An important subset of fluorinated compounds contains a difluoromethylene (CF_2) group. This group could be obtained by direct fluorination[3] using fluorinating agents [diethylaminosulfur trifluoride (DAST), SF_4, CF_3OF, HF, etc.] which are in general toxic, hazardous and often aggressive towards the substrate. The second strategy using appropriate fluorinated synthons provides a convenient approach to such compounds as more and more new fluorinated building blocks are developed and easily available.[4] 1,1-Difluoro-2-oxygenated ethylenes such as 1,1-difluoro-2-(*N*,*N*-diethylcarbamato)ethylene (**1**)[5] and 2,2-difluorovinyl tosylate (**2**;[6] Figure 1) were shown to be highly valuable synthons. However, the preparation and the chemistry of their 1-nitrogenated homologues have been poorly described.[7]

Our group had previously demonstrated the use of *N*-alkenyl oxazolidin-2-ones as dipolarophile in the [3+2] cycloaddition of nitrones[8] and as dienophile in the [4+2] cycloaddition of oxadienes.[9] We next attempted to extend this study to unknown β,β-difluorinated *N*-vinyloxazolidin-2-ones **3** in which the chirality could be introduced via an alkyl group at the 4-position of the oxazolidinone moiety. Interestingly, no example of such heterocycloadditions involving heterosubstituted *gem*-difluoroalkenes as 2π component has been reported to date in the literature.

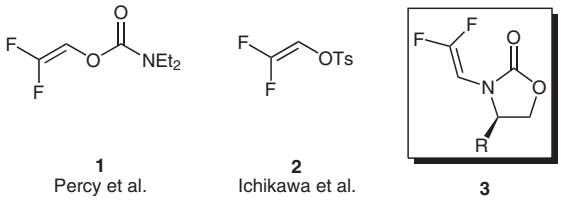
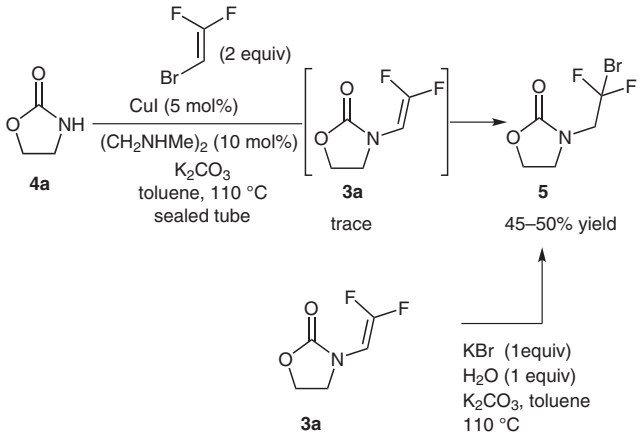


Figure 1

We now report the first synthesis of *N*-(β,β-difluorovinyl)oxazolidin-2-ones **3** by a practical method and their application in [3+2]- and [4+2]-heterocycloaddition-type reactions with electron-deficient partners.

Our initial attempts to access **3a** in one step from **4a** started by using the modified Buchwald's procedure,[8c] which gave excellent yields of *N*-vinyloxazolidin-2-ones starting from the corresponding oxazolidin-2-ones and vinyl bromides (Scheme 1). When **4a** was treated with 1-bromo-2,2-difluoroethene under these conditions, the desired product **3a** was formed but rapidly transformed into **5** in moderate yield (50%). In order to validate the difluoroenamide as a transient intermediate of **5**, **3a** obtained by another method (described later) was heated with KBr and K_2CO_3 in wet toluene and gave rise to **5**[11] in a comparable yield (45%).



Scheme 1

The same phenomenon has also been reported for related compounds such as chlorotrifluoroethylene[10] or tosylate **2**;[6b] the presence of two fluorine atoms at the β-position of the double bond in **3a** could enhance the reactivity of this

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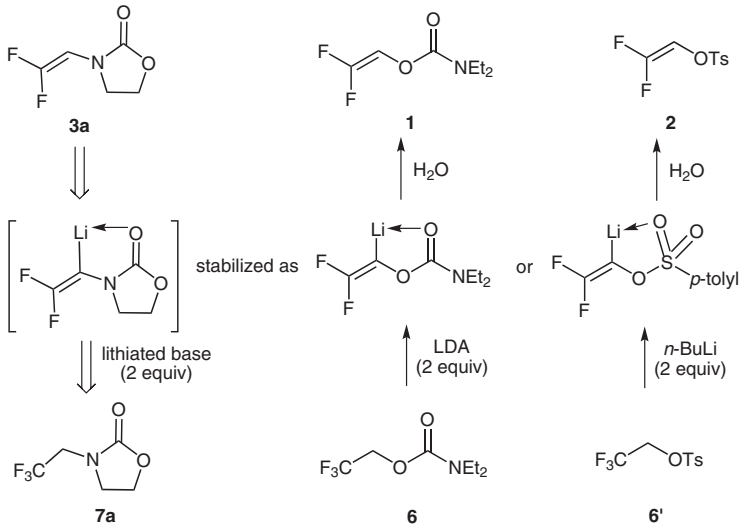


Scheme 2

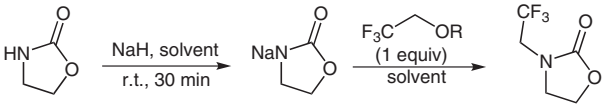
carbon center toward a weak nucleophile such as a bromide ion.

A simple structural comparison between **1**, **2** and **3a** revealed that their corresponding lithiated anions at the carbon atom are all stabilized by the neighboring Lewis bases such as lone-pair oxygen of CO or SO_2 groups and by a strong electron-withdrawing effect of the CF_2 moiety (Scheme 2). The product **3a** could therefore be prepared in the same manner as that employed for **1**[5f] or **2**[6c] starting from the corresponding *N*-(β,β,β-trifluoroethyl)oxazolidin-2-one **7a** via β-elimination of an HF molecule promoted by a lithiated base.

Thus, we attempted a new indirect approach to **3a** starting via the intermediate **7a** that would be reached through *N*-2,2,2-trifluoroethylation of **4a** (Table 1).

Initially, we considered that product **7a** could be obtained by treatment of the corresponding sodium salt of **4a**, produced via exposure of **4a** to NaH, with CF_3CH_2OTs in THF at room temperature (Table 1, entry 1). However, no desired product formation was observed, even at higher temperature (65 °C, Table 1, entry 2). A better solvent for the alkylation such as DMF was next used. At 65 °C, the reaction proceeded, but slowly (5% of conversion after 24 h, entry 3). By increasing the reaction temperature up to 150 °C, the conversion could be notably enhanced (Table 1, entries 4 and 5). Nevertheless, at this temperature, other side reactions occurred with DMF and rendered the purification more difficult, thus lowering the yield. The sluggish reaction with CF_3CH_2OTs was attributed to the fact that a strong electron-withdrawing trifluoromethyl group (CF_3) could effectively stabilize the neighboring CO bond, which rendered the tosylate group hard to remove. On this basis, we envisioned that trifluoromethanesulfonate as leaving group should certainly provide the desired product **7a**. This reaction was inefficient when conducted in THF (Table 1, entry 6) but to our delight, this reaction carried out in DMF smoothly afford-

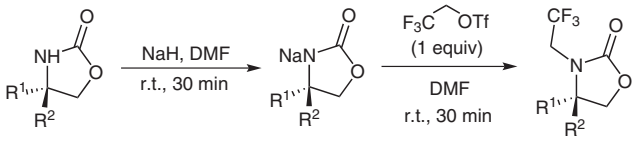
Table 1 Preparation of **7a** via *N*-2,2,2-Trifluoroethylation of **4a**



Entry	R	Conditions[a]	Conversion[b] (%)
1	Ts	THF, r.t., 24 h	0
2	Ts	THF, 65 °C, 24 h	0
3	Ts	DMF, 60 °C, 24 h	5
4	Ts	DMF, 150 °C, 24 h	60
5	Ts	DMF, 150 °C, 72 h	90[c]
6	Tf	THF, 65 °C, 24 h	0
7	Tf	DMF, r.t., 0.5 h	100[d]

[a] Concentration = 1 M (1 mmol of **4a**, 1 mL of solvent).
[b] Based on ^{1}H NMR signals of CH_2N protons of **4a** and **7a**.
[c] Yield of isolated product: 40%.
[d] Yield of isolated product: 75%.

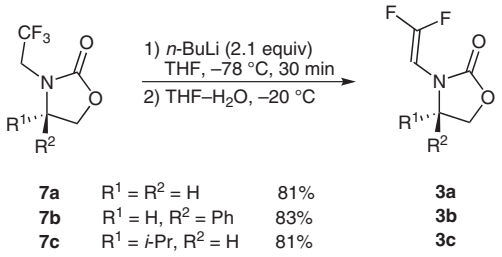
ed the product **7a** at room temperature. The white slurry of the sodium salt of **4a** disappeared rapidly at the end of the addition of CF_3CH_2OTf [11] (Table 1, entry 7). The optimized conditions were next applied to give **7b**,**c**[11] in excellent yields (Scheme 3).



4a	$R^1 = R^2 = H$	75%	**7a**
4b	$R^1 = H$, $R^2 = Ph$	90%	**7b**
4c	$R^1 = i$-Pr, $R^2 = H$	80%	**7c**

Scheme 3

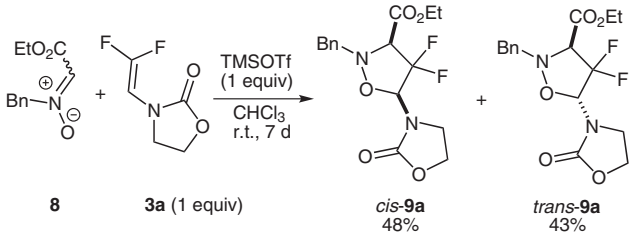
With **7a–c** in hand, we then focused on the elimination reaction of HF to prepare **3a–c**. We were pleased to find that *n*-BuLi could be used effectively and the products **3a**,**c** were obtained in high yields (Scheme 4).[11]



7a	$R^1 = R^2 = H$	81%	**3a**
7b	$R^1 = H$, $R^2 = Ph$	83%	**3b**
7c	$R^1 = i\text{-Pr}$, $R^2 = H$	81%	**3c**

Scheme 4

Our first attempts to carry out a [3+2]-dipolar cycloaddition reaction involving the difluoroenamide **3a** as the dipolarophile were conducted under thermal solvent-free conditions[8c] and resulted in the degradation of nitrone **8** and in the recovery of **3a** (Scheme 5). At this time, we turned to a specific activation of nitrone **8** with TMSOTf[12] which was found to promote efficiently the addition–cyclization reaction between **8** and β,β-di-C-substituted *N*-vinyloxazolidin-2-ones.[8b] Treatment of an equimolar mixture of **8** and **3a** with a stoichiometric amount of TMSOTf at room temperature and in $CHCl_3$ led to the clean formation of the adduct **9a**. However, completion of the reaction (monitored by NMR) required one week.[11]



Scheme 5

After basic workup (aq $NaHCO_3$) the adduct **9a** was obtained as a nearly equimolar mixture of *cis* and *trans* isomers which could be easily separated by column chromatography (48% *cis*-**9a**, 43% *trans*-**9a**). The relative configuration of these isolated adducts was determined by ^1H NMR NOESY experiments as shown for compounds *cis*-**9a** and *trans*-**9a** (Figure 2); the presence of a correlation peak between H-3 and H-5 allowing to deduce the *cis* relationship between the ester and oxazolidinone moieties.

The same conditions applied to the reaction between chiral enamide **3b** and **8** led to the formation of a 50:30:20:0 mixture of the corresponding adduct **9b** in 83% global yield (Scheme 6).[11,13]

In the literature, examples of heterosubstituted *gem*-difluoroalkenes acting as dienophiles was restricted to homo-Diels–Alder reactions with electron-rich dienes.[5a,f] The

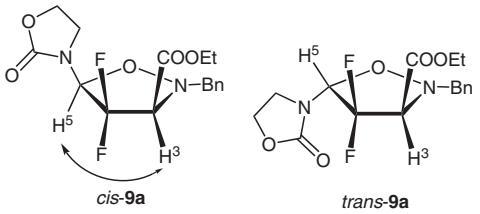
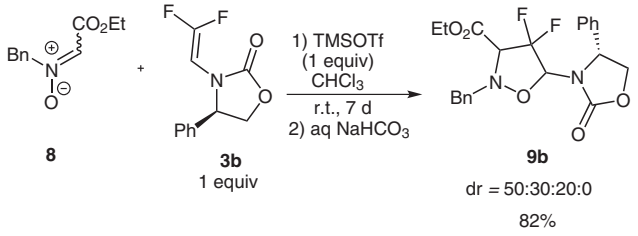


Figure 2



Scheme 6

heterocycloaddition of a *gem*-difluorinated Danishefsky's diene with aldehydes and imines to give difluorinated heteroadducts was described by Uneyama's group.[14] In contrast, to the best of our knowledge, no report concerned hetero-Diels–Alder reactions involving *gem*-difluoroalkenes as dienophiles toward oxadienes.

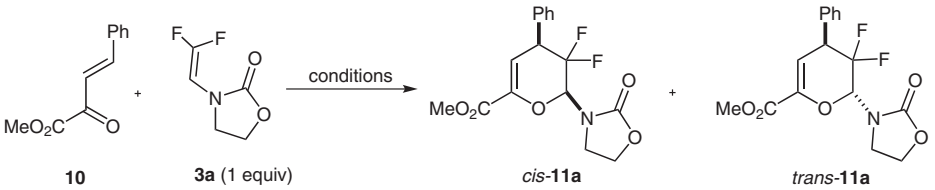
Our study on the reactivity of the difluoroenamides **3** was thus expanded to the [4+2]-cycloaddition with the representative oxadiene **10** (Table 2) under various conditions. Initial investigations began with uncatalyzed solvent-free thermal conditions which proved to promote the cycloaddition, albeit with a low *cis* selectivity (Table 2, entry 1). Application of previously reported conditions using Lewis acids,[9] such as $Eu(fod)_3$-catalyzed or $SnCl_4$-promoted reactions, proved ineffective when applied to the difluoroenamide **3a**, with either recovery of starting materials (entry 2) or low conversion (entry 3). Interestingly, once again TMSOTf was shown to be highly efficient and led to the clean formation of the desired adduct **11a** in good yield and moderate selectivity (entry 4).[11] We next thought to improve the selectivity of the cycloaddition process by lowering the reaction temperature to –20 °C. In order to ensure an appropriate reaction time, the concentration must be as high as possible (entry 5). Under these conditions, a total conversion was observed after 72 hours with a slight enhancement of yield and selectivity (*cis*:*trans* up to 88:12).

The geometry of both adducts could be conveniently deduced from the NOESY experiments as demonstrated in Figure 3 for *cis*-**11a** with intense correlation peak between H-6 and H-4, absent for *trans*-**11a**.

Finally, the same conditions were applied to the reaction between chiral enamide **3b** and **10** and led to the formation of the four possible adducts in good yield and poor selectivity (Scheme 7).[11,15]

In this study, *N*-(β,β-difluorovinyl)oxazolidin-2-ones **3a–c** were synthesized in good yields by a two-step sequence

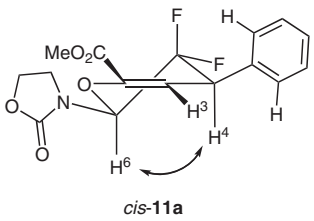
Table 2 [4+2]-Cycloaddition of Oxadiene **10** with Difluoroenamide **3a**



10 **3a** (1 equiv) *cis*-**11a** *trans*-**11a**

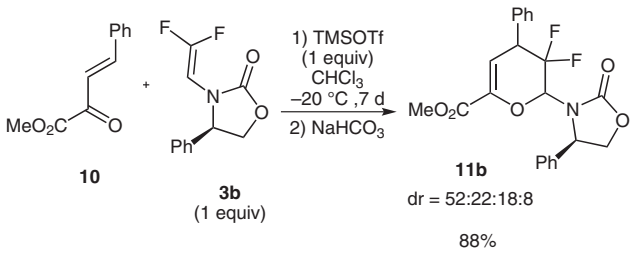
Entry	Conditions	Ratio[a] *cis*/*trans*	Yield[b] (%)
1	130 °C, 16 h	67:33	74
2	$Eu(fod)_3$[c] (5 mol%), 80 °C, 72 h *c* = 0.2 M (0.2 mmol **10** in 1 mL cyclohexane)	–	0
3	$SnCl_4$ (1 equiv), r.t., 24 h *c* = 0.2 M (0.2 mmol **10** in 1 mL CH_2Cl_2)	83:17	<20[d]
4	TMSOTf (1 equiv.), r.t., 72 h *c* = 0.2 M (0.2 mmol **10** in 1 mL $CHCl_3$)	84:16	89
5	TMSOTf (1 equiv), –20 °C, 72 h *c* = 2 M (2 mmol **10** in 1 mL $CHCl_3$)	88:12	96

[a] Based on ^1H NMR of crude mixture.
[b] Yield of of isolated product
[c] fod: 6,6,7,7,8,8,8-heptafluoropropyl-2,2-dimethyl-3,5-octanedianato.
[d] Conversion: 20%.



cis-**11a**

Figure 3



10 **3b** (1 equiv) **11b** dr = 52:22:18:8 88%

Scheme 7

from oxazolidin-2-ones. Their reaction with ester nitrone **8** and with heterodiene **10** under TMSOTf-promoted conditions afforded in high yields a set of original adducts containing a CF_2 moiety with a total regioselectivity. This unprecedented use of azadifluoroalkenes as cycloreactants opens a way to a new family of cycloadducts hardly accessible by conventional strategies and of potent biological interest. Further application of difluoroenamides **3** and of the corresponding heterocycloadducts **9** and **11** are currently under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) From the NMR study on adduct **11b**, the *cis*/*trans* distribution (*cis* I/*cis* II/*trans* I/*trans* II = 52:22:18:8) was deduced.