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Diastereoselective Diels−Alder Reactions of α-Fluorinated α,β-Unsaturated Carbonyl Compounds: Chemical Consequences of Fluorine Substitution.† 2‡

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Two α-fluoro α,β-unsaturated carbonyl compounds, i.e., benzyl 2-fluoroacrylate (**3**) and 2-fluorooct-1-en-3-one (**4**), as well as the corresponding nonfluorinated parent compounds, were synthesized and subjected to Diels−Alder reactions with cyclopentadiene. The cycloadditions were conducted thermally, microwave-assisted, and Lewis acid-mediated ($TiCl_4$). The fluorinated dienophiles exhibited a lower reactivity and exo diastereoselectivity, while the corresponding nonfluorinated parent compounds reacted endo selectively. DFT calculations suggest that kinetic effects of fluorine determine the stereoselectivity rather than higher thermodynamic stability of the exo products.

Introduction

During the past decades, interest in fluorinated compounds has increased significantly due to the unique influence of the fluorine substituent on the chemical, physical, and physiological properties of these compounds.[1] Diels−Alder reactions of monofluorinated olefins are an attractive approach toward a range of selectively fluorinated cyclohexenes, many of which have potential biological activity. However, regarding simple vinyl fluorides, just the reactions of some fluorostyrenes with the highly reactive diphenylisobenzofuran[2] and with some fluorinated dienes[3] are known. Several more reactions of this type, which solely take place with strongly activated dienophiles such as 2-fluoroacroleins,[4] α,β-unsaturated α-fluorocarboxylic acid derivatives[5] and α-fluoro ketones,[6] fluorinated vinyl sulfones,[7] or a fluorinated electron-poor vinyl sulfoxide[8] have been published.[9]

Actually, there is little knowledge concerning the effect of a single fluorine substituent on the electronic properties, the stability, and the reactivity of the π-system of simple vinyl fluorides.[1,10,11] These studies revealed significant differences in reactivity compared both to nonfluorinated and higher fluorinated olefins. Only fluoroethylene itself and several of its substituted derivatives have been investigated by experimental and theoretical methods,[12] showing that there is a weak influence of a single fluorine substituent. Investigations of fluoroethylene by means of photoelectron and electron transmission spectroscopy show the ability of the fluorine substituent to exert p−π-interaction (+M effect) on the double bond.[13] Qualitatively, the ground state of a monofluoroalkene can be described as illustrated by the structures **1** and **2**, where the electron-withdrawing effect

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‡ For part 1, see ref 2b.

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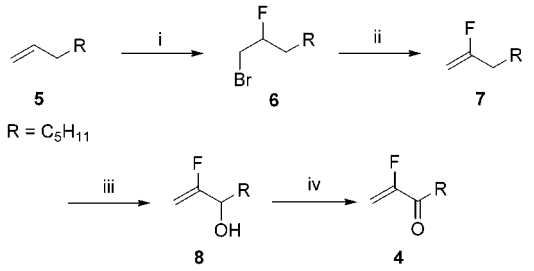
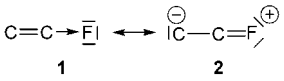
SCHEME 1[a]



[a] Reagents and conditions: (i) NBS, $Et_3N{\cdot}3HF$, CH_2Cl_2; (ii) KO^{t}Bu, pentane (60% over two steps); (iii) SeO_2, ^{t}BuOOH, HOAc (cat.), CH_2Cl_2 (54%); (iv) PDC, MS 10 Å, CH_2Cl_2 (81%).

(−I effect) of fluorine may be offset by its p−π-interaction (+M effect):[14]



2-Fluoropropene has been treated in ab initio calculations to show that there is a +M effect of fluorine, but this interaction was considered less significant compared to the −I effect.[15] Ab initio calculations of fluoroethylene and ethylene revealed the LUMO and HOMO energy of the first compound to be lowered slightly (0.09 and 0.21 eV) compared to ethylene,[12d] suggesting that fluorine acts as a weak electron acceptor. However, the ionization energy of vinyl fluoride is only 0.14 eV higher than that of ethylene, proving a weak interaction of the π-bond with the 2p-orbital of the fluorine atom.[16] Investigations on the Diels−Alder reactions of α- and β-fluorostyrenes with 1,3-diphenylisobenzofuran suggested that the fluorine substituent has an electron-donating effect rather than a withdrawing one.[2b]

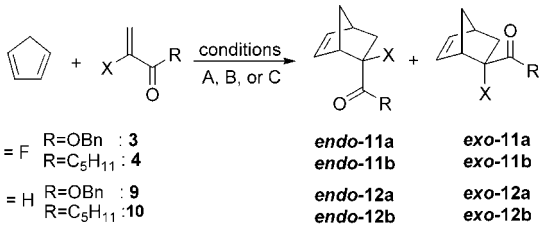
In the present paper, we describe our results of experimental investigations on 2-fluorooct-1-en-3-one (**4**) and benzyl 2-fluoroacrylate (**3**) as moderate dienophiles in [4 + 2]-cycloadditions with cyclopentadiene. These Diels−Alder reactions were conducted thermally, microwave-assisted, and Lewis acid-mediated ($TiCl_4$) and compared with the cycloadditions of the corresponding nonfluorinated dienophiles.

Results and Discussion

Synthesis of Dienophiles. We recently described syntheses of 2-fluoroalk-1-en-3-ols by bromofluorination of terminal olefins, subsequent dehydrobromination of the thus-formed bromofluorides, and allylic hydroxylation of vinyl fluorides by SeO_2 oxidation (shown in Scheme 1 for the terminal olefin oct-1-ene (**5**)).[17] This sequence furnished **8** in an overall yield of 32% over three steps. Subsequent pyridinium dichromate−oxidation of **8** yielded 2-fluorooct-1-en-3-one (**4**) in 81% yield (Scheme 1).

The other fluorinated dienophile, benzyl 2-fluoroacrylate (**3**), was prepared previously.[18] For means of comparison in the Diels−Alder reactions described below, two nonfluorinated dienophiles were also synthesized: Benzyl acrylate (**9**) was obtained in a new one-pot reaction of 3-chloropropionic acid with benzyl bromide and triethylamine in 40% yield, and oct-1-en-3-one (**10**) was prepared according to a literature procedure[19] starting from commercially available oct-1-en-3-ol.

SCHEME 2[a]



[a] Reagents and conditions: (A) toluene, 110 °C; (B) microwaves, 500 W; (C) $TiCl_4$, CH_2Cl_2.

TABLE 1. Thermal Diels−Alder Reactions of α,β-Unsaturated Carbonyl Compounds with Cyclopentadiene

entry	X	R	time (h)	cycloadduct	endo/exo[a]	yield (%)
1	F	OBn	16	**11a**	31:69	73
2	H	OBn	1.5	**12a**	78:22	91
3	F	C_5H_{11}	0.9	**11b**	27:73	59
4	H	C_5H_{11}	0.5	**12b**	75:25	54

[a] Determined by GC of the crude reaction product.

Thermal Diels−Alder Reactions. To elucidate the influence of a vinylic fluorine substituent on reactivity and stereoselectivity, the two different fluorinated dienophiles benzyl 2-fluoroacrylate (**3**) and 2-fluorooct-1-en-3-one (**4**), and their nonfluorinated parent compounds **9** and **10** were investigated conducting systematic studies on their Diels−Alder reactions with cyclopentadiene. These Diels−Alder reactions with normal electron demand[20] were carried out thermally, microwave-assisted, and Lewis acid-mediated ($TiCl_4$) (Scheme 2).

The thermal [4 + 2]-cycloadditions were performed conventionally, using a sealed flask with toluene as a solvent that was heated at 110 °C. The results of these reactions are summarized in Table 1.

Evaluating the data in Table 1, it can be stated that the esters **3** and **9**, either fluorinated or nonfluorinated, reacted significantly slower compared to the ketones **4** and **10**. The fluorinated dienophiles reacted significantly slower compared to the nonfluorinated parent compounds, which hints at an increased π-electron density of the C=C double bond caused by the fluorine substituent.[2b] Moreover, the yields of the norbornenyl esters **11a** and **12a** are higher than those of the corresponding ketones **11b** and **12b**. In all reactions depicted in Table 1, no byproducts were observed by GC, except dicyclo-

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pentadiene. However, the most striking difference is the following: Nonfluorinated Diels−Alder products are generally formed endo selectively. This was assigned to secondary orbital interactions (SOI),[21] although these observations could also be interpreted in terms of classical concepts such as solvent effects, steric interactions, hydrogen bonds, electrostatic forces, and others.[22] In contrast, the cycloadditions of fluorinated dienophiles **3** and **4** proceeded exo-selectively[23] for reasons that have not been completely understood yet (cf. theoretical calculations). Exo selectivity has already been reported in some cases for Diels−Alder reactions of monofluorinated or cis-1,2-difluorinated vinylic compounds.[5d−f,8,24] Steric factors could partly contribute but cannot account for this selectivity completely. For example, regarding the endo-selective [4 + 2]-cycloadditions of cyclopentadiene with simple dienophiles such as acrylic acid, methyl acrylate, and acrolein, experimental data reveal that a methyl group in the α-position of these dienophiles induces reversal of diastereoselectivity toward the exo-adducts.[25] The same is true for Lewis acid-mediated [4 + 2]-cycloadditions of cyclopentadiene with α-bromoacrolein[26] and acroleins or acrylates bearing a methyl group in the α-position.[26,27] Analogously, in optically active acrylic acid derivatives, an α-methyl group as well as an α-chlorine substituent induced exo-selectivivity.[5d] Considering also the complete exo directing effect of an α-fluorine substituent in the respective reactions,[5d] steric repulsion in the transition state is unlikely to be the dominating factor controlling diastereoselectivity.

Prolonged reaction time for **3** (Table 1, entry 3, 2 days) did not result in any change of the ratio of diastereomers, suggesting that the Diels−Alder adducts resulting from the fluorinated dienophiles **3** or **4** are stable under these conditions.

Microwave-Assisted Diels−Alder Reactions. The conventional thermal reactions (Scheme 2) depicted in Table 1 were also investigated using a commercial 500 W microwave oven (Table 2).[28]

We first investigated these reactions in toluene, though this solvent is known to absorb microwave energy poorly,[29] since the fluorinated α,β-unsaturated carbonyl compounds used here are susceptible to decomposition. Thus, toluene dilutes the reaction mixture to impede polymerization. Additionally, toluene shall consume a part of the energy that is absorbed by the reactants and thereby effect milder reaction conditions. However, subsequent investigations without any solvent did not show a big difference except the lower yield for entry 2. Compared to the conventional thermal Diels−Alder-reactions, slightly diminished yields were found in the case of the fluorinated dienophiles **3** and **4**, while **12b** was furnished with increased yields (Table 2, entries 7 and 8). Most strikingly, the reaction times were shortened significantly with respect to the conventional thermal reaction, especially in the reactions without solvent.

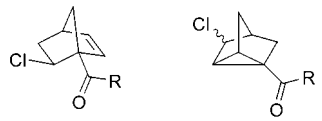
TABLE 2. Microwave-Assisted Diels−Alder Reactions of α,β-Unsaturated Carbonyl Compounds with Cyclopentadiene

entry	X	R	solvent	time[a] (min)	cycloadduct	endo/exo[b]	yield (%)
1	**F**	OBn	toluene	66	**11a**	30:70	54[c]
2	**F**	OBn		72	**11a**	29:71	44[d]
3	**H**	OBn	toluene	36	**12a**	76:24	88
4	**H**	OBn		12	**12a**	74:26	91
5	**F**	C_5H_{11}	toluene	46	**11b**	22:78	44
6	**F**	C_5H_{11}		16	**11b**	22:78	48
7	**H**	C_5H_{11}	toluene	12	**12b**	78:22	61
8	**H**	C_5H_{11}		10	**12b**	79:21	64

[a] The reaction mixture was irradiated a maximum of 15 min without a break to prevent overheating of the microwave oven. [b] Determined by GC of the crude reaction product. [c] 90% conversion (GC). [d] 92% conversion (GC).

Additionally, benzyl 2-fluoroacrylate (**3**) was attempted to react with furan under conventional thermal conditions (sealed flask, toluene, 125 °C, 22 h) or microwave irradiation (without solvent, 16 min), but no cycloadducts were observed.

$TiCl_4$-Mediated Diels−Alder Reactions. It is well-known in the literature that Diels−Alder reactions can be catalyzed with Lewis acids.[21c,30] During our first experiments with $TiCl_4$, we realized that stoichiometric or slightly substoichiometric amounts were needed to mediate the corresponding reactions of **3** and **4** with cyclopentadiene (Scheme 2).[31] Contrary to the thermal reactions described above, in the presence of $TiCl_4$ not only the expected cycloadducts **11a** and **11b**, respectively, were formed, but also some chlorine-containing side products (*exo*-**13a**,**b**, **14a**,**b**; see below). The results are summarized in Table 3.



***exo*-13a,b** **14a,b** (m. d.)

a: R = OBn, **b**: R = C_5H_{11}

The most striking fact is that solely the exo-products **11a**,**b** were obtained in the case of fluorinated dienophiles using stoichiometric amounts of $TiCl_4$ or reaction at room temperature (100% exo, Table 3, entries 1, 3, 5, and 9), while about 70:30 or 75:25 (exo/endo) was found in the thermal reactions (Tables 1 and 2). Regarding the non-

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(30) E.g. Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741−761.

TABLE 3. $TiCl_4$-Mediated Diels–Alder Reactions of α,β-Unsaturated Carbonyl Compounds with Cyclopentadiene

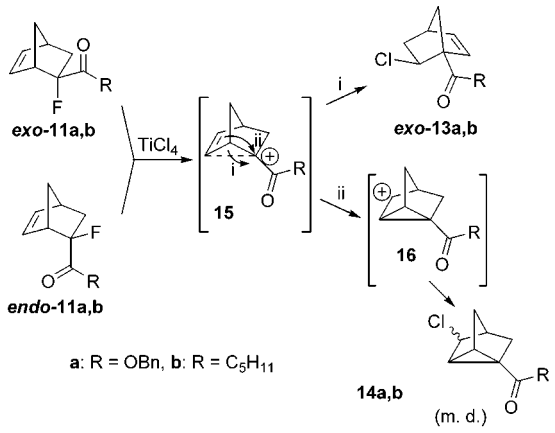
entry	X	R	$TiCl_4$ (mol %)	*T* (°C)	time	cycloadduct	endo/exo[a]	yield (%)	*exo*-**13**[b]	**14**[b,c]
1	**F**	OBn	100	−55	18 h	**11a**	0:100	53[d]	5	31 [30][e]
2	**F**	OBn	50	−55	13 d[f]	**11a**	27:73	24[f]		
3	**F**	OBn	50	rt[g]	90 min	**11a**	0:100	14	3 [2]	13 [13][e]
4	**F**	OBn	20	−55	13 d[h]	**11a**	29:71	41[h]		
5	**F**	OBn	20	rt[g]	120 min	**11a**	0:100	57[i]	6	20 [17][e]
6	**H**	OBn	100	−55	28 min	**12a**	96:4	75		
7	**H**	OBn	50	−55	28 min	**12a**	96:4	75		
8	**H**	OBn	20	−55	28 min	**12a**	96:4	86		
9	**F**	C_5H_{11}	100	−55	170 min	**11b**	0:100	3	8	10/37 [11][e]
10	**F**	C_5H_{11}	70	−78 → 0	24 h	**11b**	9:91	46	5	6/5
11	**F**	C_5H_{11}	50	−55	170 min	**11b**	10:90	15	10	11 [3]/16 [4]
12	**F**	C_5H_{11}	20	−55	14 h	**11b**	38:62	48		
13	**H**	C_5H_{11}	20	−55	15 min	**12b**	96:4	73		

[a] Determined by GC of the crude reaction product. [b] Share in the crude reaction product (GC); the value in brackets refers to isolated yield. [c] Denotes the mixture of diastereomers. [d] Isolated product **11a** containing 6% of *exo*-**13a** (GC). [e] Isolated as a mixture of diastereomers. [f] 48% conversion (GC). [g] Reagents were mixed at 0 °C. Under these reaction conditions, the formation of benzyl chloride (up to 20% isolated yield) was observed. [h] 55% conversion (GC). [i] Isolated product **11a** containing 8% of *exo*-**13a** (GC).

fluorinated parent compounds, enhanced endo diastereoselectivity was observed (96% endo, Table 3, entries 6–8, and 13) compared to the thermal reactions (about 75:25 or 80:20, endo/exo, Tables 1 and 2). As already observed for the conventional thermal and the microwave mediated Diels–Alder reactions, the fluorinated dienophiles **3** and **4** exhibited lower reactivity compared to their nonfluorinated counterparts **9** and **10**. Benzyl 2-fluoroacrylate (**3**) was already that unreactive that the reaction was incomplete being mediated by 50 or 20 mol % $TiCl_4$ at −55 °C. Similar behavior was found for 2-fluorooct-1-en-3-one (**3**), although conversion came to completion after prolonged reaction time. These observations are in agreement with the results by Taguchi et al.[5d] These authors used mostly overstoichiometric amounts of the Lewis acid to mediate the reaction of optically active 2-fluoroacrylic amides with cyclopentadiene. In contrast, the reaction of the nonfluorinated benzyl acrylate (**9**) was not dependent on the $TiCl_4$ concentration (Table 3, entries 6–8) with regard to reactivity, diastereoselectivity, and yield. Almost complete endo selectivity was also found in the reaction of oct-1-en-3-one (**10**) with cyclopentadiene in the presence of 20 mol % of $TiCl_4$ (Table 3, entry 13), while mainly decomposition was observed for Lewis acid concentrations of 50 mol % and higher.

A remarkable effect was observed studying the diastereoselectivities of the Diels–Alder reactions of benzyl 2-fluoroacrylate (**3**) and cyclopentadiene: Solely the exo-cycloadduct **11a** was obtained either with stoichiometric amounts of Lewis acid at −55 °C (Table 3, entry 1) or elevated temperatures and 20 mol % of $TiCl_4$ (Table 3, entries 3 and 5). Unfortunately, the result of reactions with fluorinated dienophiles **3** and **4** is falsified when carried out at room temperature or using high concentrations of $TiCl_4$. Chlorinated, rearranged byproducts *exo*-**13a**,**b** and **14a**,**b** formed from the primary cycloadducts **11a** or **11b** were observed (vide supra). The structures of these products were confirmed by two-dimensional NMR experiments. Depending on the respective conditions, in the $TiCl_4$-mediated reactions *exo*-**13a** or *exo*-**13b**, respectively (3–10%, GC), and the diastereomers **14a** (13–31%, GC) or **14b** (11–47%, GC) were observed in the crude product mixtures. In the case of **14b**, the diastereomers were separated by HPLC. The amount of these byproducts rises with elevated Lewis acid concentrations or elevated temperatures. Under mild reaction conditions, no chlorinated byproducts were observed (Table 3, entries 2, 4, and 12). The formation of *exo*-**13** and **14** was shown to arise from the fluorinated Diels–Alder adducts *exo*-**11** or *endo*-**11** by subjecting the latter to stoichiometric amounts of $TiCl_4$ at room temperature and was rationalized by substitution of a fluorine atom by chlorine with rearrangements (concerted or nonconcerted) of the Wagner–Meerwein-type and π-participations as depicted in Scheme 3. The exclusive formation of *exo*-**13** over the corresponding endo-compound can be explained by a concerted reaction of **11**, which should be kinetically favored in the case of the endo-isomer. An attack of the carbenium ion resulting from **15** after Wagner–Meerwein rearrangement (Scheme 3, i) by chloride is not probable as this should result in *endo*-**13** due to steric hindrance by the methylene group in β-position to the carbonyl group. Also for the formation of **14** (Scheme 3, ii), in case of a concerted mechanism, *endo*-**11** should react faster compared to *exo*-**11**. This observation would also explain why the endo-products **11a**,**b** were not found in case of Diels–Alder reactions in the presence of stoichiometric amounts of $TiCl_4$ or reaction at room temperature (vide supra).

SCHEME 3



For the reaction of **11b** (exo/endo = 69:31) under the above-mentioned conditions, 13% *exo*-**13b**, 31% **14b** (major epimer), and 16% **14b** (minor epimer) were isolated (ratio in crude product as determined by GC: 31:43:26). With respect to the reaction of **11a** with $TiCl_4$,

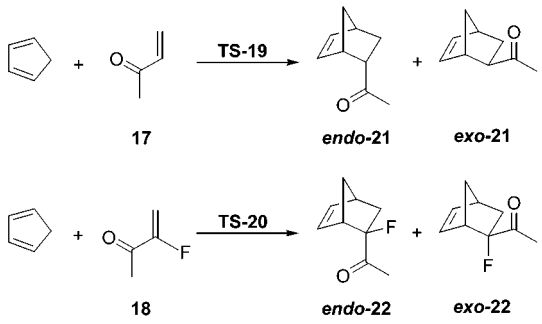
TABLE 4. Calculated Activation Barriers for Diels–Alder Reactions of Cyclopentadiene with the Vinyl Ketones[a]

		endo		exo	
dienophile	product	s-cis[b]	s-trans[b]	s-cis[b]	s-trans[b]
17	(**TS-19**) $\Delta H^{\ddagger}$ (0 K)	16.4	19.7	16.3	21.1
	→ **21** ΔH_R (0 K)	−14.6		−15.4	
18	(**TS-20**) $\Delta H^{\ddagger}$ (0 K)	17.5	21.9	16.4	22.9
	→ **22** ΔH_R (0 K)	−16.2		−16.7	

[a] Energies ((U)B3LYP/6-31G(d)//(U)B3LYP/6-31G(d)) are given in kcal mol^{-1}, include zero-point corrections, and are relative to the separated reactants (s-cis conformers). [b] Conformation of the vinyl ketone in the TS.

the crude product was analyzed by GC/MS coupling and the chlorinated products shown to be identical with *exo*-**13a** and **14a** (diastereomeric mixture) isolated from the corresponding Diels–Alder reactions.

Theoretical Calculations. To investigate the influence of a fluoro substituent on the barrier and reaction energy, density functional calculations (B3LYP/6-31G(d)) of the cycloaddition of cyclopentadiene with but-3-enone (**17**) and 3-fluorobut-3-enone (**18**) have been performed.[32] We have optimized the transition structures and the products of the two reactions. The calculated reaction enthalpies at 0 K (including zero point corrections) are given in Table 4. For both dienophiles, the s-cis conformer is calculated to be more stable than s-trans (0.3 kcal mol^{-1} for **17**, 2.6 kcal mol^{-1} for **18**).[33] Therefore, the relative energies are given with respect to the s-cis conformers.



In agreement with earlier findings by Jorgensen et al.,[34] the s-cis conformer of methyl vinyl ketone (**17**) is more reactive than the s-trans isomer. Our calculations predict faster formation of the exo Diels–Alder product for the s-cis conformer of both but-3-enone (**17**) and 3-fluorobut-3-enone (**18**). If the dienophiles react in the s-trans conformation, the opposite stereoselectivity (endo) is predicted.

For the cycloaddition of but-3-enone (**17**) and cyclopentadiene, experiments have given a barrier of $\Delta H^{\ddagger} =$ 12.8 kcal mol^{-1} in isooctane, a low selectivity (3.85:1 in favor of the endo product) was observed in excess of cyclopentadiene.[35] Without any inclusion of entropical and solvent effects, we predict a slightly higher barrier of 16.3 kcal mol^{-1} and a very low selectivity in favor of the exo product.

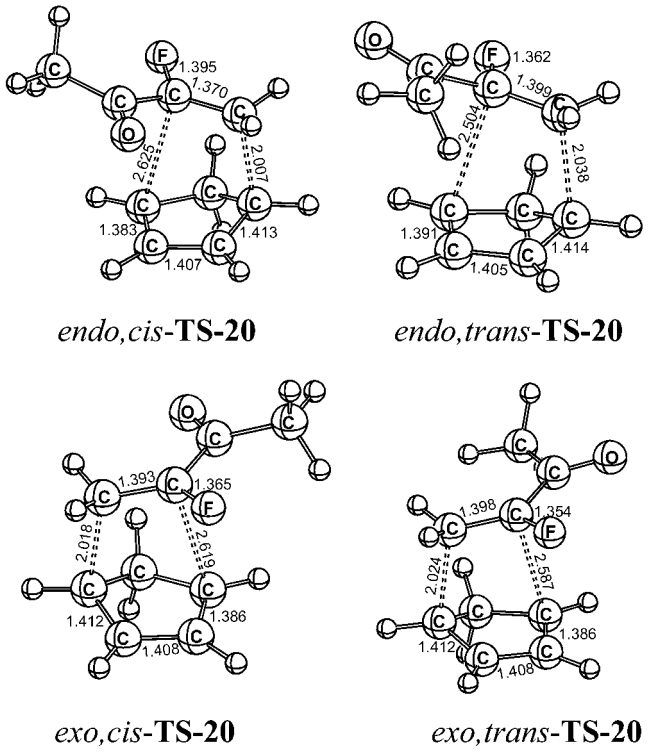


FIGURE 1. Geometries (B3LYP/6-31G(d)) of transition structure in the reaction of cyclopentadiene and 3-fluorobut-3-enone (**18**).

Figure 1 shows the geometries of the four optimized transition states in the reaction of the 3-fluorobut-3-enone (**18**). The two single bonds are formed very asynchronously, which is also a characteristic of the but-3-enone (**17**) transition structures (**TS-19**) depicted in the Supporting Information. However, we find no evidence for a charge separation between the two reaction partners at the saddle points.

(31) During the time of our investigations on Lewis acid-mediated Diels–Alder reactions of **3** and **4**, Taguchi et al. (ref 5d) published [4 + 2]-cycloadditions of optically active 2-fluoroacrylic amides, and recently these authors used Et_2AlCl as a mediator for the reaction of benzyl 2-fluoroacrylate (**3**) with cyclopentadiene (ref 5e).

(32) All minimum and transition structures were fully optimized without symmetry restrictions using the GAUSSIAN program. For the transition structures, unrestricted wave functions were used. No spin contamination was found, indicating the closed shell character of the saddle points. The nature of the stationary points was proven by calculation of the force constants, yielding one (TS) or no imaginary frequency. Gaussian 98 (Revision A.7): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

(33) At least for **17**, the preferred conformer in gas phase and solution is s-trans, although the two conformers differ by only 0.34–0.8 kcal mol^{-1}: Durig, J. R.; Little, T. S. *J. Chem. Phys.* **1981**, *75*, 3660–3668.

(34) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936–2942.

(35) (a) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901–1904. (b) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

Compared with but-3-enone (**17**), the fluorine substituent in **18** raises all activation barriers in the reaction with cyclopentadiene except for *exo,cis*-**TS-20**. The barriers for the s-trans conformers are increased by ca. 2 kcal mol^{-1}, for the *endo,cis*-**TS-20** by only 1 kcal mol^{-1}. From the four TS structures and the analysis of the molecular orbitals, the origin of the fluorine effect on the relative barriers is difficult to assess.

The relative thermodynamic stabilities of the reaction products reflect the tendency of both substituents, halogen and acetyl group, to be in the exo-position. The relative stability of *exo*-6-acetyl-norbornene **21** (−0.8 kcal mol^{-1} compared to the endo-isomer) is diminished by the presence of the fluorine atom (−0.5 kcal mol^{-1}) in *exo*-6-acetyl-6-fluoronorbornene **22**. Still, however, the carbonyl group preferably takes the exo-position. This implies that the reversal of stereoselectivity in the formation of the ester **11a** and the ketone **11b** is not due to the thermodynamic stability of the products but a kinetic effect of fluorine.

AM1 calculations[36] of the energy of formation of the cycloadducts **11a** and **11b** are consistent with the results of the DFT models, predicting the exo products to be over 1 kcal mol^{-1} more stable (cf. Supporting Information).

Conclusion

We presented a simple and flexible four-step synthesis for the α-fluorinated α,β-unsaturated ketone **4**. This compound as well as benzyl 2-fluoroacrylate (**3**) were shown to be moderate dienophiles in conventional thermal, microwave-assisted, and $TiCl_4$-mediated Diels−Alder reactions with cyclopentadiene having normal electron demand. Comparative experiments with the appropriate nonfluorinated parent compounds **9** and **10** showed the fluorine substituent to decrease the reactivity of the dienophile in these [4 + 2]-cycloadditions as the fluorine atom seems to increase the π-electron density of the carbon−carbon double bond, which is consistent with earlier results.[2b] While the expected endo-products were formed from cyclopentadiene and nonfluorinated α,β-unsaturated carbonyl compounds, reverse stereopreference was observed for the corresponding α-fluorinated analogues. In the case of $TiCl_4$-mediated reactions of fluorinated dienophiles, chlorinated byproducts *exo*-**13** and **14** were formed that arose from the primary cycloadducts. The formation of such products could be suppressed at low temperature and/or low concentrations of the Lewis acid. Theoretical calculations on but-3-enone (**17**) and 3-fluorobut-3-enone (**18**) as model compounds have shown that the fluorine substituent in the α-position of vinyl ketones leads to preferred formation of the exo-product in the cycloaddition with cyclopentadiene. Ab initio calculations suggest that kinetic effects of fluorine determine the stereoselectivity rather than higher thermodynatic stability of the exo-products.

Experimental Section

General Methods. NMR spectra were recorded at 300, 400, or 600 MHz (^{1}H), at 75, 100, or 150 MHz (^{13}C), and at 282 MHz (^{19}F) and are reported in ppm downfield from TMS (^{1}H), acetone-d_6 (^{13}C), $CDCl_3$ (^{13}C), 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). Thin-layer chromatography was done on coated plate 60 F_{254}; preparative TLC on coated plate 60 F_{254} (1 mm). Column chromatography was done with silica gel 60 (0.063−0.2 mm). HPLC was performed using a Nucleosil 50−7 column (250 × 10 mm). Elemental analyses: Mikroanalytisches Laboratorium, Organische Chemie, Universität Münster. 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; solvents for chromatography and cyclopentadiene were distilled prior to use. 2-Fluorooct-1-en-3-ol (**8**),[17] benzyl 2-fluoroacrylate (**3**),[18] and oct-1-en-3-one (**10**)[19] were prepared according to literature methods.

2-Fluorooct-1-en-3-one (4). Powdered molecular sieves 10 Å (6.80 g) and powdered pyridinium dichromate (PDC, 3.81 g, 10.1 mmol) were suspended in CH_2Cl_2 (20 mL), and under stirring 2-fluorooct-1-en-3-ol (**8**) (860 mg, 5.9 mmol) was added, resulting in a color change of the suspension from orange to brown. The reaction mixture was stirred for 18 h at room temperature, and then Et_2O (15 mL) was added. After filtration, the solvent was evaporated. The obtained crude product was subjected to a column filtration (silica gel, 2 × 4 cm, pentane/Et_2O 1:1) to give **4** containing a small amount of pyridine. For removal of the pyridine, the filtrate was evaporated under reduced pressure to approximately 20 mL and washed with 2 N HCl (3 × 20 mL), H_2O (20 mL), and 5% aqueous $NaHCO_3$ (20 mL). Drying over $MgSO_4$ was followed by removal of the solvent under reduced pressure. Compound **4** was obtained (690 mg, 81%) as a light yellow oil that can be stored at −20 °C but may polymerize occasionally. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81−0.98 (m, 3 H), 1.20−1.43 (m, 4 H), 1.64 (pseudo qui, J = 7.4 Hz, 2 H), 2.63 (dt, J = 7.3, 1.7 Hz, 2 H), 5.18 (dd, J = 3.3, 14.3 Hz, 1 H), 5.54 (dd, J = 3.3, 45.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 22.3, 23.0, 31.2, 37.9, 100.0 (dt, J = 17.8 Hz), 159.8 (d, J = 267.1 Hz), 194.4 (d, J = 30.5 Hz); GC-MS, ^{19}F NMR and part of the ^{1}H NMR data can be found in ref 37 and agree with those obtained in this study.

Benzyl Acrylate (9). Benzyl bromide (13.6 mL, 124.5 mmol) was added to a solution of 3-chloropropionic acid (12.0 g, 111 mmol) and triethylamine (33.3 g, 330 mmol) in 75 mL of DMSO at room temperature and stirred for 18 h. After addition of water (45 mL), the aqueous layer was extracted using Et_2O (3 × 45 mL). The combined organic layer was washed with H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was subjected to a column filtration (silica gel, 4 × 6 cm, pentane/Et_2O 9:1) to give benzyl acrylate (**9**) (7.2 g, 40%) as a light yellow oil. Spectroscopic data agree with published data.[38]

General Procedure for Thermal Diels−Alder Reactions with Cyclopentadiene (A). A solution of the α,β-unsaturated carbonyl compound (2.0 mmol) and cyclopentadiene (0.33 mL, 4.0 mmol) in toluene (3 mL) was stirred at 110 °C in a sealed glass tube with a Young-tap for the time indicated in Table 1. The degree of conversion was followed by gas chromatography. After the mixture was cooled to room temperature, toluene and excess cyclopentadiene were removed under reduced pressure and the crude product was purified by column chromatography as described below.

General Procedure for Microwave-Assisted Diels−Alder Reactions with Cyclopentadiene (B). A solution of the α,β-unsaturated carbonyl compound (2.0 mmol) and cyclopentadiene (0.33 mL, 4.0 mmol) in toluene (3 mL) or without solvent in a sealed glass tube with a Young-tap was placed into a microwave oven and irradiated for the time indicated

(36) Heats of formation (H_f) for the Diels−Alder adducts **11** and **12** calculated on AM1 level are given in the Supporting Information.

(37) Elkik, E.; Dahan, R.; Parlier, A. *Bull. Soc. Chim. Fr.* **1981**, *II*, 353−360.

(38) Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063−13078.

in Table 2 (after each irradiation intervall, which should not exceed 15 min to prevent overheating of the microwave oven, the reaction apparatus was allowed to cool to room temperature). The degree of conversion was followed by gas chromatography. After the mixture was cooled to room temperature, toluene and cyclopentadiene were removed under reduced pressure, and the crude product was purified by column chromatography as described below.

General Procedure for Lewis Acid-Mediated Diels−Alder Reactions with Cyclopentadiene (C). To a stirred solution of $TiCl_4$ (amount as indicated in Table 3, 0.30 M in CH_2Cl_2) at −55 °C (if not stated otherwise in Table 3) was added a solution of the α,β-unsaturated carbonyl compound (0.5−2.0 mmol, 0.30 M in CH_2Cl_2) dropwise via a syringe. After 10 min, 12 mol equiv of cyclopentadiene was added in the same manner. The degree of conversion was followed by gas chromatography. After the time indicated in Table 3, the reaction mixture was quenched by addition of 5% aqueous $NaHCO_3$ (15 mL), resulting in a white precipitate. After neutralization with 5% aqueous $NaHCO_3$, Et_2O (20 mL) was added and the mixture was stirred for 10 min. The precipitate was filtered off, the organic layer separated, and the aqueous layer extracted with Et_2O two times. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Crude products were purified by column chromatography as described below.

Benzyl 2-Fluorobicyclo[2.2.1]hept-5-ene-2-carboxylate (11a). Following the general procedure (A, B, or C), the crude products were subsequently purified (silica gel, cyclohexane/ethyl acetate 40:1).[39] Yields are given in Tables 1−3. *exo*-**11a** could not be separated from *endo*-**11a** by column chromatography (cyclohexane/ethyl acetate 40:1, 150:1 or HPLC (cyclohexane/$CHCl_3$ 10:1)). **11a** is a colorless oil. Anal. Calcd for $C_{15}H_{15}O_2F$: C, 73.15; H, 6.14. Found: C, 72.95; H, 6.43. *exo*-**11a**: GC-MS *m*/*z* 246 (6) [M^+], 226 (2), 181 (4), 135 (2), 91 (52), 66 (100). Other analytical data agree with those in ref.[5c,d] *endo*-**11a**: GC−MS *m*/*z* 246 (5) [M^+], 226 (0.5), 181 (3), 135 (2), 91 (85), 66 (100). Other analytical data agree with those in ref 5c.

In the Lewis acid-mediated Diels−Alder reactions of benzyl 2-fluoroacrylate (**3**) and cyclopentadiene, a repeated column chromatography may be necessary (just for reactions that were conducted at room temperature) to separate the cycloadducts from polymers. Furthermore, byproducts were formed (see Table 3) that were separated as a mixture with *exo*-**11a** (in the case of benzyl *exo*-6-chlorobicyclo[2.2.1]hept-2-ene-1-carboxylate (*exo*-**13a**)) or by further elution of the column (benzyl *rel*-(1*S*,2*S*,3*R*,4*R*,6*R*)- and benzyl *rel*-(1*S*,2*S*,3*S*,4*R*,6*R*)-3-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-1-carboxylate (**14a**)). Complete separation of *exo*-**11a** from the diastereomeric mixture of **14a** was achieved by HPLC (cyclohexane/ethyl acetate 80:1), although *exo*-**13a** could not be separated completely from *exo*-**11a** by this procedure (86% purity by GC). Final purification of *exo*-**13a** was achieved by preparative TLC (cyclohexane/ethyl acetate 20:1; 2 runs): ^{1}H NMR[40] (acetone-d_6, 300 MHz) δ 1.87−2.15 (m, 4 H), 2.92−2.98 (m, 1 H), 4.07 (ddd, *J* = 7.2, 3.1, 1.7 Hz, 1 H), 5.23 (d, *J* = 1.4 Hz, 2 H), 6.08 (d, *J* = 5.2, 1 H), 6.37 (dd, *J* = 5.2, 2.9 Hz, 1 H), 7.31−7.45 (m, 5 H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 39.2, 41.5, 46.6, 60.1, 66.4, 128.3, 128.3, 128.7, 133.4, 136.8, 141.7, 171.0;[41] GC−MS *m*/*z* 264/262 (0.5/2) [M^+], 200 (54), 155 (43), 108 (52), 93 (97), 91 (100), 65 (31); HRMS *m*/*z* calcd for $C_{15}H_{15}O_2ClNa^+$ [M + Na^+]: 285.0658, 287.0634, found 285.0673, 287.0654. ***rel*-(1*S*,2*S*,3*R*,4*R*,6*R*)-14a** could not be separated from ***rel*-(1*S*,2*S*,3*S*,4*R*,6*R*)-14a.** The mixture is a colorless oil. Both compounds have identical retention times in GC: GC−MS *m*/*z* 264/262 (3/8) [M^+], 227 (1), 157/155 (25/83), 107 (7), 91 (100), 65 (22). Anal. Calcd for $C_{15}H_{15}ClO_2$: C, 68.57; H, 5.75. Found: C, 68.30; H, 5.87. **14a**, major epimer: ^{1}H NMR (acetone-d_6, 600 MHz) δ 1.59 (pseudo dt, *J* = 11.0, *J* = 1.6 Hz, 1 H), 1.62 (pseudo dq, *J* = 11.0, 1.3 Hz, 1 H), 1.67 (dd, *J* = 11.1, 1.3 Hz, 1 H), 2.04 (pseudo dq, *J* = 5.7, 1.4 Hz, 1 H), 2.12 (dt, *J* = 5.7, *J* = 1.1 Hz, 1 H), 2.16−2.22 (m, 2 H), 4.11 (pseudo t, *J* = 1.4 Hz, 1 H), 5.14 (s, 2 H), 7.28−7.40 (m, 5 H); ^{13}C NMR (acetone-d_6, 150 MHz):δ 25.9, 27.9, 30.0, 31.0, 32.4, 39.3, 64.6, 66.4, 128.7, 128.8, 129.3, 137.5, 172.5. **14a**, minor epimer: ^{1}H NMR (acetone-d_6, 600 MHz) δ 1.58 (pseudo dt, *J* = 10.9, 1.3 Hz, 1 H), 1.67 (dd, *J* = 10.9, 1.8 Hz, 1 H), 1.72 (pseudo dt, *J* = 10.9, 1.6 Hz, 1 H), 2.01 (pseudo dq, *J* = 10.9, 1.6 Hz, 1 H), 2.03−2.06 (m, 1 H), 2.14 (dt, *J* = 5.1, 1.3 Hz, 1 H), 2.16−2.21 (m, 1 H), 4.12 (pseudo t, *J* = 1.7 Hz, 1 H), 5.12 (s, 2 H), 7.28−7.40 (m, 5 H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 23.4, 29.0, 31.1, 32.2, 39.5, 63.8, 66.4, 128.7, 128.8, 129.3, 137.5, 172.0.[42]

Benzyl Bicyclo[2.2.1]hept-5-ene-2-carboxylate (12a). Following the general procedure (A, B, or C), the crude products were subsequently purified (silica gel, cyclohexane/ethyl acetate 40:1). Yields are given in Tables 1−3. *endo*-**12a** could not be separated from *exo*-**12a** by column chromatography using different mixtures of cyclohexane and ethyl acetate. The mixture of diastereomers is a colorless oil. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.87; H, 7.04. *endo*-**12a**: GC−MS *m*/*z* 228 (4) [M^+], 163 (6), 156 (8), 137 (8), 91 (100), 66 (86). Other analytical data agree with those given in ref 38. *exo*-**12a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25−1.42 (m, 2 H), 1.47 (dm, *J* = 8.4 Hz, 1 H), 1.78−1.92 (m, 1 H), 2.17−2.24 (m, 1 H), 2.80−2.86 (m, 1 H), 2.97−3.01 (m, 1 H), 5.06 (s, 2 H), 6.01 (dd, *J* = 5.5, 2.9 Hz, 1H), 6.05 (dd, *J* = 5.5, 2.9 Hz, 1H), 7.18−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.3, 41.6, 43.1, 46.3, 46.6, 66.1, 128.0, 128.0, 128.5, 135.7, 136.3, 138.0, 175.9; *m*/*z* 228 (3) [M^+], 163 (7), 156 (12), 137 (14), 91 (75), 66 (100).

***exo*-1-(6-Chlorobicyclo[2.2.1]hept-2-en-1-yl)hexan-1-one (*exo*-13b) and *rel*-(1*S*,2*S*,3*R*,4*R*,6*R*)- and *rel*-(1*S*,2*S*,3*S*,4*R*,6*R*)-1-(3-Chlorotricyclo[2.2.1.$0^{2,6}$]hept-1-yl)hexan-1-one (14b)**. Following general procedure C, **11b** (exo/endo = 69:31; 17 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) instead of the α,β-unsaturated carbonyl compound and cyclopentadiene were added to the $TiCl_4$ solution (0.30 M in CH_2Cl_2, 0.27 mL, 0.08 mmol) at 0 °C. After being warmed to room temperature, the reaction mixture was stirred for 45 min. The crude product contained 31% *exo*-**13b**, 43% **14b (**major epimer**)**, and 26% **14b (**minor epimer**)** as determined by GC and was separated by HPLC (cyclohexane/ethyl acetate 99:1). Yields: *exo*-**13b:** 2.4 mg (13%); **14b**, major epimer: 5.7 mg (31%); **14b**, minor epimer: 2.9 mg (16%). Spectroscopic data for these compounds agree with those given above.

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Supporting Information Available: B3LYP/6-31G(d) energies of compounds **17** and **18**, HOMO/LUMO energies (AM1) of cyclopentadiene and the applied dienophiles, heats of formation (AM1) for **11a**,**b** and **12a**,**b** together with the corresponding Cartesian coordinates for all calculations, experimental details and spectroscopic data of **11b**, **12b**, *exo*-**13b** and **14b**, as well as copies of ^{1}H and ^{13}C NMR spectra for compounds *exo*-**13a**,**b** and **14b** (major epimer). This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) In the case of incomplete conversion of the reactants, separation of 2-fluorobenzyl acrylate (**3**) by column chromatography is incomplete, but small amounts of **3** can be evaporated in oil pump vacuum at room temperature or by repeated HPLC (cyclohexane/ethyl acetate 80:1).

(40) All NMR data for this compound were obtained from a 12:88 mixture with *exo*-**11a**.

(41) The signal of the quarternary bridghead-carbon could not be assigned from the available spectrum.

(42) The signal of the quarternary α-carbonyl carbon could not be assigned from the available spectrum.