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Asymmetric Diels–Alder reactions of 2-fluoroacrylic acid derivatives. Part 2: A remarkable effect of fluorine substituent on the diastereoselectivity

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Abstract

An efficient construction of a chiral monofluorinated tertiary carbon was achieved by a highly *exo*- and diastereofacial selective Diels–Alder reaction of a 2-fluoroacrylic acid derivative derived from 8-phenylmenthol, and cyclopentadiene. The substituent effect of the fluorine on the selectivities is remarkable as compared with the other substituents at the α-position of the acrylate.

1. Introduction

The importance of organofluorine compounds, in particular in the field of medicinal chemistry, requires the development of an efficient method for the construction of chiral molecules in enantiomerically pure form.[1] In the preceding paper, for the construction of chiral monofluorinated tertiary carbon, we described the Lewis acid mediated asymmetric Diels–Alder reaction of 2-fluoroacrylic acid derivatives bearing a chiral oxazolidinone moiety.[2] Although high diastereoselectivities could be achieved in the reactions with isoprene and cyclopentadiene, the *exo*/*endo*-selectivity was not satisfactory and the requirement of an extremely low temperature to obtain a high diastereoselectivity was also problematic. Therefore, it was necessary to find a more effective chiral auxiliary. The efficiency of the 8-phenylmenthyl group in asymmetric reactions has been well documented for the asymmetric Diels–Alder reaction.[3] We report herein the Diels–Alder reaction of chiral 2-fluoroacrylic acid derivatives **1a** under Lewis acid catalyzed conditions (Scheme 1). We also examined the Diels–Alder reaction of the α-substituted acrylic acid derivatives **1b** and **1c** to reveal the effect of the fluorine-substituent on the reactivity and selectivity.

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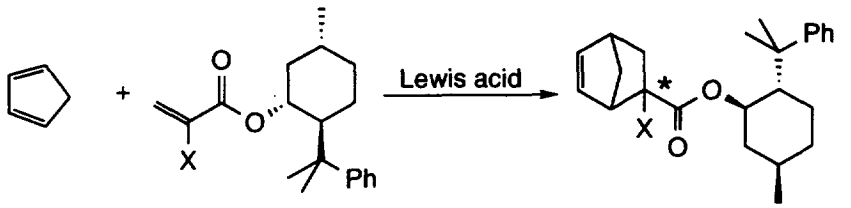


1a; X = F
1b; X = Cl
1c; X = Me

2a; X = F
2b; X = Cl
2c; X = Me

Scheme 1.

2. Results and discussion

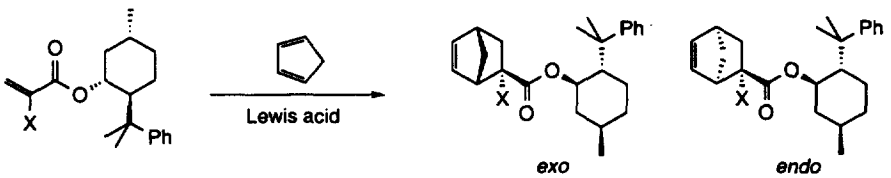
The Lewis acid promoted Diels–Alder reactions of **1a**[4] with cyclopentadiene are summarized in Table 1 (entries 1–3). In the presence of 1.5 equivalents of diethylaluminum chloride, the Diels–Alder reaction of **1a** proceeded at between 0°C and ambient temperature to give the cycloadduct **2a** in 79% yield with high diastereoselectivity (95% de, entry 1). The exclusive formation of the *exo*-adduct observed in this system should also be noted, while no appreciable *endo*/*exo*-selectivity was realized in the case of the oxazolidinone derivative.[2] The absolute stereochemistry of the newly formed stereogenic center of **2a** was determined, after conversion to its benzyl ester, by comparing the specific rotation with that of the authentic sample.[2] We also examined the effect of the Lewis acid. In the case of titanium tetrachloride, the reaction proceeded in a highly diastereo- and *exo*-selective manner as in the case of diethylaluminum chloride (entry 2). On the other hand, in the case of trimethylaluminum, which has one coordination site, the diastereoselectivity decreased (entry 3). In all cases examined here, the direction of chiral induction was not affected by the Lewis acid employed.

To examine the influence of the fluorine substituent on the diastereo- and *exo*/*endo*-selectivity, the Diels–Alder reactions of **1b**[5] and **1c** with cyclopentadiene were conducted and the results are summarized in Table 1 (entries 4–9), also the results of the hydrogen-substituted substrate **1d** reported by Oppolzer et al.[3b] also shown (entries 10 and 11). Regarding the *exo*/*endo*-selectivity, introduction of a substituent at the α-position (**1b**, **1c**) resulted in an *exo*-predominant reaction as commonly observed in the Diels–Alder reaction of acrylate derivatives with cyclopentadiene. With the chlorinated compound **1b** (entries 4–6), the best selectivity was obtained with the use of titanium tetrachloride, but both the diastereo- and *exo*/*endo*-selectivities were lower than those of the fluorinated compound **1a**. The Diels–Alder reaction of the methyl substituted compound **1c** also showed an *exo*-selectivity similar to that of **1b** but the diastereoselectivity was moderate (entries 7–9).

Determination of the absolute stereochemistry of compound **2b**-*exo* (X=8-phenylmenthyloxy, 93% de) and **2c**-*exo* (X=8-phenylmenthyloxy, 74% de) was easily accomplished as shown in Scheme 2. Reduction of compound **2b**-*exo* was achieved in a two step procedure to afford the alcohol **3** (*exo*/*endo*, 1/3.2). This isomeric mixture could be separated after conversion to the benzoyl derivatives. By comparing the specific rotation of **3**-*endo* with the reported value (lit.[3b] $[\alpha]_D^{25}$ 67.7 for ent-**3**-*endo*, 70% ee), the absolute chemistry of compound **2b**-*exo* was unambiguously established. To determine the stereochemistry of compound **2c**-*exo*, this was converted to the known compound **5** (lit.[6] $[\alpha]_D^{25}$ 16.8 for ent-**5**, 72% ee).

The mechanism of the diastereoselectivity could be considered as shown in Fig. 1. The α-fluoroacrylate **1a** showed higher diastereoselectivity than the acrylate **1d**. The *ab initio*-based force field modelling study of the transition state by Houk et al. indicates the preference of the s-*trans* conformer in the case of the Lewis acid mediated Diels–Alder reaction of acrylic acid 8-phenylmenthyl ester,[7] due to the steric repulsion between the Lewis acid and the β-proton on the acrylic ester moiety in the s-*cis*

Table 1
The Diels–Alder reaction of **1a**, **1b**, **1c**, and **1d** with cyclopentadiene



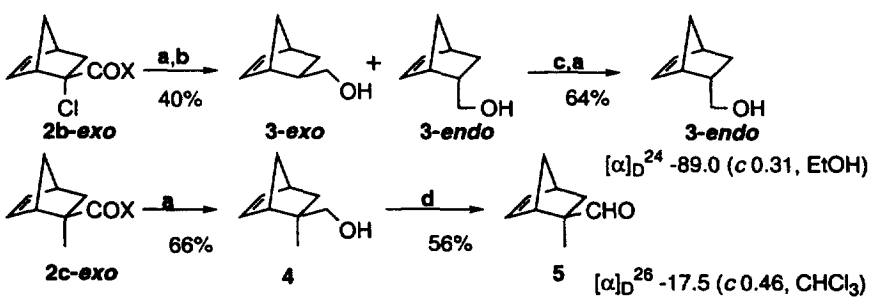
1a; X = F
1b; X = Cl
1c; X = Me
1d; X = H

2a; X = F
2b; X = Cl
2c; X = Me

2d; X = H

Entry	Substrate	Lewis acid	Equivalent	Temp. (°C)	Time (h)	Yield (%)[a,b]	de (%)[c,d]	*exo* : *endo*[c]
1	**1a**	Et_2AlCl	1.5	0 - r.t.	8	79	95	*exo* only[g]
2	**1a**	$TiCl_4$	1.2	-20	10	77	95	*exo* only[g]
3	**1a**	Me_3Al	1.1	0 - r.t.	10	77	84	*exo* only[g]
4	**1b**	Et_2AlCl	1.5	0	7	86	73	3.1 : 1
5	**1b**	$TiCl_4$	1.2	- 20	7	72	93	10 : 1
6	**1b**	Me_3Al	1.1	0 - r.t.	10	91	78	6.4 : 1
7	**1c**	Et_2AlCl	1.5	0	5	68	54	6.1 : 1
8	**1c**	$TiCl_4$	1.2	- 20	5	34	74	6.9 : 1
9	**1c**	Me_3Al	1.1	0 - r.t.	5	75	54	5.2 : 1
10[e]	**1d**	Me_2AlCl	1.5	0	3.5	95	64[f]	1 : 8.1
11[e]	**1d**	$TiCl_4$	1.5	- 20	3.5	83	90[f]	1 : 8.1

a) All reactions were carried out in dichloromethane. b) Isolated yield. c) The ratio was determined by 400 MHz ^{1}H NMR. d) The diastereomer ratio was determined for the *exo* product. e) See ref. 3c. f) The diastereomeric ratio was determined for the *endo* product. g) The *endo* isomer could not be detected by 400 MHz ^{1}H NMR.



Reagent and conditions: **a** $LiAlH_4$, ether, 0 °C; **b** $ZnCl_2$, $NaBH_3CN$, ether, reflux; **c** BzCl, Et_3N, CH_2Cl_2, r.t., separation of isomer; **d** $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, then Et_3N;

Scheme 2.

conformer (**C**, X=H). In the case of the α-fluoroacrylate **1a**, the facial selectivity of the double bond in the Diels–Alder reaction was similar to that with the acrylate **1d**. This suggests that the α-fluoroacryloyl moiety would have s-*trans* conformation because of the small steric difference of the fluorine and

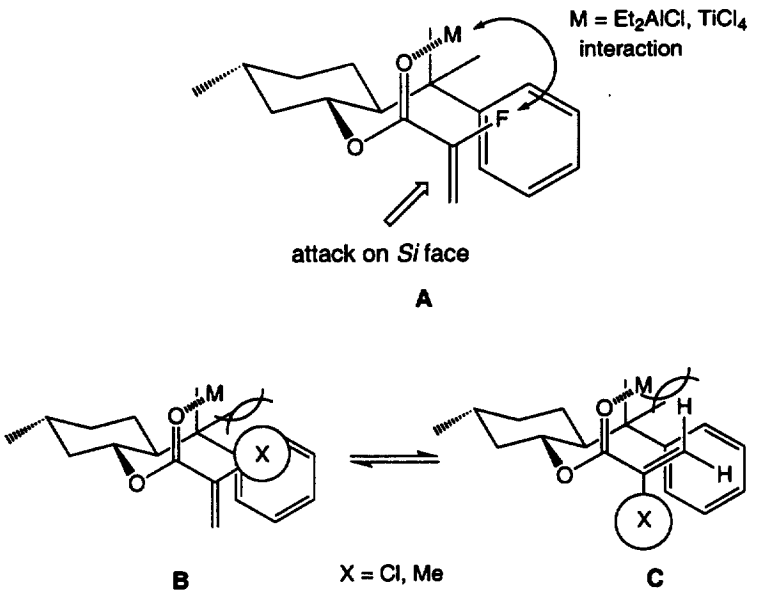


Fig. 1.

hydrogen atoms. Recently, Maruoka et al. reported a significant interaction between a fluorine atom and aluminum metal.[8] One of the speculative mechanisms for the observed high diastereoselectivity, formation of the five-membered intermediate (**A**) based on the interaction of the fluorine atom with aluminum metal possibly plays an important role. On the other hand, the steric bulkiness of α-chloro or α-methyl substituents should result in the s-*trans* conformer being more unfavourable than in the case of the α-fluoro or α-hydrogen substituent thus resulting in the decrease in diastereoselectivity as shown in Fig. 1.

In summary, we have demonstrated that the Diels–Alder reaction of 2-fluoroacrylic acid bearing the 8-phenylmenthyl group provides an efficient constructive method of chiral fluorine-substituted tertiary carbons.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared absorption spectra were recorded using Perkin–Elmer FTIR-1710. ^{1}H and ^{13}C NMR spectra were obtained using Varian Gemini 300 (300 MHz), Brucker dpx 400 (400 MHz), and Bruker drx 500 (500 MHz). ^{19}F NMR spectra were obtained using a Bruker dpx 400. In the ^{1}H, ^{13}C, and ^{19}F NMR spectra, chemical shifts are expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm), $CDCl_3$ (77.01 ppm), and benzotrifluoride (0 ppm), respectively. Mass spectra were recorded using HITACHI M-80, Finnigan MAT TSQ700, and VG Auto Spec. Column chromatography was performed on silica gel, Fuji silysia silica gel BW80S. All nonaqueous reactions were carried out under an argon atmosphere with freshly distilled solvents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride.

3.2. (1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl 2-fluoropropenoate **1a**

Under an argon atmosphere, to a solution of (−)-8-phenylmenthol (633 mg, 2.7 mmol) and triethylamine (0.58 ml, 4.2 mmol) in CH_2Cl_2 (2 ml) was added a solution of 2-fluoroacryloyl chloride (426 mg, 3.8 mmol) in CH_2Cl_2 (2 ml) at 0°C. After being stirred for 3 h at 0°C, 4-dimethylaminopyridine (158 mg, 1.1 mmol) was added to the reaction mixture and then stirred for 8 h at ambient temperature. After addition of water, the mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 7/2), the compound **1a** (2.29 g, 9.13 mmol) was obtained in 64% yield (based on 8-phenylmenthol).

1a: $[\alpha]_D^{25}$ −43.7 (*c* 1.43, $CHCl_3$); IR (neat) 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.00 (5H, m), 5.00 (1H, dd, *J*=12.8, 3.2 Hz), 4.98 (1H, dd, *J*=44.3, 3.2 Hz), 4.94 (1H, ddd, *J*=10.8, 10.8, 4.4 Hz), 2.20–0.78 (8H, m), 1.32 (3H, s), 1.22 (3H, s), 0.88 (3H, d, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 22.0, 25.4, 26.8, 28.2, 31.5, 34.7, 39.8, 41.6, 50.5, 76.3, 102.3 (d, *J*=15.0 Hz), 125.4, 125.5, 128.3, 151.3, 153.3 (d, *J*=258.2 Hz), 159.6 (d, *J*=36.8 Hz); ^{19}F NMR ($CDCl_3$) δ −54.6 (dd, *J*=44.3, 12.8 Hz). HRMS calcd for $C_{19}H_{25}FO_2$ 304.1839, found 304.1822.

3.3. Typical procedure for the Lewis acid mediated Diels–Alder reaction of **1a** with cyclopentadiene

Under an argon atmosphere, to a solution of **1a** (102.6 mg, 0.335 mmol) in CH_2Cl_2 (4 ml) was added a solution of diethylaluminum chloride (0.95 M in hexane, 0.53 ml, 0.504 mmol) at 0°C. After being stirred for 30 min, cyclopentadiene (1.0 ml, 10.3 mmol) was added to the reaction mixture at 0°C and the mixture was stirred at ambient temperature for 8 h. After addition of saturated aqueous ammonium chloride, the mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. After purification by silica gel column chromatography (hexane/chloroform, 7/2), **2a**-*exo* (98.3 mg, 0.264 mmol) was obtained in 79% yield.

3.4. 4-(1R,2S,5R,3′S,4′S,6′S)-[5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyloxycarbonyl]-4-fluoro-bicyclo[2.2.1]heptene **2a**-exo

$[\alpha]_D^{25}$ −57.7 (*c* 3.46, $CHCl_3$); IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (4H, m), 7.20–7.10 (1H, m), 6.43 (1H, dd, *J*=5.6, 3.0 Hz), 6.06 (1H, dd, *J*=5.6, 3.0 Hz), 4.98 (1H, dd, *J*=10.6, 10.6, 4.3 Hz), 3.08 (1H, bs), 2.87 (1H, bs), 2.20–0.7 (12H, m), 1.39 (3H, s), 1.27 (3H, s), 0.88 (3H, d, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 26.2, 27.0, 27.6, 31.3, 34.4, 39.3 (d, *J*=20.1 Hz), 40.0, 41.5, 42.0, 48.8, 50.0, 51.2 (d, *J*=21.2 Hz), 76.3, 100.6 (d, *J*=195.8 Hz), 125.3, 125.5, 128.0, 132.4 (d, *J*=5.7 Hz), 140.0, 150.7, 171.8 (d, *J*=29.0 Hz); ^{19}F NMR ($CDCl_3$) δ −94.2 (dd, *J*=24.0, 13.0 Hz). HRMS calcd for $C_{24}H_{31}FO_2$ 370.2308, found 370.2290.

3.5. 4-(1R,2S,5R,3′S,4′S,6′S)-[5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyloxycarbonyl]-4-chloro-bicyclo[2.2.1]heptene **2b**-exo

$[\alpha]_D^{26}$ −34.9 (*c* 3.46, $CHCl_3$); IR (neat) 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.26 (4H, m), 7.20–7.10 (1H, m), 6.38 (1H, dd, *J*=5.5, 3.0 Hz), 6.15 (1H, dd, *J*=5.5, 3.0 Hz), 4.90 (1H, dd, *J*=10.7, 10.7, 4.3 Hz), 3.22 (1H, bs), 2.89 (1H, bs), 2.10–1.90 (2H, m), 1.70–0.70 (10H, m), 1.37 (3H, s), 1.26 (3H, s), 0.87 (3H, d, *J*=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 25.3, 27.2, 28.7, 31.3, 34.5, 40.1, 41.0, 41.1,

42.5, 48.2, 48.8, 50.1, 51.9, 71.9, 77.3, 125.3, 125.6, 128.1, 133.6, 139.4, 150.7, 170.6. HRMS calcd for $C_{24}H_{31}ClO_2$ 386.2013, found 386.2008.

3.6. 4-(1R,2S,5R,3′S,4′R,6′S)-[5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyloxycarbonyl]-4-methyl-bicyclo[2.2.1]heptene **2a**-exo

$[\alpha]_D^{25}$ −26.3 (*c* 1.34, $CHCl_3$); IR (neat) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.26 (4H, m), 7.18–7.10 (1H, m), 6.20 (1H, dd, *J*=5.6, 3.0 Hz), 6.04 (1H, dd, *J*=5.6, 3.0 Hz), 4.88 (1H, dd, *J*=10.6, 10.6, 4.3 Hz), 2.88 (1H, bs), 2.78 (1H, bs), 2.29 (1H, dd, *J*=12.1, 4.0 Hz), 2.20–1.80 (2H, m), 1.60–0.70 (8H, m), 1.35 (3H, s), 1.25 (3H, s), 1.00 (3H, s), 0.85 (3H, d, *J*=6.4 Hz), 0.66 (1H, dd, *J*=12.1, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.1, 25.2, 27.2, 28.8, 31.3, 34.5, 36.8, 40.1, 41.6, 42.8, 48.8, 49.6, 50.0, 50.4, 75.2, 125.2, 125.5, 128.0, 133.6, 138.7, 151.0, 177.9. HRMS calcd for $C_{25}H_{34}O_2$ 366.2559, found 366.2537.

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