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Dienophilic reactivity of perfluoroalkenyl ketones in Diels–Alder reactions

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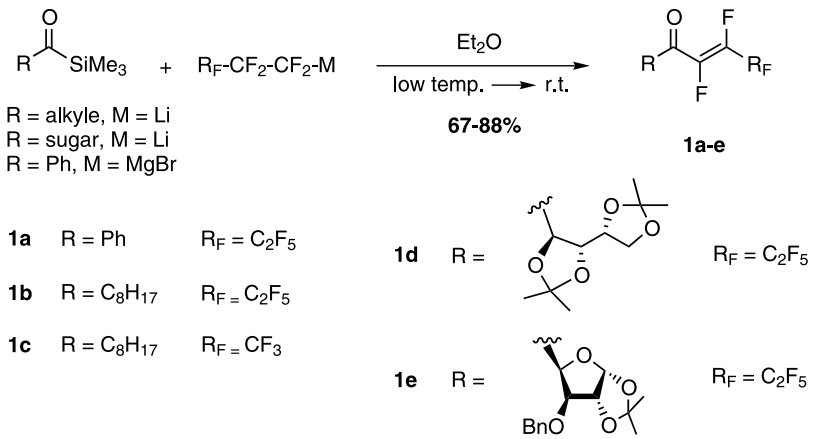
Abstract—Perfluoroalkenyl ketones, obtained by reaction of perfluoroorganometallic reagents with acylsilanes, are shown to be versatile dienophiles in Diels–Alder reactions with various dienes.

Fluorine substituents in organic compounds significantly change the physico-chemical properties, the chemical reactivity and the biological activity of particular molecules.[1,2] There are two contributions to the effect of a single fluorine at a double bond, the strong electron withdrawing effect on the σ-orbitals ($-I_\sigma$ effect) and the p-π-interaction, which increases π-electron density (+M effect) (PE spectroscopy).[3] Generally, the latter effect is dominating. However, in many cases it is not easy to predict the electronic behavior of a given double bond, because its properties are also affected by other substituents attached directly to the double bond or close to it. Simple vinyl fluorides such as α- or β-fluorostyrenes are quite unreactive in [4+2]-cycloadditions and only with the super diene, diphenylisobenzofuran, the corresponding *endo*/*exo*-isomeric Diels–Alder adducts were formed in moderate yields.[4] Additional electron withdrawing substituents attached to the double bond increase the reactivity of vinyl fluorides in these reactions. Consequently, several [4+2]-cycloadditions of 2-fluoroacroleins, fluorinated α,β-unsaturated carboxylic acid derivatives, fluorinated vinyl sulfones and vinyl sulfoxides have been described.[5–7] Mostly *exo*-products have been formed



Scheme 1.

Keywords: Diels–Alder reactions; enones; perfluoroalkenyl compounds; organofluorine.

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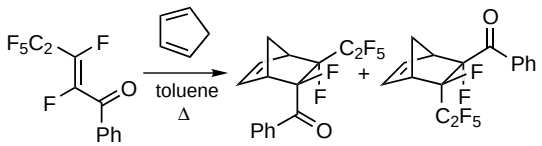
from cyclopentadiene or furan and monofluorinated or *cis*-1,2-difluorinated vinylic compounds. Recently, we observed diastereoselective Diels–Alder reactions of 2-fluoroalk-1-en-3-ones with cyclopentadiene.[8] A second fluorine substituent attached to the double bond seems to increase the reactivity of the corresponding alkenes in Diels–Alder reactions. Several reactions of cyclopentadiene with enol-derivatives of difluoroacetaldehyde,[9] of furan with perfluoropropene or a corresponding sulfonylfluoride,[10] and of trifluoroethylene with several substituted furans have been published recently.[11] Fluorinated vinylic systems, such as hemifluorinated enones, bearing two activating groups at the double bond, should be excellent dienophiles. Hemifluorinated enones were first prepared from perfluoroalkyl iodides via a perfluoroalken-1-yl magnesium bromide,[12] and then organo copper reagents.[13] Some years ago, we reported a general and high yielding synthesis of hemifluorinated enones from acylsilanes and perfluoroalkyl iodides (Scheme 1).[14] These perfluorinated enones proved to be versatile building blocks, either as isolated starting substrates or generated in situ, for the synthesis of elaborated fluorinated derivatives.[15]



1a *endo*-**2a** *exo*-**2a**

Scheme 2.

endo-**2a** *exo*-**2a**

Scheme 3.

Table 1. Synthesis of cycloadducts **2a–e**

Compound	*t* (min)	Yield (%)	Ratio *endo*:*exo*
2a	90	75	89:11[a]
2b	90	84	82:18[b]
2c	90	76	83:17[b]
2d	90	78	89:11[b]
2e	180	75	89:11[b]

[a] The two diastereoisomers were separated by silica gel flash chromatography (P.E./EtOAc:99/1).
[b] Unseparable mixture.

Using our procedure, we have prepared various (aliphatic, aromatic, sugar derived) hemifluorinated enones **1a–1e** (Scheme 1) in order to investigate their reactivity as dienophiles in Diels–Alder reactions. In this preliminary account, we report the results of an exploratory study with some representative cyclic and acyclic dienes.

A toluene solution of enone **1a** and cyclopentadiene was heated at 155°C in a sealed tube. Total conversion was observed within 90 min, confirming the better reactivity of this type of vinyl fluorides, activated by a perfluoroalkyl group and an acyl group compared to α-fluoro-α,β-unsaturated ketones.[8] This cycloaddition is stereoselective, giving **2a** as a 89/11 mixture of diastereomers (Scheme 2) which were separated by silica gel chromatography.

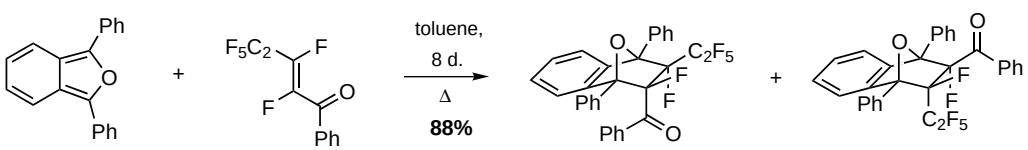
Compound **2a** was fully characterized,[16] and the stereochemistry of the diastereoisomers was assigned according to NOE measurements (Scheme 3).

The major isomer proved to have the *endo* configuration (concerning the acyl group), in contrast to the cycloadducts of monofluorinated analogues[8] with cyclopentadiene. Under the same conditions, enones **1a–1e** gave with cyclopentadiene similar results, with stereoselectivity ranging from 82/18 to 89/11 in favor of the *endo* isomer (Table 1).

The comparison of the ^{19}F NMR spectra of compounds **2b–2e** with the corresponding spectrum of **2a** allowed unambiguously to confirm that the *endo*-diastereoisomer is the major product in each case. Furthermore, a comparison of the ^{19}F NMR spectrum of the cycloadduct **2c** with a similar norbornene derivative described in the literature[17] corroborates these assignments.

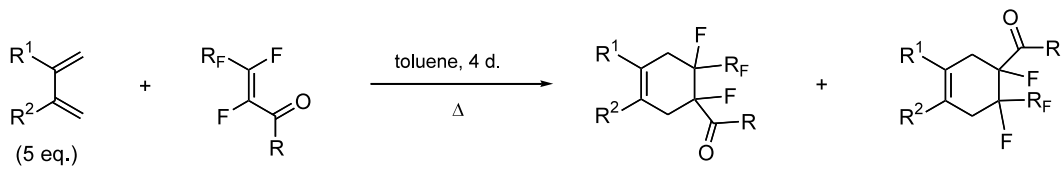
Furan proved to be unreactive under similar conditions. In contrast, the highly reactive diphenyl isobenzofuran reacted with enone **1a** to give a high yield (88%) of a 50/50 non-separable *endo*/*exo* mixture of cycloadducts **3a** in a very slow reaction (8 days for total conversion) (Scheme 4).

Four days were needed to complete the reactions of 2,3-dimethylbutadiene with the hemifluorinated enones



(5 eq.) **1a** *endo*-**3a** 50 : *exo*-**3a** 50

Scheme 4.



$R^1 = R^2 = Me$	**1a, 1b, 1d**	**71-77%**	**4a, 4b, 4d**	
$R^1 = Me, R^2 = H$	**1a**	**64%**	**5a**	62:38
	1b	**65%**	**5b**	59:41

Scheme 5.

1a, **1b** and **1d**, giving good isolated yields of the corresponding cyclohexene derivatives **4a**, **4b** and **4d**. On the other hand, reaction of **1a** and **1b** with isoprene gave **5a** and **5b**, respectively, as a mixture of regioisomers, whose structures were attributed according to the NMR spectra (Scheme 5).[18] The major compound is the one expected from a 'normal' enone, but the low regioselectivity probably results from the counter effect of the β-perfluoroalkyl substituent.

The structure of the acyl moiety has no influence on the dienophilic properties of these hemifluorinated enones, neither from the kinetic nor from the stereoselectivity point of view. Furthermore, we explored the reactivity of hemifluorinated enones with furan, and attempted to modify the regioselectivity of the cycloaddition with isoprene, using Lewis acid ($TiCl_4$ or $BF_3{\cdot}Et_2O$) as activator. In each case, the experiments were unsuccessful: no reaction occurred at low temperature whereas total decomposition was observed at room temperature.

In summary, the presented results disclose the unprecedented application of hemifluorinated enones in [4+2] cycloadditions, giving new cyclic or bicyclic fluorinated compounds of potential synthetic interest. Extension of the scope of these reactions as well as synthetic applications will be reported in due course.

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16. Compound *endo*-**2a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (m, 1H, H7), 2.56 (dm, 1H, $J=11.9$ Hz, H7′), 3.17 (m, 1H, H4), 3.29 (m, 1H, H1), 6.23 (m, 1H, H5), 6.28 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.2 (C7), 48.6 (d, $J=22.1$ Hz, C4), 50.7 (d, $J=20.9$ Hz, C1), 134.0 (m, C5), 136.6 (m, C6), 195.2 (dd, $J=28.9$ Hz, $J=4.5$ Hz, C=O); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −159.6 (ddt, 1F, $J=13.3$ Hz, $J=7.6$ Hz, F_{endo}), −162.1 (d, 1F, $J=5.7$ Hz, F_{exo}). Compound *exo*-**2a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (m, 1H, H7), 2.25 (m, 1H, H7′), 3.18 (m, 1H, H4), 3.40 (m, 1H, H1), 6.13 (m, 1H, H5), 6.53 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.5 (C7), 48.6 (d, $J=20.9$ Hz, C4), 52.1 (d, $J=22.1$ Hz, C1), 131.8 (m, C5), 137.1 (m, C6), 195.0 (dd, $J=29.0$ Hz, $J=4.4$ Hz, C=O); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −159.0 (dd, 1F, $J=26.7$ Hz, $J=22.9$ Hz, F_{exo}), −162.9 (m, 1F, F_{endo}).
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18. For **5a**, major regioisomer, $\delta_{CF3}=-79.8$ ppm, d, $J=13.3$ Hz. For **5b**, minor regioisomer, $\delta_{CF3}=-79.9$ ppm, d, $J=13.3$ Hz. The assignment of the structure of the regioisomers was established after aromatization and NOE measurements on the aromatic derivatives. The details will be reported in a forthcoming full paper.