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Enantioselective Diels–Alder reactions of α-fluorinated α,β-unsaturated carbonyl compounds Part 5. Chemical consequences of fluorine substitution☆,☆☆

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Abstract

α-Fluoro-α,β-unsaturated carbonyl compounds, compared with the corresponding non-fluorinated parent compounds, are less reactive in Diels–Alder reactions with normal 1,3-dienes. The cycloadducts of such dienophiles with 2,3-dimethylbutadiene (**1**) or *o*-quinodimethane (**6**) exhibit low stability whereas the corresponding cycloaddducts formed with cyclopentadiene (**7**) are stable compounds. While the cycloadditions of oct-1-en-3-one (**2e**) or benzyl acrylate (**10b**) with **7** are endo-selective, the corresponding reactions with 2-fluorooct-1-en-3-one (**2a**) or benzyl 2-fluoroacrylate (**10a**) are exo-selective. Applying Lewis acids as mediators, the reactions with non-fluorinated dienophiles become even more endo-selective, while the corresponding reactions with the fluorinated analogues become more exo-selective. Using enantiopure Lewis acidic metal complexes such as titanium TADDOLates, low enantioselectivity is observed in reactions of **7** with **2e** or **10b**. Moderate enantioselectivity (max. 43% enantiomeric excesses (ee)) is found in the corresponding cycloadditions of **7** with **2a**, whereas **10a** shows practically no enantioselectivity. The more efficient chiral induction in reactions with the fluorinated dienophile **2a** might be caused by a chelate-like complexation of the carbonyl compound involving the fluorine substituent.

Keywords: Asymmetric synthesis; Transition metal-catalyzed reactions; Enantiopure titanium TADDOLate complexes; [4+2]-Cycloaddition; Vinyl fluorides; 1,3-Dienes

1. Introduction

Diels–Alder reactions gain an increasing interest for the synthesis of selectively fluorinated mono- or polycyclic cyclohexene derivatives [1,2]. This type of reaction has been shown to be of particular interest in syntheses of fluorinated analogues of biologically active compounds like cantharidin and endothall [3] or D-homosteroids [4]. We have shown that simple vinyl fluorides such as α- or β-fluorostyrenes are quite sluggish dienophiles and solely react with highly reactive dienes such as diphenylisobenzofuran [5,6] or some fluorinated cyclohexa-2,4-dienones [7]. Electron withdrawing substituents such as carbonyl functions, sulfoxide- or sulfonyl groups attached to the fluorovinyl moiety increase the reactivity of the dienophiles. Consequently, 2-fluoroacroleins [8,9], α,β-unsaturated α-fluorocarboxylic acid derivatives [10–15], and unsaturated α,β-difluoroketones [16], fluorinated vinylsulfones [17,18] or an electron-poor fluorinated vinyl sulfoxide [19] were shown to be moderate or good dienophiles.

Very recently, we investigated the diastereoselectivity of Diels–Alder reactions of cyclopentadiene with 2-fluorooct-1-en-3-one (**2a**) or benzyl 2-fluoroacrylate (**10a**) [20]. We now report some additional applications of this reaction type to synthesize several substituted 4-fluorocyclohexenes. Additionally, the first examples of asymmetric [4+2]-cycloadditions of cyclopentadiene with 2-fluorooct-1-en-3-one (**2a**) and benzyl 2-fluoro-acrylate (**10a**) in comparison with the non-fluorinated parent compounds oct-1-en-3-one (**2e**) and benzyl acrylate (**10b**), mediated by enantiopure Lewis acidic titanium complexes, will be described.

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☆☆ For Part 4, cf. [4].
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2. Results and discussion

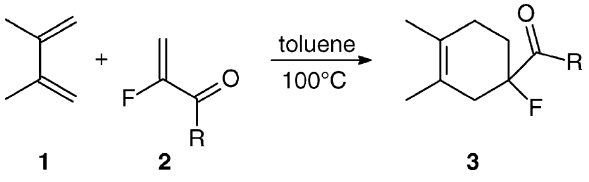
2.1. Thermal Diels–Alder reactions

First, we examined [4+2]-cycloadditions of 2,3-dimethylbutadiene (**1**) with some 2-fluoroalk-1-en-3-ones **2**. The ketones **2** were prepared in three steps by bromofluorination of the corresponding terminal alkenes [21], subsequent HBr elimination [22], and allylic oxidation of the formed vinyl fluorides [23]. The Diels–Alder reactions with normal electron demand were conducted in a conventional thermal manner, using a sealed flask with toluene as a solvent which was heated at 100 °C for 2 days (Scheme 1). The results are summarized in Table 2.

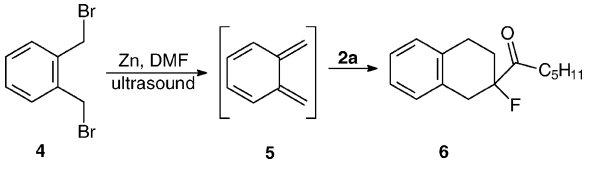
In comparison with the cycloadducts obtained after [4+2]-cycloaddition of cyclopentadiene (**7**) with 2-fluorooct-1-en-3-one (**2a**) or benzyl 2-fluoroacrylate (**10a**) [20], the Diels–Alder adducts **3a-d** showed significantly lowered stability, e.g. partial decomposition of **3a-d** on silica gel was observed.

Recently, we described the Diels–Alder reactions of α- and β-fluorostyrenes with the highly reactive 1,3-diphenylisobenzofuran [6]. Now, we have investigated reactions of more reactive dienophiles such as 2-fluorooct-1-en-3-one (**2a**) with a simple *o*-quinodimethane. Since 5,6-dimethylenecyclohexa-1,3-diene (**5**) is not stable due to its high reactivity, it has to be generated in situ prior to cycloaddition. Different methods have been described for the generation of *o*-quinodimethanes [24]. One possibility is the reductive dehalogenation of 1,2-di(bromomethyl)benzene (**4**) with activated zinc using ultrasound [25]. This method was chosen here for the in situ generation of **5**, which subsequently was reacted with **2a** to furnish the tetrahydronaphthalene **6** (Scheme 2). As mentioned above for the cycloadducts **3** (Table 1), compound **6** was also susceptible to decomposition and therefore obtained just as a crude product after column filtration (48% yield).

The latter reaction might be interesting as many steroids were synthesized by intramolecular Diels–Alder reactions of in situ generated *o*-quinodimethanes [26,27].



Scheme 1.



Scheme 2.

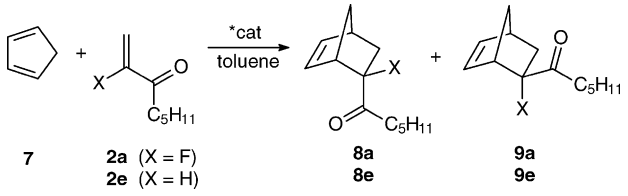
Table 1
Results for the thermal Diels–Alder reactions of fluorinated dienophiles **2** with 2,3-dimethylbutadiene (**1**)

Entry	Dienophile	R	Cycloadduct	Yield [%][a]
1	**2a**	C_5H_{11}	**3a**	35
2	**2b**	C_7H_{15}	**3b**	66[b]
3	**2c**	C_9H_{19}	**3c**	68[b]
4	**2d**	$OCH_2C_2F_4H$	**3d**	68

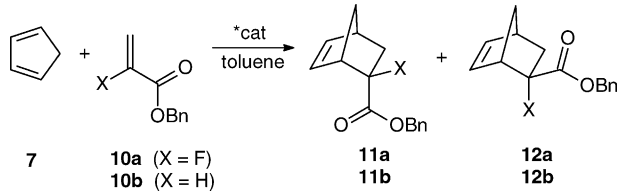
[a] Yields suffer from partial decomposition of cycloadducts on silica gel.
[b] Crude product, GC >90% after column filtration.

2.2. Enantioselective Diels–Alder reactions mediated by enantiopure titanium complexes

Our previous investigations have shown that the thermal Diels–Alder reaction of cyclopentadiene with fluorooct-1-en-3-one (**2a**) and benzyl 2-fluoroacrylate (**10a**) are exo-selective, while the reactions with the corresponding non-fluorinated parent compounds **2e** and **10b** are endo-selective [20]. In the presence of $TiCl_4$ as a Lewis acidic mediator, all reactions became more selective [20]. Taguchi and co-workers already demonstrated that $TiCl_4$ is a valuable mediator for the conversion of optically active 2-fluoroacrylic acid derivatives [13,14] and recently these authors used Et_2AlCl as a mediator for the reaction of cyclopentadiene (**7**) with benzyl 2-fluoroacrylate (**10a**) to give the exo-carboxylate exclusively [15]. Our interest was in asymmetric Diels–Alder reactions [28] of prochiral dienophiles bearing a fluorovinyl functionality, using enantiopure titanium complexes as Lewis acidic mediators. No examples for this type of reaction have been reported in the literature to date. Due to the low stability of the fluorinated cycloadducts **3a-d** and **6**, cyclopentadiene (**7**) was chosen for the following [4+2]-cycloadditions with two different fluorinated dienophiles, i.e. 2-fluorooct-1-en-3-one (**2a**) and benzyl 2-fluoroacrylate (**10a**), and their non-fluorinated parent compounds oct-1-en-3-one (**2e**) and benzyl acrylate (**10b**), mediated by enantiopure titanium complexes (Fig. 1 and Schemes 3 and 4).



Scheme 3.



Scheme 4.

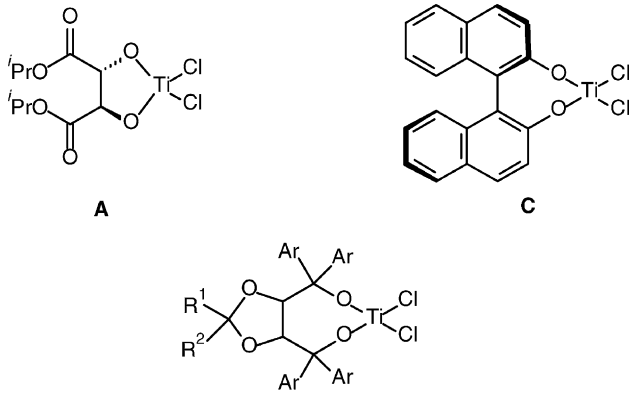


Fig. 1. Enantiopure, Lewis-acidic mediators.

Thus, cyclopentadiene (**7**) was reacted with **2a** or **2e** in dry toluene in the presence of the enantiopure Lewis acidic titanium complexes **A**, **B** or **C** under the conditions listed in Table 2. From the results, it becomes obvious that the fluorinated dienophile **2a** is much less reactive compared to **2e**. First, we employed L-(+)-diisopropyltartratodichlorotitanium **A** as a mediator (Table 2, Fig. 1), which has already been used in the Diels–Alder reaction of **7** with methyl acrylate [29]. Mediator **A** was prepared according to [30][1] using L-(+)-diisopropyltartrate instead of the corresponding α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL). Compared to the non-catalyzed thermal reaction, the diastereoselectivity, both for the fluorinated and the non-fluorinated dienophiles **2a** and **2e** increased, but both endo- and exo-products were isolated as racemates (Table 2, entries 1–6).

Consequently, we next employed Seebach's more complex titanium TADDOLates **B** (Fig. 1). The TADDOLs were synthesized according to the procedures given in [31–33] and subsequently converted to the titanium TADDOLates, following a procedure by Altava et al. [30]. The BINOL-$TiCl_2$ complex **C** (Fig. 1) was prepared in two different manners according to references [34,35].[2] Both types of complexes were already used in Diels–Alder reactions of non-fluorinated dienophiles [30,36–41].

[1] For the preparation of titanium complex **A**, L-(+)-diisopropyltartrate was used instead of the corresponding TADDOL.

[2] After preparation of the titanium BINOLate **C**, which is formed in equilibrium with the reactants, isopropanol was removed azeotropically to shift the equilibrium towards **C** (see Section 4). This method has been used earlier for titanium TADDOLates **B** [33,37]. The role of the molecular sieves in titanium BINOLate mediated reactions has been discussed.

Employing titanium TADDOLates **B**, the best selectivity with the dienophile **2e** of 34% ee was observed with 100 mol% of complex **Bd** (Table 2, entry 15). This mediator also gave the best diastereoselectivity of 79% in favor of the exo-product **9a**. All other titanium TADDOLates **Ba** to **Bc** (Table 2, entries 12–14) were shown to be less selective. Using lower concentrations of the mediator led to lower conversion and lower selectivity. The enantioselectivity of the reaction of **2e** in the presence of **Bd** (Table 2, entries 10, 11) was lower (max. 19% ee), while the diastereomeric ratio 94:6 in favor of the endo-product **8e** was higher in comparison with the corresponding thermal reaction [20].

The necessity for equimolar or overstoichiometric amounts of the Lewis acids **B** may be assigned to particular properties of dienophiles bearing a fluorovinyl functionality. Also Taguchi and coworkers [13–15] used the corresponding Lewis acids in excess in the Diels–Alder reactions of enantiopure and achiral 2-fluoroacrylates. A possible explanation for that phenomenon would be firm coordination of the Lewis acid to the fluorinated dienophile which still persists after the cycloadduct is formed.

On column chromatographic separation of the crude product mixtures resulting from the TADDOLate mediated [4+2]-cycloadditions, the corresponding TADDOLs could be recovered [39] in 82–97% yield. Almost the same selectivity achieved with TADDOLates **B**, was observed for the reaction of cyclopentadiene (**7**) with oct-1-en-3-one (**2e**) in the presence of the BINOL derivative **C** (entries 16 and 17). Analogously to the reactions of **7** with **2a** in the presence of **Bd**, the corresponding reaction in the presence of **C** was more selective, with a maximum enantioselectivity of 43% (Table 2, entry 19). Both reactions were more enantioselective when the Lewis acidic mediator **C** was used after removal of the molecular sieves 4 Å. This observation is in agreement with results described by other authors [35].

After we acquired some experience with the asymmetric Diels–Alder reactions of **2a** and **2e**, respectively, with cyclopentadiene (**7**), we next considered the cycloadditions of benzyl 2-fluoroacrylate (**10a**) and benzyl acrylate (**10b**) with **7** (Scheme 4) to compare the results with the enantioselectivities obtained in the cycloadditions with **2a** and **2e** (Scheme 3 and Table 2). For these investigations, the titanium TADDOLates **Bd** and **Be** were chosen. The results are summarized in Table 3.

Due to the titanium TADDOLates **B** being significantly less reactive compared to titanium tetrachloride and the benzyl acrylates **10b** and **10a** used being less reactive than the ketones **2a** and **2e** (Table 3) [20], the experiments were not conducted at −55 °C (cf. the experiments with $TiCl_4$ [20]), but at −20 °C or room temperature. While the non-fluorinated acrylate **10b** reacted with cyclopentadiene (**7**) at −20 °C, mediated by 50 or 100 mol% titanium TADDOLate **Bd** and showing a conversion of ≥84% after 18 days (Table 3, entries 2, 3), even 45 days at RT were needed in case of fluoroacrylate **10a** to obtain a similar degree

Table 2
Selected examples of Diels–Alder reactions of oct-1-en-3-one (**2e**) and 2-fluorooct-1-en-3-one (**2a**) with cyclopentadiene (**7**) mediated by enantiopure Lewis acidic complexes in toluene

Entry	Dienophile	Mediator [mol%]	Temperature [°C]	Time [h]	Conversion [%]	Combined yield [%]	Ratio **8**:**9**	ee [%][a] **8/9**
1	**2e**	–	110	0.5	>95	54	75:25[b]	–
2	**2e**	**A** [100]	−60	20	>95	89	97:3	0/0
3	**2a**	–	110	0.9	>95	59	27:73[b]	–
4	**2a**	**A** [20]	0	116	19	14	27:73	0/0
5	**2a**	**A** [100]	−40	40	35	20	23:77	0/0
6	**2a**	**A** [100]	−60	48	20	12	22:78	0/0
7	**2e**	**Bc** [100]	−60	0.5	>95	76	95:5	4/n.d.
8	**2e**	**Bc** [125]	−60	0.5	>95	89	99:1	3/n.d.
9	**2e**	**Bd** [20]	−78	45	56	37	94:6	4/n.d.
10	**2e**	**Bd** [100]	−78	45	n.d.	68	94:6	18/n.d.
11	**2e**	**Bd** [100]	−60	15	>95	87	94:6	19/n.d.
12	**2a**	**Ba** [125]	−65	92	89	73	29:71	0/8
13	**2a**	**Bb** [100]	−65	17	>95	75	32:68	0/3
14	**2a**	**Bc** [100]	−60	19	>95	76	33:67	0/6
15	**2a**	**Bd** [100]	−40	100	n.d.	51	21:79	n.d./34
16	**2e**	**C** [110][c]	−60	2.5	>95	87	99:1	13/n.d.
17	**2e**	**C** [110][d]	−60	15	>95	89	97:3	17/n.d.
18	**2a**	**C** [50][c]	−40	28	85	58	32:68	28/8
19	**2a**	**C** [110][d]	−20	138	88	62	28:72	28/43

[a] Determined by chiral GC (Beta-Dex® 120, isothermal; 117 °C for **8e**, 107 °C for **8a** and **9a**).
[b] Taken from [20].
[c] In the presence of molecular sieves 4 Å (cf. Section 4 and [34]).
[d] BINOL derivative **C** was prepared in the presence of molecular sieves 4 Å, which were subsequently removed before conducting the Diels–Alder reaction (cf. [35]).

Table 3
Selected examples of Diels–Alder reactions of benzyl acrylate (**10b**) and benzyl 2-fluoroacrylate (**10a**) with cyclopentadiene (**7**) mediated by enantiopure Lewis acidic complexes in toluene

Entry	Dienophile	Mediator [mol%]	Temperature [°C]	Time [days]	Conversion [%]	Combined yield [%]	Ratio **11**:**12**	ee [%][a] **11/12**
1	**10b**	–	110	1.5 h	>95	91	78:22[b]	–
2	**10b**	**Bd** [100]	−20	18	94	89	97:3	12/n.d.
3	**10b**	**Bd** [50]	−20	18	84	80	96:4	13/n.d.
4	**10a**	–	110	16 h	>95	73	31:69[b]	–
5	**10a**	**Bd** [100]	RT[c]	45	89	70	26:74	<3/<3
6	**10a**	**Bd** [50]	RT[c]	45	90	79	26:74	<3/<3
7	**10a**	**Be** [100]	RT[c]	45	82	58	26:74	<3/<3
8	**10a**	**Be** [50]	RT[c]	45	90	63	26:74	<3/<3

[a] The enantiomeric excesses (ee) of the products were determined ^{19}F NMR spectroscopically using Eu(hfc)$_3$ as a chiral shift reagent (82 mol% for **11a**, 70 mol% for **12a**) or by chiral GC (Beta-Dex® 120, isothermal; 144 °C, compound **11b**).
[b] Taken from [20].
[c] No conversion at −20 °C, negligible conversion at 0 °C.

of conversion (Table 3, entries 5, 6). Unfortunately, in the latter two experiments as well as in the experiments with TADDOLate **Be** (entries 7, 8) practically no enantioselectivity could be observed, whereas for the non-fluorinated endo-norbornenyl benzyl ester **11b** a low enantiomeric excess (max. 13%) was achieved (entries 2, 3). Also the diastereomeric ratio is higher in case of the non-fluorinated dienophile **10b** (max. 97:3, entry 2) compared with the fluorinated compound **10a** (max. 26:74, entries 5–8). Because of the enantioselectivities depicted in Table 3, further investigations with other titanium TADDOLates **B** or BINOLates **C** seemed not promising. Future investigations with double bond fluorinated enoyloxazolidinones may exhibit higher enantioselectivities as is the case for the non-fluorinated parent compounds [41].

The slightly higher enantioselectivity of the reactions with the fluorinated dienophile **2a** compared to **2e** was rather surprising. Earlier theoretical calculations (B3LYP/6-31G-(d)) of Diels–Alder reaction of **2** with but-3-enone or 3-fluorobut-3-enone have shown that the s-*cis*-conformers of

these model dienophiles are more stable compared to the s-*trans*-conformers [20]. In agreement with earlier results, the s-*cis* conformer of but-3-enone is calculated to be more reactive than the s-*trans*-isomer [42]. Our calculations further predicted formation of the exo-cycloadduct for the s-*cis* conformer of both but-3-enone and 3-fluorobut-3-enone. If the dienophiles would react in the s-*trans* conformation, the opposite diastereoselectivity (endo) is predicted [20]. The higher enantioselectivity in case of the fluorinated dienophile **2a** might be due to a chelating complexation of **2a** with **Bd** or **C** including both the carbonyl group and the fluorine substituent. Such an interaction has already been suggested by Taguchi and coworkers for a chiral 2-fluoroacrylate [14]. Interaction of carbon-bound fluorine with metal centers is already known from another complex [43,44]. On the other hand **2e** cannot be complexed in this way. However, the effect is very small in the cases described here.

3. Conclusion

We have presented the first enantioselective Diels–Alder reactions of vinyl fluorides with cyclopentadiene (**7**) using enantiopure Lewis acidic metal complexes. With titanium BINOLate and TADDOLates, low enantioselectivity is observed in reactions of **7** with **2e** or **10b**. Moderate enantioselectivity (max. 43% ee) is found in the corresponding cycloadditions of **7** with **2a**, whereas **10a** shows practically no enantioselectivity. The more efficient chiral induction in reactions with the fluorinated dienophile **2a** might be caused by a chelate-like complexation of the carbonyl compound involving the fluorine substituent.

Furthermore, thermal [4+2]-cycloadditions of 2,3-dimethylbutadiene (**1**) and *o*-quinodimethane (**5**) with some 2-fluoroalk-1-en-3-ones **2** were presented. The resulting cycloadducts **3** and **6** exhibited low stability whereas the corresponding cycloaddducts **8** and **9** or **11** and **12**, respectively, formed with cyclopentadiene (**7**) are stable compounds.

4. Experimental

4.1. General remarks

NMR spectra were recorded at 300 MHz (^{1}H), at 75 MHz (^{13}C) and at 282 MHz (^{19}F) and are reported in ppm downfield from TMS (^{1}H and ^{13}C, $CDCl_3$ as internal standard, $\delta = 77.0$ ppm), or $CFCl_3$ (^{19}F). Mass spectra were recorded by GC/MS coupling (EI, 70 eV) or by GC/MS/CI (chemical ionization). Gas chromatographic analyses were performed using a column HP-5 (30 m; ∅, 0.32 mm; film, 0.25 μm; carrier gas, N_2). The enantiomeric excesses were determined either gas chromatographically using a β-cyclodextrin coated capillary Beta Dex® 120 (30 m; ∅, 0.25 mm; film, 0.25 μm; carrier gas, N_2) at 117 °C (compound **8e**), 107 °C (compounds **8a** and **9a**) and 144 °C (compound **11b**) or ^{19}F NMR spectroscopically using Eu(hfc)$_3$ as a chiral shift reagent (82 mol% for compound **11a**, 70 mol% for compound **12a**). The optical rotation [α] was determined at $\lambda = 589$ nm (Na_D) in chloroform. Thin-layer chromatography was performed using a coated silica gel plate Merck 60 F_{254}. Column chromatography was performed with silica gel Merck 60 (0.063–0.2 mm). All reactions involving air-sensitive agents were conducted under argon atmosphere applying Schlenk-techniques. All reagents purchased from suppliers were used without further purification. CH_2Cl_2 was dried and distilled over P_2O_5, toluene was dried by azeotropic distillation, followed by distillation over sodium. Solvents for chromatography and cyclopentadiene were distilled prior to use. 2-Fluorooct-1-en-3-one (**2a**) [20], oct-1-en-3-one (**2e**) [45] and the titanium complexes **A** [30], **B** [31–33], and **C** [34,35] were prepared according to literature methods. Tetrafluoroethyl α-fluoroacrylate was a gift from the Hoechst AG, Frankfurt/Main.

4.2. Synthesis of the 2-fluoroalk-1-en-3-ones 2

4.2.1. 2-Fluorodec-1-en-3-one (2b)

In accordance with the procedure described for **2a** [20], 2-fluorodec-1-en-3-ol [23] (760 mg, 4.4 mmol) was converted to 2-fluorodec-1-en-3-one (**2b**) (600 mg, 80%). Due to its susceptibility for polymerization, **2b** was not washed with 2N HCl and aqueous $NaHCO_3$ and therefore contains a small amount of pyridine. Spectroscopic data agree with those published [46].

4.2.2. 2-Fluorododec-1-en-3-one (2c)

In accordance with the procedure described for **2a** [20], 2-fluorododec-1-en-3-ol (**7c**) [23] (560 mg, 2.7 mmol) was converted to 2-fluorododec-1-en-3-one (**2c**) (480 mg, 86%), which froze at −20 °C and contained some pyridine. ^{1}H NMR: δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.20–1.40 (m, 12H), 1.63 (pseudo qui, $J = 7.1$ Hz, 2H), 2.63 (dt, $J = 7.2$, 1.9 Hz, 2H), 5.17 (dd, $J = 3.3$, 14.3 Hz, 1H), 5.54 (dd, $J = 3.3$, 45.0 Hz, 1H); ^{13}C NMR: δ 14.0, 22.6, 23.4, 29.0, 29.2, 29.3, 29.3, 31.8, 38.0, 99.9 (dt, $J = 17.8$ Hz), 159.9 (d, $J = 269.6$ Hz), 194.4 (d, $J = 30.9$ Hz); ^{19}F NMR: δ −117.5 (dd, $J = 45.8$, 13.4 Hz); GC/MS: *m/z* (%) 200 [M^+], 185 [$M^+ - CH_3$], 110, 88, 73, 69, 57, 55, 43.

4.3. Diels–Alder reactions of 2,3-dimethylbutadiene (1) with 2-fluoroalk-1-en-3-ones 2 and tetrafluoroethyl α-fluoroacrylate (2d)

4.3.1. 1-(1-Fluoro-3,4-dimethylcyclohex-3-enyl)-hexan-1-one (3a)

A solution of 2-fluorooct-1-en-3-one (**2a**) (240 mg, 1.7 mmol) and 2,3-dimethylbutadiene (209 mg, 2.6 mmol) in toluene (3 ml) was stirred at 100 °C in a sealed glass tube with a Young-tap for 2 days. After cooling down to room temperature, the solvent was removed under reduced

pressure and the crude product was purified by column chromatography (cyclohexane/ethyl acetate 20:1) but suffered from partial decomposition on silica gel. Yield: 140 mg (35%). ^{1}H NMR: δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.22–1.41 (m, 6H), 1.63 (s, 3H), 1.68 (s, 3H), 1.52–2.60 (m, 6H), 2.67 (m, 2H); ^{13}C NMR: δ 13.9, 18.7, 18.7, 22.4, 22.6, 27.1 (dt, $J = 5.1$ Hz), 28.8 (dt, $J = 20.3$ Hz), 31.4, 36.8, 38.0 (dt, $J = 25.4$ Hz), 99.4 (d, $J = 180.6$ Hz), 120.8, 124.8, 212.2 (d, $J = 30.5$ Hz); ^{19}F NMR: δ −164.7 (m); GC/MS: *m/z* (%) 226 [M^+], 206 [M^+ − HF], 191, 150, 135, 127, 107, 99, 43.

4.3.2. 1-(1-Fluoro-3,4-dimethylcyclohex-3-enyl)-octan-1-one (**3b**)

In accordance with the procedure described above for **3a**, 2-fluorodec-1-en-3-one (**2b**) (180 mg, 1.0 mmol) was reacted to afford **3b**. Owing to the susceptibility for decomposition, the crude **3b** was just separated from polymers by column filtration (silica gel, cyclohexane/ethyl acetate 20:1). Yield: 170 mg (66%). ^{1}H NMR: δ 0.89 (t, $J = 6.6$ Hz, 3H), 1.18–1.40 (m, 10H), 1.62 (s, 3H), 1.66 (s, 3H), 1.49–2.60 (m, 6H), 2.68 (m, 2H); ^{13}C NMR: δ 14.0, 18.7, 18.7, 22.5, 23.0, 27.1, 28.8 (dt, $J = 22.9$ Hz), 29.0, 29.1, 31.7, 36.8, 38.0 (dt, $J = 22.8$ Hz), 99.4 (d, $J = 180.6$ Hz), 120.8, 124.8, 212.2 (d, $J = 28.0$ Hz); ^{19}F NMR: δ −164.7 (m); GC/MS: *m/z* (%) 254 [M^+], 234 [M^+ − HF], 219, 155, 150, 135, 127, 107, 57.

4.3.3. 1-(1-Fluoro-3,4-dimethylcyclohex-3-enyl)-decan-1-one (**3c**)

In accordance with the procedure described above for **3b**, 2-fluorododec-1-en-3-one (**2c**) (209 mg, 1.0 mmol) was reacted to afford **3c** (190 mg, 65%). ^{1}H NMR: δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.13–1.36 (m, 14H), 1.62 (s, 3H), 1.66 (s, 3H), 1.48–2.60 (m, 6H), 2.67 (ddt, $J = 7.4$, 3.3, 1.4 Hz, 2H); ^{13}C NMR: δ 14.1, 18.7, 18.7, 22.6, 23.0, 27.2 (dt, $J = 5.1$ Hz), 28.6, 28.8 (dt, $J = 22.9$ Hz), 29.2, 29.4, 29.5, 31.8, 36.9, 38.0 (dt, $J = 25.4$ Hz), 99.4 (d, $J = 183.1$ Hz), 120.8, 124.9, 212.3 (d, $J = 27.9$ Hz); ^{19}F NMR: δ −164.8 (m); GC/MS: *m/z* (%) 282 [M^+], 262 [M^+ − HF], 247, 155, 150, 135, 127, 107, 85, 71, 57, 55, 43.

4.3.4. 2,2,3,3-Tetrafluoropropyl 1-fluoro-3,4-dimethylcyclohex-3-ene carboxylate (**3d**)

According to the procedure described above for **3a**, 2,2,3,3-tetrafluoropropyl 2-fluoroacrylate (**2d**) (204 mg, 1.0 mmol) was reacted to afford **3d**. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 9:1). Yield: 210 mg (68%). ^{1}H NMR: δ 1.64 (s, 3H), 1.66 (s, 3H), 1.90–2.80 (m, 6H), 4.58 (tt, $J = 12.6$ Hz, $J = 1.4$ Hz, 2H), 5.52 (tt, $J = 53.2$ Hz, $J = 3.8$ Hz, 1H); ^{13}C NMR: δ 18.3, 18.3, 26.9 (dt, $J = 5.4$ Hz), 29.1 (dt, $J = 22.2$ Hz), 38.1 (dt, $J = 23.6$ Hz), 60.3 (tt, $J = 30.5$ Hz), 93.2 (d, $J = 184.5$ Hz), 111.1 (tt, $J = 251.5$ Hz, $J = 37.5$ Hz), 114.0 (tt, $J = 249.7$ Hz, $J = 27.8$ Hz), 125.1, 128.9, 170.5 (d, $J = 26.4$ Hz); ^{19}F NMR: δ −123.5 (m, 2F), −137.4 (d, $J = 53.4$ Hz, 2F), −162.1 (m, 1F); GC/MS: *m/z* (%) 286 [M^+], 266 [M^+ − HF], 251, 223, 159, 151, 141, 127, 109, 107, 95, 91. Anal. calcd. for $C_{12}H_{15}F_5O_2$: C, 50.35; H, 5.28. Found C, 49.93; H, 5.18.

4.4. Diels–Alder reaction of o-quinodimethane (**5**) with 2-fluorooct-1-en-3-one (**2a**)

4.4.1. 1-(2-Fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-hexan-1-one (**6**)

Zinc dust (500 mg, 7.6 mmol) was stirred with saturated aqueous NH_4Cl. Then the zinc was washed with water, ethanol, diethyl ether, and dimethyl formamide (DMF). The zinc activated in this way was placed into a 10 ml round-bottomed flask, which was cooled by water circulation through an external jacket. 2-Fluorooct-1-en-3-one (**2a**) (144 mg, 1.0 mmol) was dissolved in this flask in DMF (2 ml) and 0.3 ml of a solution of 1,2-bisbromomethylbenzene (**4**) (530 mg, 2.0 mmol) in DMF (1.5 ml) were added. Being water-cooled, the solution was sonicated with an ultrasonic-finger for 15 min. Subsequently, the solution of **4** (0.3 ml) was added and sonicated in the same fashion. This procedure was repeated until **4** was consumed completely. Then the solution was sonicated for another 30 min, diethyl ether (10 ml) was added and the solid was removed using a centrifuge. The solution was washed with water (3 × 10 ml), dried over $MgSO_4$ and the solvent was evaporated. The crude product was separated from polymers by column filtration (silica gel, cyclohexane/ethyl acetate 20:1). Unreacted 2-fluorooct-1-en-3-one (**2a**) was removed in oil-pump vacuum at room temperature. Further purification was not possible as **6** decomposes on silica gel. Yield: 120 mg (48%). ^{1}H NMR: δ 0.91 (t, $J = 6.9$ Hz, 3H), 1.18–1.71 (m, 6H), 1.85–2.10 (m, 2H), 2.74 (dt, $J = 7.2$, 3.3 Hz, 2H), 2.77–3.09 (m, 3H), 3.27 (dd, $J = 39.6$, 17.6 Hz, 1H), 6.95–7.18 (m, 4H); ^{13}C NMR: δ 13.9, 22.4, 22.6, 24.6 (dt, $J = 5.1$ Hz), 29.2 (dt, $J = 22.9$ Hz), 31.4, 35.8 (dt, $J = 22.9$ Hz), 36.8, 99.1 (d, $J = 185.7$ Hz), 126.2, 126.3, 128.5, 129.1, 134.7, 139.4, 211.7 (d, $J = 30.5$ Hz); ^{19}F NMR: δ −164.9 (m); GC/MS: *m/z* (%) 228 [M^+ − HF], 172, 157, 129, 99, 71, 43.

4.5. Lewis acid mediated Diels–Alder reactions of cyclopentadiene (**7**) with the dienophiles **2** and **10**

4.5.1. Preparation of titanium BINOLate ***C***

To a suspension of powdered molecular sieves 4 Å (250 mg) in dry toluene (3 ml) under an argon atmosphere, 0.88 ml (0.25 mmol) of a 0.28 molar solution of di(isopropoxy)titanium dichloride in dry toluene and (*R*)-(+)-binaphthol (71.5 mg, 0.25 mmol) were added under stirring at RT. Isopropanol was removed azeotropically from the brown-red suspension without heating under reduced pressure until the solvent was reduced to ca. half of its volume. The mediator suspension thus obtained was used directly in the corresponding Diels–Alder reactions.

4.5.2. Titanium complex mediated Diels–Alder reactions

To a suspension of the corresponding freshly prepared titanium complex in dry toluene, under an argon atmosphere at the temperature given in 3, 1 mol eq. of a 0.30 M solution of the dienophiles **2** or **10** in dry toluene was injected dropwise using a syringe. After stirring this suspension at the given temperature for 10 min, 12 mol equivalents of cyclopentadiene (**7**) were injected dropwise and stirring was continued at this temperature for the time given in Tables 2 and 3. The degree of conversion was followed by gas chromatography. Then the reaction mixture was treated with water (15 ml), resulting in precipitation of a white solid. This mixture was neutralized with a 5% $NaHCO_3$-solution and diethyl ether (15 ml) was added. After shaking the two-phase mixture was filtered (Büchner funnel), the precipitate was washed with diethyl ether (20 ml) and the phases were separated. The aqueous phase was extraced with diethyl ether (2×20 ml) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue was purified as described earlier for the achiral Diels–Alder reactions of **2a**, **2e**, **10a** and **10b** with cyclopentadiene (**7**) [20].

*4.5.2.1. (−)-exo-1-(2-Fluoro-bicyclo[2.2.1]hept-5-en-2-yl)-hexan-1-one (−)-(**8a**).* Yields are given in Table 2. $[\alpha]_D^{23}$ −54.6 ($c = 0.68$, $CHCl_3$, 36% ee, determined by chiral GC). Spectroscopic data agree with those reported for the racemic compound in [20].

*4.5.2.2. endo-1-(2-Fluoro-bicyclo[2.2.1]hept-5-en-2-yl)-hexan-1-one (**9a**), endo-/exo-1-(bicyclo[2.2.1]hept-5-en-2-yl)-hexan-1-one (**8e** and **9e**).* Yields are given in Table 2. Spectroscopic data agree with those reported in [20].

*4.5.2.3. endo-/exo-benzyl 2-fluoro-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**11a** and **12a**) and endo-/exo benzyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (**11b** and **12b**).* Yields are given in Table 3. Spectroscopic data agree with those reported in [20].

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