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COMMUNICATION

A Diels–Alder approach to the enantioselective construction of fluoromethylated stereogenic carbon centers†

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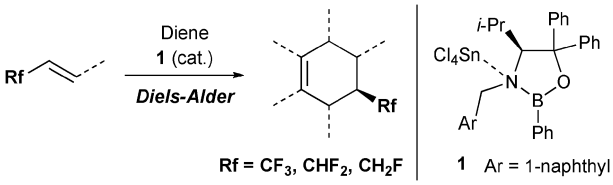
Highly enantioselective Diels–Alder reactions of β-fluoromethylacrylates were carried out in the presence of a Lewis acid activated chiral oxazaborolidine catalyst. These reactions yielded fluoromethylated cyclohexenes, including trifluoromethyl-, difluoromethyl-, and monofluoromethyl cyclohexenes, as nearly pure enantiomers. The resulting fluoromethyl cyclohexenes were converted into potential synthetic intermediates for bioactive compounds.

Selective incorporation of fluorine-containing substituents into organic molecules is a highly valuable process in drug discovery.[1] Fluoromethyl groups (tri-, di-, and monofluoromethyl groups) have been widely used for modifying the biological properties of drug candidates because the corresponding fluoromethylated molecules often have higher lipophilicity, metabolic stability, and bioavailability than do their parent compounds. However, developing methods for the highly enantioselective construction of fluoromethylated stereogenic centers remains a challenging task;[2–5] in particular, there are only few known catalytic methods for introducing di- and monofluoromethyl groups in an enantioselective manner.[4,5]

Diels–Alder reaction using fluoromethylolefins as the dienophile is an attractive approach for the formation of fluoromethylated stereogenic carbon centers. The resulting fluoromethylcyclohexenes are pharmaceutically attractive building blocks since the cyclohexene backbone is an important framework in drug design. Thus, significant efforts for this reaction have been made over the past six decades.[6–8] However, there is no published report on the enantioselective version of the Diels–Alder reaction with fluoromethylolefins.[9] In this communication, we describe a new catalytic route to enantioenriched fluoromethyl cyclohexenes, including tri-, di-, and monofluoromethylated cyclohexenes, *via* the asymmetric Diels–Alder reaction of β-fluoromethylacrylates (Scheme 1).

Initially, we focused on the Diels–Alder reaction of ethyl (*E*)-β-trifluoromethylacrylate [(*E*)-**2**] with cyclopentadiene in the presence of 10 mol% of Lewis acid activated chiral



Scheme 1 Synthetic strategy for chiral fluoromethyl cyclohexenes.

oxazaborolidine **1**, which was developed by Yamamoto *et al.*[10,11] The reaction proceeded smoothly at −78 °C to yield the desired product **4a** with good *exo* selectivity[12] (Table 1, entry 1). To our delight, both diastereomers were obtained as a nearly single enantiomer (99% ee).[13] It is noteworthy that the non-fluorinated dienophile (ethyl crotonate) did not react at all under the same reaction conditions (entry 3). This indicates that the strong electron withdrawing effect of a trifluoromethyl group accelerates the reaction. We then used furans as dienes. As shown in entry 4, the reactions in the presence of 30 mol% of **1** yielded the corresponding adducts with excellent enantioselectivity. The diastereoselectivity in this reaction was virtually the same as that in the reaction with cyclopentadiene (*exo* selective, entry 1 *vs.* 4). In contrast, the reactions of ethyl (*Z*)-β-trifluoromethylacrylate [(*Z*)-**2**] yielded the desired adducts **4c** and **5b** with high *endo* selectivity (entries 5 and 6). Subsequently, substituted furans were used as dienes. Interestingly, when 3-substituted furans were used, *endo* adducts were preferentially formed with high diastereoselectivity (**5c** and **5d** in entries 7 and 8, respectively).[14] On the other hand, the *exo* adduct was formed exclusively when using a 2-substituted furan (**5e** in entry 9). Nearly optically pure products were obtained in all cases.

Next, we shifted our focus to the synthesis of difluoromethylcyclohexenes from the dienophile ethyl (*E*)-β-difluoromethylacrylate (**6**), which was synthesized according to a reported procedure.[15] The results are summarized in Table 2. The reaction of **6** with unsubstituted cyclopentadiene or furan proceeded smoothly to yield the corresponding product (**7** or **8a**, respectively) as a nearly 1 : 1 diastereomixture with excellent enantioselectivity (entries 1 and 2). On the other hand, high diastereoselectivity was achieved when using substituted furans (entries 3–5), as in the case of the reaction with (*E*)-**2** (see Table 1, entries 7–9).

The Diels–Alder reaction of monofluoromethylacrylates was also examined. (*E*)-β-Monofluoromethylacrylate (**9**) was synthesized in good yield by using a modified literature procedure[15] (see ESI† for details). The Diels–Alder reaction

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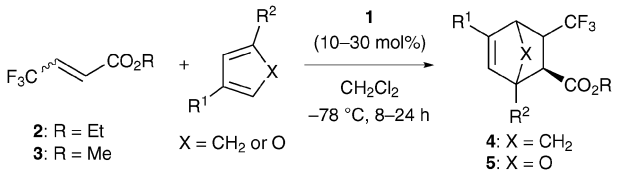
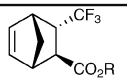
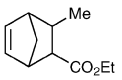
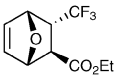
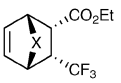
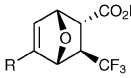
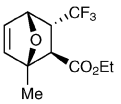
† Electronic supplementary information (ESI) available: Experimental procedures, characterization of all new compounds. CCDC 822839. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15889a

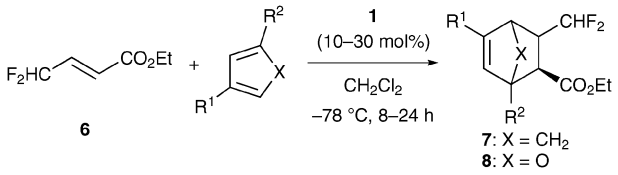
Table 1 Asymmetric Diels–Alder reaction of β-CF_3-acrylates[a]

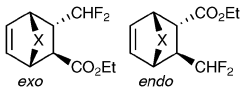
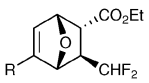
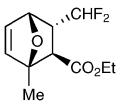


Entry	Dienophile	Major product		Yield[b] (%) (*exo*/*endo*)	ee[c] (%) (*exo*, *endo*)
1	(*E*)-**2**		**4a**: R = Et	81 (78/22)	99, 99
2	(*E*)-**3**		**4b**: R = Me	78 (76/24)	99, 99
3	Ethyl crotonate			0	—, —
4[d]	(*E*)-**2**		**5a**	94 (76/24)	99, 99
5	(*Z*)-**2**		**4c**: X = CH_2	75 (1/99)	nd, 99
6[d]	(*Z*)-**2**		**5b**: X = O	67 (1/99)	nd, 99
7[d,e]	(*E*)-**2**		**5c**: R = Br	89 (1/99)	nd, 99
8[d,f]	(*E*)-**2**		**5d**: R = Me	88 (9/91)	nd, 99
9[d,g]	(*E*)-**2**		**5e**	99 (99/1)	99, nd

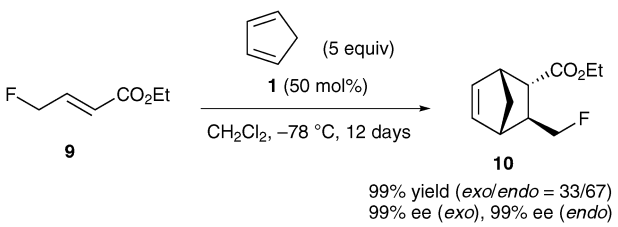
[a] All reactions were carried out for 8 h with 10 mol% of **1**, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral GC analysis. [d] Reactions were carried out for 24 h with 30 mol% of **1**. [e] 3-Bromofuran was used. The absolute configuration of **5c** was determined by X-ray crystallographic analysis (see Scheme 5). [f] 3-Methylfuran was used. [g] 2-Methylfuran was used.

Table 2 Asymmetric Diels–Alder reaction of β-CHF_2-acrylates[a]



Entry	Major product		Yield[b] (%) (*exo*/*endo*)	ee[c] (%) (*exo*, *endo*)
1[d]		**7**: X = CH_2	90 (57/43)	99, 99
2	*exo* *endo*	**8a**: X = O	99 (53/47)	99, 99
3[e]		**8b**: R = Br	68 (1/99)	nd, 99
4[f]		**8c**: R = Me	87 (1/99)	nd, 99
5[g,h]		**8d**	74 (99/1)	99, nd

[a] All reactions were carried out for 24 h with 30 mol% of **1**, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. [d] Reactions were carried out for 8 h with 10 mol% of **1**. [e] 3-Bromofuran was used. [f] 3-Methylfuran was used. [g] 2-Methylfuran was used. [h] Reaction was carried out for 48 h.

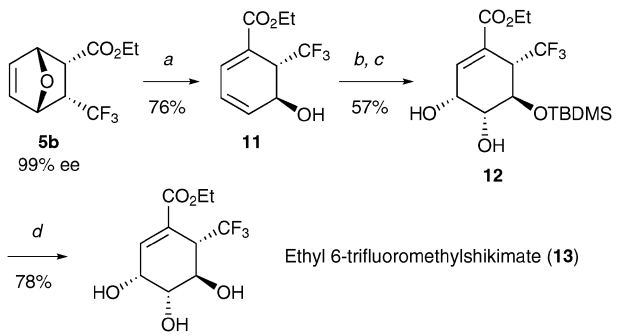


Scheme 2 Asymmetric Diels–Alder reaction of β-CH_2F-acrylates.

of **9** with cyclopentadiene in the presence of 50 mol% of **1** afforded the desired adduct **10** in high yield, with good *endo* selectivity and excellent enantioselectivity, although the reaction was sluggish (Scheme 2).

We then attempt to convert the fluoromethylated cycloadducts into potential synthetic intermediates for bioactive compounds. First, the optically pure trifluoromethyl cycloadduct **5b** was converted into 6-trifluoromethyl-shikimate **13** *via* the reported procedure (Scheme 3).[16] Treatment of **5b** with lithium hexamethyldisilazide (LiHMDS) resulted in β-elimination of the bridgehead oxygen to yield cyclohexadienol **11**. After the protection of the hydroxy group of **11** with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), the resulting silyl ether was osmylated with osmium tetroxide and subsequently reduced with sodium bisulfate to afford the diol **12**. Deprotection with tetrabutylammonium fluoride (TBAF) yielded **13**, and thus, the first asymmetric synthesis of 6-CF_3-shikimate was accomplished.

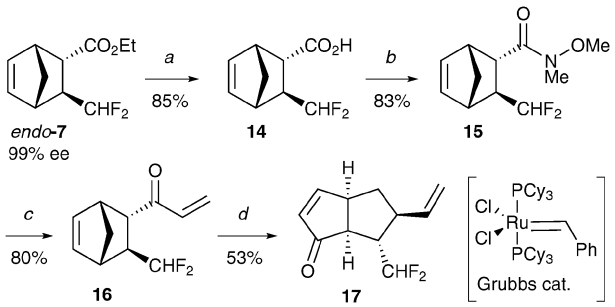
Next, the difluoromethylated cycloadduct *endo*-**7** was converted to a bicyclic enone **17** *via* the procedure developed by Aubé.[17] He reported the synthesis of a similar non-fluorinated enone and its conversion to dendrobatid alkaloid 251F.[18] Weinreb amide **15** was synthesized in good yield by the hydrolysis of *endo*-**7** and subsequent condensation with *N*,*O*-dimethylhydroxylamine. Treatment of **15** with a vinyl Grignard reagent and subsequent olefin metathesis with the first-generation



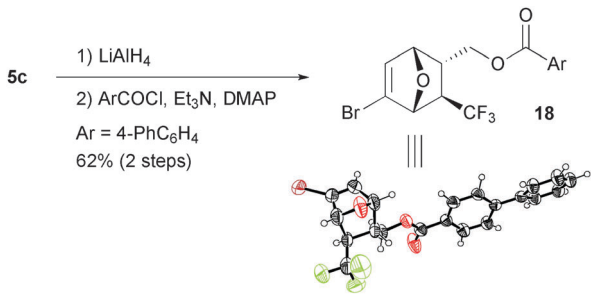
Scheme 3 Synthesis of 6-trifluoromethylshikimate **13**. *Reaction conditions*: (a) LiHMDS, THF, −78 °C to rt, 2 h; (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h; (c) OsO_4, pyridine, rt, 8 h, then $Na_2S_2O_5$, pyridine, rt, 20 min; (d) TBAF, THF, rt, 6 h.

Grubbs catalyst yielded the desired bicyclic diene **17** with a difluoromethyl function (Scheme 4).

Finally, to establish the stereochemistry of these Diels–Alder adducts, we synthesized 4-phenylbenzoate **18** from **5c** by a simple two-step transformation (Scheme 5). Single-crystal X-ray crystallographic analysis of **18** revealed the absolute and relative stereochemistry and regiochemistry, as shown in the ORTEP drawing.[19]



Scheme 4 Derivatization of *endo*-**7** to bicyclic enone **17**. *Reaction conditions*: (a) 10% aq. NaOH, reflux, 2 h; (b) BOP, Et_3N, HNMe(OMe)·HCl, CH_2Cl_2, rt, 24 h; (c) CH_2=CHMgBr, Et_2O, rt, 1.5 h; (d) Grubbs cat. (5 mol%), ethylene, CH_2Cl_2, rt, 20 h.



Scheme 5 X-Ray crystallographic analysis.

In conclusion, we have accomplished the highly enantioselective Diels–Alder reaction of β-fluoromethylacrylates with cyclic dienes in the presence of a Lewis acid activated chiral oxazaborolidine catalyst. The reaction successfully afforded fluoromethylated cyclohexenes, including tri-, di-, and monofluoromethylcyclohexenes. The most striking feature of this reaction is that the cycloadducts are obtained as nearly pure enantiomers.

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Notes and references

1 (*a*) *Fluorine in medicinal chemistry and chemical biology*, ed. I. Ojima, Wiley & Sons, New York, 2009; (*b*) J.-P. Bégué and D. Bonnet-Delphon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley & Sons, Hoboken, 2008.

2 For reviews on the asymmetric construction of trifluoromethylated stereogenic centers from prochiral trifluoromethylated substrates, see: (*a*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455; (*b*) K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1.

3 For reviews on enantioselective trifluoromethylation, see: (*a*) G. Valero, X. Companyó and R. Rios, *Chem.–Eur. J.*, 2011, **17**, 2018; (*b*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*c*) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633; (*d*) T. Billard and B. R. Langlois, *Eur. J. Org. Chem.*, 2007, 891.

4 For an example of the enantioselective difluoromethylation and related reviews on the diastereoselective reaction, see: (*a*) C. Ni, F. Wang and J. Hu, *Beilstein J. Org. Chem.*, 2008, **4**(21), DOI: 10.3762/bjoc.4.21; (*b*) C. Ni and J. Hu, *Synlett*, 2011, 770; (*c*) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465; (*d*) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921; (*e*) See also ref. 3*c*.

5 For the enantioselective monofluoromethylation using α-fluoro-(phenylsulfonyl)methane (FSM) derivatives as a synthetic equivalent of a monofluoromethide, see: (*a*) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura and T. Toru, *Angew. Chem., Int. Ed.*, 2006, **45**, 4973; (*b*) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; (*c*) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2008, **47**, 8051; (*d*) W.-B. Liu, S.-C. Zheng, H. He, X.-M. Zhao, L.-X. Dai and S.-L. You, *Chem. Commun.*, 2009, 6604; (*e*) S. Zhang, Y. Zhang, Y. Ji, H. Li and W. Wang, *Chem. Commun.*, 2009, 4886; (*f*) A.-N. Alba, X. Companyó, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 7035; (*g*) F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun and A. Córdova, *Chem.–Eur. J.*, 2009, **15**, 10013; (*h*) H. W. Moon, M. J. Cho and D. Y. Kim, *Tetrahedron Lett.*, 2009, **50**, 4896; (*i*) For pioneering studies on the nucleophilic fluoromethylation with FSM derivatives, see ref. 4*b–d*.

6 For early studies on the Diels–Alder reaction of fluoromethylolefins, see: (*a*) E. T. McBee, C. G. Hsu, O. R. Pierce and C. W. Roberts, *J. Am. Chem. Soc.*, 1955, **77**, 915; (*b*) E. T. McBee, C. G. Hsu and C. W. Roberts, *J. Am. Chem. Soc.*, 1956, **78**, 3389; (*c*) E. T. McBee, C. W. Roberts and C. G. Hsu, *J. Am. Chem. Soc.*, 1956, **78**, 3393.

7 For recent reports and reviews, see: (*a*) Y.-H. Lam, S. J. Stanway and V. Gouverneur, *Tetrahedron*, 2009, **65**, 9905; (*b*) T. Hanamoto, R. Anno, K. Yamada, K. Ryu, R. Maeda, K. Aoi and H. Furuno, *Tetrahedron*, 2009, **65**, 2757; (*c*) V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova and G. Haufe, *J. Fluorine Chem.*, 2007, **128**, 818; (*d*) T. Billard, *Chem.–Eur. J.*, 2006, **12**, 974; (*e*) J. Leuger, G. Blond, R. Fröhlich, T. Billard, G. Haufe and B. R. Langlois, *J. Org. Chem.*, 2006, **71**, 2735, and earlier references cited therein.

8 The results of our preliminary study on the Diels–Alder reaction of **2** with achiral Lewis acid are shown in ESI†.

9 For an example of the diastereoselective reaction, see: B. Linclau, P. J. Clarke and M. E. Light, *Tetrahedron Lett.*, 2009, **50**, 7144.

10 (*a*) K. Futatsugi and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 1484; (*b*) K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa and H. Yamamoto, *J. Am. Chem. Soc.*, 2010, **132**, 5625.

11 For other reports on the asymmetric Diels–Alder reaction with Lewis acid activated chiral oxazaborolidine, see: (*a*) S. Mukherjee and E. J. Corey, *Org. Lett.*, 2010, **12**, 632; (*b*) D. Liu, E. Canales and E. J. Corey, *J. Am. Chem. Soc.*, 2007, **129**, 1498.

12 *Endo*/*exo* nomenclature is related to the stereochemistry of the carbonyl substituent.

13 We confirmed that the optical purity of **4a** and **5a** does not change even after chromatographic purification using achiral silica gel or solvent evaporation (samples with an ee of 90% were used for checking). For the self-disproportionation effect of the enantiomers of perfluorinated compounds, see: (*a*) V. A. Soloshonok, *Angew. Chem., Int. Ed.*, 2006, **45**, 766; (*b*) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi and D. A. Singleton, *J. Am. Chem. Soc.*, 2007, **129**, 12112; (*c*) H. Ueki, M. Yasumoto and V. A. Soloshonok, *Tetrahedron: Asymmetry*, 2010, **21**, 1396.

14 The origin of the diastereoselection is discussed in ESI†.

15 (*a*) K. Tamura, T. Yamazaki, T. Kitazume and T. Kubota, *J. Fluorine Chem.*, 2005, **126**, 918; (*b*) M. Jagodzinska, F. Huguenot and M. Zanda, *Tetrahedron*, 2007, **63**, 2042.

16 For non-asymmetric synthesis of *t*-butyl 6-trifluoromethylshikimate, see: J. Leroy, N. Fischer and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1281.

17 A. Wrobleski, K. Sahasrabudhe and J. Aubé, *J. Am. Chem. Soc.*, 2002, **124**, 9974.

18 T. F. Spande, H. M. Garraffo, H. J. C. Yeh, Q.-L. Pu, L. K. Pannell and J. W. Daly, *J. Nat. Prod.*, 1992, **55**, 707.

19 One of the two molecules in the asymmetric unit is shown for clarity.