Chiral Allylic Fluorides

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A Concise Synthesis of Enantioenriched Fluorinated Carbocycles**

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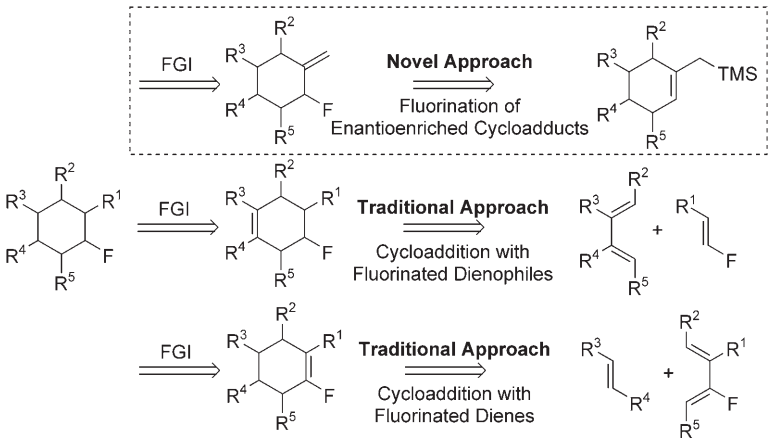
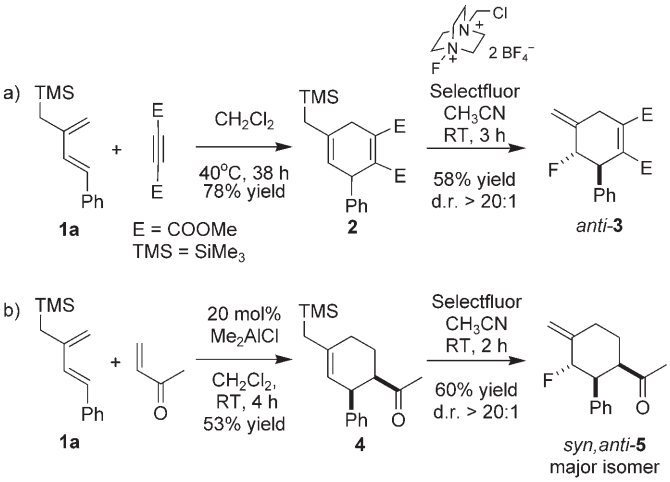
Since the discovery by Fried et al.[1] that fluorocortisone is much more potent than the non-fluorinated parent compound, the incorporation of fluorine in drug design has been a powerful strategy to improve properties such as bioavailability and lipophilicity.[2] In addition, with the role of chirality firmly established in medicinal chemistry, efficient methods for the selective formation of fluorinated stereogenic centers are in increasing demand. With few exceptions,[3] mainly α-fluorinated carbonyl derivatives are accessible using the asymmetric fluorinations reported to date.[4] Other chiral fluorinated building blocks, especially those with multiple stereocenters, remain difficult to access. We reported that enantioenriched allylic fluorides can be prepared using a reagent-controlled enantioselective fluorodesilylation of prochiral allylsilanes, affording fluorinated carbocycles with a single stereogenic center.[5] In pursuit of a general strategy for the enantioselective synthesis of fluorinated six-membered carbocycles featuring multiple stereocenters, one of which is fluorinated, it is tempting to resort to the Diels–Alder reaction using a monofluorinated diene[6] or dienophile (Scheme 1).[7] However, an asymmetric catalytic approach has yet to be developed, not least because of reactivity and selectivity issues, and the need to prepare the fluorinated reactants with perfect control of their *E*/*Z* geometry.[6c] We reasoned that these problems could be addressed if the cycloaddition event takes place before fluorination. Herein, we report a general and concise strategy leading to enantioenriched fluorinated carbocycles relying on asymmetric Diels–Alder reactions of silylated dienes followed by a highly stereoselective electrophilic fluorination of the silylated adducts (Scheme 1). We targeted fluorinated products featuring an exocyclic double bond,[8] a structural motif found, for example, in fluorinated analogues of vitamin D_3.[9]



Scheme 1. Diels–Alder approaches to fluorinated carbocycles. FGI = functional-group interconversion, TMS = trimethylsilyl.



Scheme 2. Sequential cycloaddition–fluorination.

Before embarking on the development of an asymmetric variant of the proposed sequence, we validated its feasibility with the fluorination of two racemic adducts, **2**[10] and **4**,[11] derived from the readily accessible silylated diene **1a**[12a] (Scheme 2). The fluorination of allylsilane **2** was performed using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor),[13] and afforded *anti*-**3** as a single diastereomer (d.r. > 20:1) in 58% yield (Scheme 2a). Adduct **4** was fluorinated to give *syn,anti*-**5** in 60% yield with a d.r. of > 20:1 (Scheme 2b).

Prompted by these encouraging results, we considered two asymmetric variants to access enantioenriched fluorinated carbocycles (Table 1). In the first approach, the Diels–Alder reaction of **1a** with the chiral *N*-acyloxazolidinone **6**[14] gave the pure *endo* adduct **7** in 50% yield (*endo*/*exo* ratio of crude product 5:1; entry 1, Table 1). This reaction proceeded with excellent Cα-*Si* facial selectivity, in accord with Evans' rationalization invoking an s-*cis* dienophile rigidified by bidentate aluminum chelation.[14] The more challenging second approach relies on a catalytic asymmetric Diels–Alder reaction using the Evans' mild Lewis acid derived from $Cu(OTf)_2$ and the bis(oxazoline) ligand **A** (entries 2–4, Table 1).[15] Dienes **1a**,**b**[12] reacted with the *N*-acyloxazolidi-

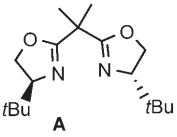


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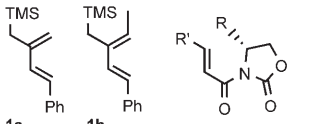
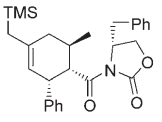
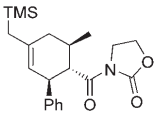
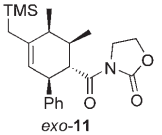
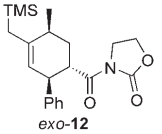
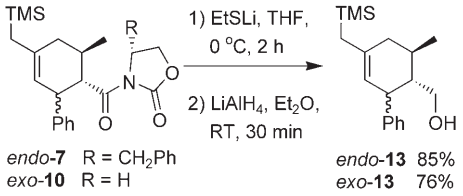
Table 1: Enantioselective Diels–Alder reactions of **1a–b** with **6**, **8–9**.



6: R=CH_2Ph, R'=Me
8: R=H, R'=Me
9: R=H, R'=H

Entry	Reacting partners	Cond.[a]	Major product	Yield [%]	d.r.	*ee* [%]
1	**1a**+**6**	I	 *endo*-**7**	50	*endo*/*exo* 5:1[b] >20:1[c]	–
2	**1a**+**8**	II	 *exo*-**10**	79	*exo*/*endo* 9:1 >20:1[c]	90[d]
3	**1b**+**8**	II	 *exo*-**11**	45	*exo*/*endo* >20:1	94[e]
4	**1b**+**9**	II	 *exo*-**12**	78	*exo*/*endo* 3:1 >20:1[c]	89[e]

[a] Conditions I: **1a** (1 equiv), **6** (1 equiv), Me_2AlCl (1.4 equiv), CH_2Cl_2, −40 °C, 3 h. II: **1a–b** (1.2 equiv), **8–9** (1 equiv), $Cu(OTf)_2$ (5 mol%), ligand **A** (5 mol%), 2–4 days, 3-Å MS. [b] Only two diastereomers were detectable in the crude mixture by ^{1}H NMR spectroscopy. [c] d.r. after purification. [d] Determined by chiral HPLC. [e] Determined by derivatization using Mosher's ester of the alcohol obtained by reductive cleavage of the oxazolidinone.

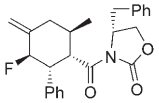
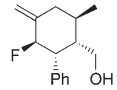
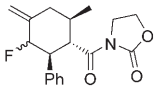
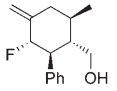
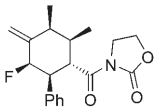
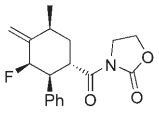


endo-**7** R = CH_2Ph
exo-**10** R = H

endo-**13** 85%
exo-**13** 76%

Scheme 3. Reductive cleavage prior to fluorination.

Table 2: Fluorination of the silylated adducts **7**, **10–13**.[a]

Entry	Substr.	Product [major shown]	d.r.[b]	Yield [%][c]
1	*endo*-**7**	 *syn,anti,syn*-**14**	>20:1	75
2	*endo*-**13**	 *syn,anti,syn*-**15**	9:1	69
3	*exo*-**10**	 *anti,anti,anti*-**16** *anti,syn,syn*-**16**	1:1	83
4	*exo*-**13**	 *anti,anti,anti*-**17**	5:1	60
5	*exo*-**11**	 *anti,syn,syn,syn*-**18**	6:1	91
6	*exo*-**12**	 *anti,syn,syn*-**19**	6:1	82

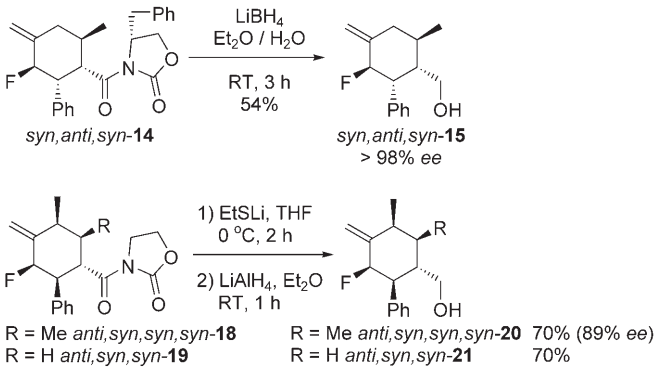
[a] Substrate (1 equiv), Selectfluor (1.1–1.3 equiv), CH_3CN, RT, 2–4 h. [b] d.r. determined on crude reaction mixtures by ^{1}H NMR spectroscopy. [c] Yields of isolated products.

nones **8** and **9** to give **10–12** in 45–79% yields. The cycloadditions were *exo* selective with up to 94% *ee*.[16] The sense of asymmetric induction is consistent with the diene approaching the less hindered face of the copper square-planar complex with the dienophile.[15]

The enantiopure silylated alcohols *endo*-**13** and *exo*-**13** were also prepared to study their subsequent fluorination. These alcohols were accessed by thioesterification of *endo*-**7** and *exo*-**10**,[17] followed by reduction (Scheme 3).

The enantioenriched silylated adducts **7** and **10–13** were then submitted to electrophilic fluorodesilylations (Table 2). All fluorinations proceeded smoothly within 4 h at room temperature using Selectfluor in CH_3CN and delivered the desired fluorinated products with 60–91% yield. The ^{1}H and ^{19}F NMR spectra of the crude mixtures showed the desired fluorinated products only. The fluorodesilylation of *endo*-**7** gave *syn*,*anti*,*syn*-**14** exclusively (entry 1, Table 2). The *anti* relationship of the fluorine with respect to the phenyl group was assigned based on its ^{1}H NMR spectrum and confirmed by X-ray crystallography,[16b] which also confirmed the sense of facial stereocontrol for the cycloaddition step. The fluorination of the alcohol *endo*-**13** afforded *syn*,*anti*,*syn*-**15** with a d.r. of 9:1 (entry 2, Table 2)). For this pair of stereochemically related adducts (**7** and **13**), the sense of stereocontrol is identical, with the level of selectivity maximal when the fluorination is performed prior to the cleavage of the chiral auxiliary. The fluorination of *exo*-**10** was not stereoselective and led to a 1:1 mixture of epimeric fluorinated products (entry 3, Table 2). In contrast, *exo*-**13**, featuring the primary hydroxy group, was fluorinated with a d.r. of 5:1 with the fluoro substituent *anti* with respect to the phenyl group (entry 4, Table 2). These results suggest that for these two substrates, it is critical to perform the fluorination after reductive cleavage of the oxazolidinone to obtain a good level of selectivity. The fluorinations of *exo*-**11** and *exo*-**12**, which both possess an additional methyl group at position 5, were both diastereoselective (d.r. 6:1) and led to **18** and **19** in 91%

and 82% yield, respectively. For both reactions, the sense of diastereocontrol was opposite to that in the reaction of *exo*-**13**. Indeed, the fluorine substituent in **18** and **19** was found to be *syn* with respect to the phenyl group (entries 5 and 6, Table 2). This was confirmed by X-ray analysis of **19**.[16b] The



Scheme 4. Reductive cleavage after fluorination.

cleavage of the oxazolidinone after fluorination was performed successfully on adducts **14**, **18**, and **19** (Scheme 4).

The stereochemical preference of fluorinations of the *endo* and *exo* adducts could be rationalized in the light of the S_E2' mechanism[18] consistent with the clean double-bond transposition observed upon fluorodesilylation.[13a] In a primary analysis, it is also reasonable to assume that the electrophilic fluorinating reagent approaches the silylated

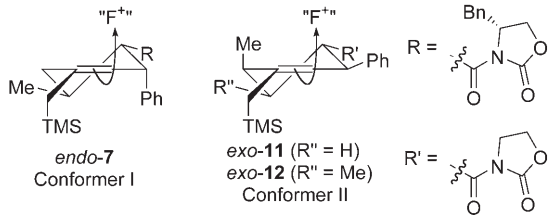


Figure 1. Stereochemical outcome of the fluorodesilylations.

cyclohexene preferentially axially and *anti* with respect to the trimethylsilyl group (Figure 1).[18b] For the *endo* adduct **7** adopting conformation I with the phenyl positioned pseudoaxial, the axial approach of Selectfluor followed by ring flip gives the experimentally observed fluorinated epimer with the F substituent *anti* with respect to the phenyl group. For *exo*-**11** and *exo*-**12** both delivering the major fluorinated products with the F substituent *syn* to the phenyl group, conformer II is likely to prevail in order to minimize the $A^{1,2}$ strain arising from the presence of the additional methyl group at position 5. The axial attack of Selectfluor on this conformer led to fluoro adducts **18** and **19** with the F and Ph groups *syn*. The stereochemical outcome is more subtle for adducts *exo*-**10** and *exo*-**13** lacking the methyl group at position 5. The lack of stereocontrol for the fluorination of *exo*-**10** suggests that Selectfluor reacts indiscriminately with the two possible conformers. However, the presence of the primary alcohol for the structurally related adduct *exo*-**13** restores some degree of stereocontrol (d.r. 5:1) allowing for the preferential formation of **17** with the F and Ph groups *anti*. A clearer understanding of how the primary alcohol acts as a remote stereodirecting group for the fluorination of *exo*-**13**, and how it is responsible for the eroded diastereocontrol for the fluorination of *endo*-**13** versus that of *endo*-**7** will require further studies.

In summary, enantioenriched, densely functionalized fluorinated carbocycles are made accessible using a short synthesis featuring an operationally simple "reverse" cycloaddition–fluorination sequence. The late introduction of fluorine is advantageous as this avoids the complications associated with the synthesis and reactivity of fluorinated reactants. This study offers a unique platform to delineate the effects responsible for the level and sense of stereocontrol of the fluorination as the substitution pattern of the adducts varies. Extension of this chemistry to the preparation of fluorinated heterocycles is in progress.

Experimental Section

General procedure for fluorination: To a stirred solution of silylated adduct (1 equiv) in CH_3CN (0.1M) under Ar was added Selectfluor (1.1–1.3 equiv) at RT. After the substrate was consumed (TLC), the solvent was evaporated in vacuo. The residue was fractionated between Et_2O and saturated $NaHCO_3$(aq). The organic phase was dried over $MgSO_4$, filtered, and concentrated to dryness to afford the crude product, which was purified by silica gel chromatography.

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[16] a) The stereochemistry of *exo*-**11** was assigned by X-ray crystallography. The absolute configuration of *exo*-**10** and *exo*-**12** was assigned by analogy with *exo*-**11**; b) CCDC 641269–641271 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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