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Recent progress in the use of fluoroorganic compounds in pericyclic reactions

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1. Introduction

Fluoroorganic chemistry continues to find widespread applications in a plethora of technological fields.[1–4] In medicinal chemistry, many organofluorine compounds are featured as potential drug candidates by virtue of their improved metabolic stabilities and useful lipophilicity profiles relative to their nonfluorinated counterparts.[5] Fluorinated polymers, with their high thermal stability and chemical inertness among other outstanding properties, have been recognized as high value-added materials.[6,7] The solubility profiles of molecules having extended fluoroalkyl chains, the so-called fluorous-tagged molecules, are substantially altered as a result of the presence of the fluorous domain. This is exploited in fluorous chemistry[8] to facilitate, inter alia, biphasic catalysis[9] or

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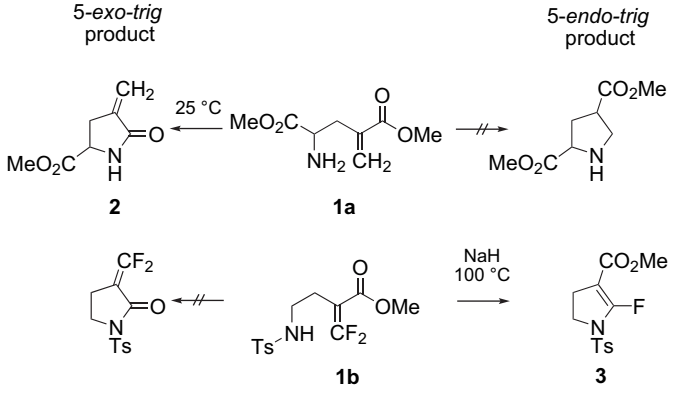
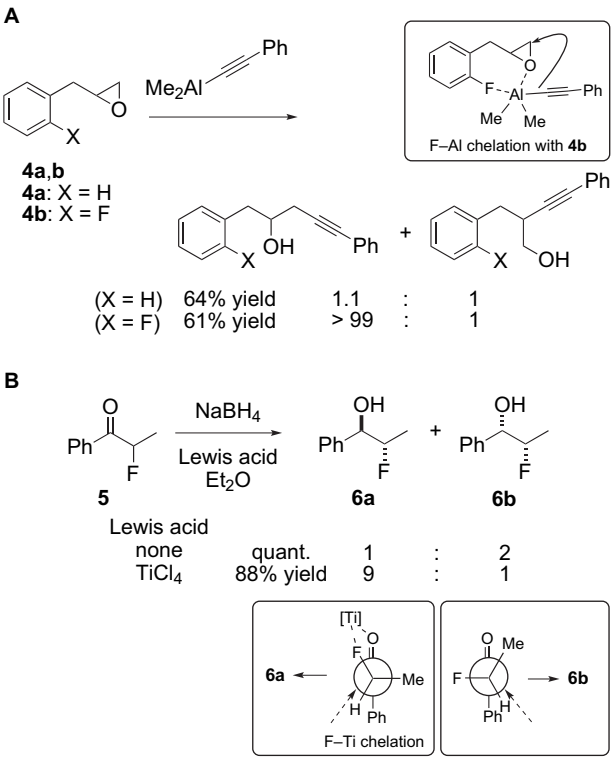
efficient product purification.[10–12] The high natural abundance and magnetic susceptibility of the fluorine-19 nucleus make organofluorine compounds good NMR probes in biological structural analyses,[13,14] while the positron-emitting activity of the fluorine-18 isotope has opened up a fertile field of research in fluoroorganic radiochemistry for positron emission tomography (PET) imaging.[15,16]

The synthetic chemistry of fluorinated compounds can be understood by considering the properties of a C–F bond, as reviewed by O'Hagan.[17] In polar reactions, fluorine-containing substituents can modify the reactivity of organic molecules through inductive effects, mesomeric effects and/or hyperconjugation. An illustrative example is shown in Scheme 1.[18] The nonfluorinated and the fluorinated amino-diesters **1a**,**b** exhibit opposite ring-closing reactivities. The former substrate **1a** was used by Baldwin and coworkers[19] to illustrate the difficulty of 5-*endo-trig* processes. In this case, the 5-*exo-trig* product **2** was isolated quantitatively. Substitution of the terminal double bond with two fluorines causes the substrate **1b** to cyclize exclusively to form the normally disfavoured 5-*endo-trig* product **3** via intramolecular addition and subsequent elimination.[18] These *anti*-Baldwin ring closures of 1,1-dihalo-1-alkenes have been studied computationally.[20,21] In difluoro-substituted systems, the two fluorines serve to lower the activation barrier through effective charge delocalization in the anionic intermediate by virtue of their high electronegativity. The dichloro and dibromo analogues cyclize with much lower yields.[18] With these substrates, computations showed that the reactions have higher activation energies and are facilitated by the good leaving-group ability of the halides, rather than the electronegativities of the halogen.[20]

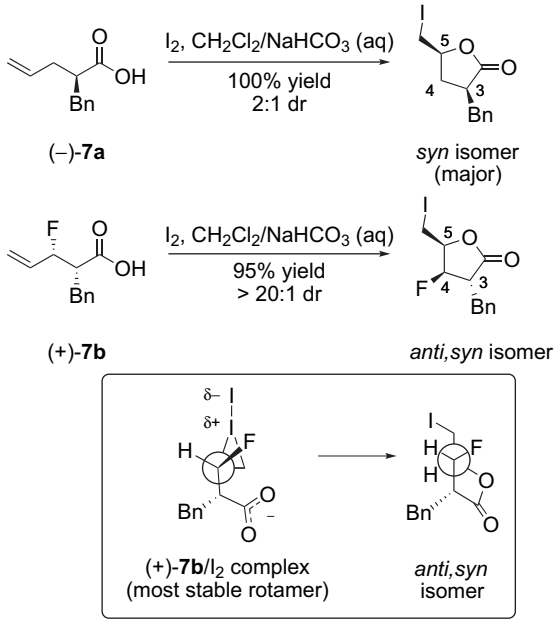


Scheme 1. Change in ring-closing reactivity patterns upon terminal difluorination of alkene.

Fluorine substituents can act as potent regiocontrol elements, as shown by the highly selective epoxide opening of the fluorinated substrate **4b**, compared to nonfluorinated **4a** (Scheme 2A).[22] Alkyl transfer from a five-coordinate aluminium complex chelating fluorine and the epoxide oxygen was postulated to account for the excellent regiocontrol. Fluorine–metal interactions are also useful in stereocontrol. The stereochemistry of the borohydride reduction of **5** depends on whether a coordinating Lewis acid is present or not (Scheme 2B).[23] In the absence of a coordinating metal ion, the Felkin–Anh product **6b** predominates. When titanium(IV) chloride is used as a Lewis acid, the reduction is under chelation control and gives **6a** as the major product. In addition, fluoro substituents can exert stereochemical control by biasing the reactive conformation of the reactants through orbital interactions. This can be exemplified by the stereochemical outcome of the iodolactonizations of acyclic olefinic carboxylic acids **7** (Scheme 3).[24] The nonfluorinated substrate **7a** cyclizes with a *syn*/*anti* ratio of 2:1. When the alkene is flanked by a fluoro substituent, as in **7b**, the product lactone



Scheme 2. (A) Fluorine as a regiocontrol element by participating in fluorine–aluminium interactions. (B) Fluorine as a stereocontrolling substituent by participating in fluorine–titanium chelation.



Scheme 3. Iodolactonization of nonfluorinated (**7a**) and fluorinated (**7b**) olefinic carboxylic acids.

featuring a pair of *syn* substituents on C4 and C5 is exclusively formed. Computational modelling of the iodolactonization transition structures revealed a distinct preference for fluorine to reside *inside*, rather than *outside* or *anti*. This '*inside* fluoro effect' is also displayed by the most stable rotamer of the **7b**/I_2 complex, and antarafacial attack by the internal carboxylate nucleophile in this conformer would give the experimentally observed major isomer. At the iodolactonization transition state, the *inside*-positioned fluoro substituent can stabilize the partial positive charge of the I_2–π

complex by its lone pairs while minimizing the interaction between the σ^*_{C-F}-orbital and the electron-deficient carbon–iodine bond. Due to the high electronegativity of fluorine, hyperconjugation involving the σ-type orbitals of the C–F bond with neighbouring orbitals is significant in perturbing the conformational preferences of reactants and transition structures.

This review considers the influence of fluorine substitution in a major category of organic reactions, the pericyclic reactions. Using recent synthetic and computational results, the scope of fluorinated molecules in cycloadditions, and sigmatropic and electrocyclic rearrangements is exemplified. Where data are available, the comparative chemical behaviour of the fluorinated and non-fluorinated molecules in these reactions is also presented. Reactions employing substrates bearing perfluorinated side chains are not covered in this review.

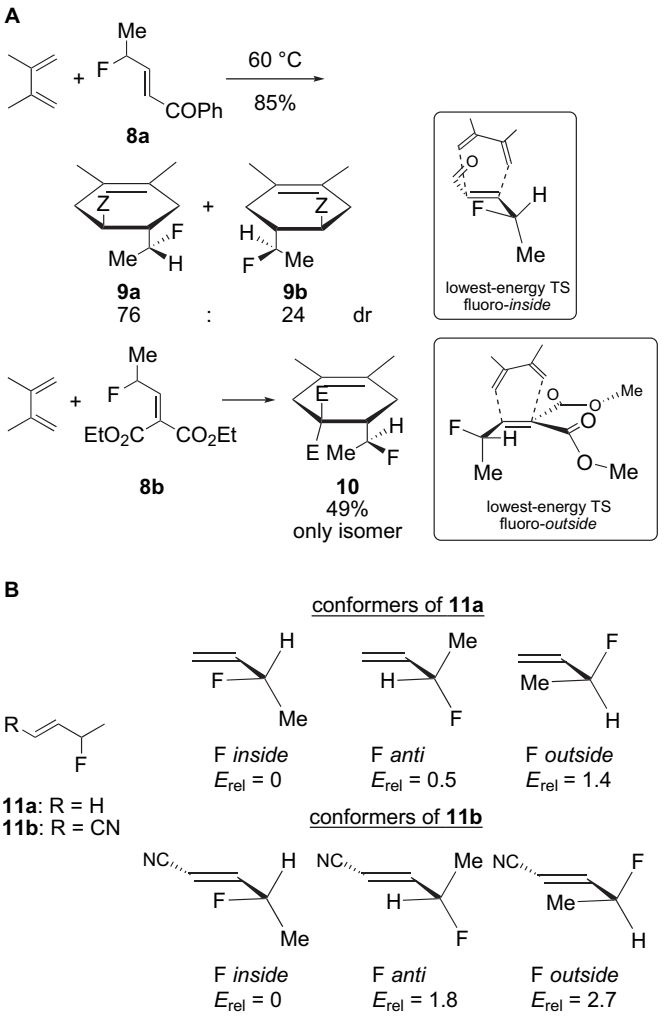
2. Cycloadditions

2.1. [4+2] Cycloadditions

The Diels–Alder reaction is an important general method for the construction of six-membered rings. Much effort has been devoted to the use of fluorinated dienes or dienophiles towards fluorinated analogues of this structural motif. This area was reviewed in 1997 by Percy, who wrote of a 'significant need' for methodology to access cyclic mono- and difluorinated compounds starting from fluorinated building blocks.[25] In this section, the new chemistry of dienophiles and dienes bearing fluoro and/or trifluoromethyl groups published in the last decade will be surveyed, focusing on systems containing fluorinated substituents either on or in proximity to the reacting system on the cycloaddition partners.

2.1.1. Dienophiles possessing fluoro substituents. Allylic fluorides of the type **8**, which possess a stereogenic fluorinated centre, were synthesized and their Diels–Alder chemistry studied using 2,3-dimethylbutadiene.[26] Different senses of diastereoselectivity were observed, depending on the structure of the allylic fluoride (Scheme 4A). Cycloadducts **9a**,**b** are formed from **8a** with moderate stereoselectivity, while only one isomer **10** results from the cycloaddition of **8b**, which is doubly substituted at the vinylic terminus. The conformations of ground-state allylic fluorides of the type **8** (Scheme 4B) and the Diels–Alder transition states were modelled by B3LYP computations.[26] The C–F bond of the terminal allylic fluoride **11a** slightly prefers to eclipse with the alkene moiety. The fluoro-*inside* preference is more pronounced in **11b**, which is substituted by a cyano group at the β-position. This is because of favourable electron donation from the allylic C–H and C–C σ-orbitals into the electron-deficient cyanoalkene π*-orbital. A similar fluoro-*inside* preference was also found in the computed Diels–Alder transition structures involving **8a**. This accounts for the sense of the experimental stereoselectivity. When a cis substituent is present on the allylic fluoride, as in **8b**, the fluorine strongly favours the *outside*, rather than the *inside*, position in the transition structure, where electronic repulsion with the carbonyl oxygen would occur. In both transition structures, the methyl group prefers to occupy the *anti* position.

A variety of α- and β-fluorostyrenes bearing different *para* substituents on the ring were investigated with regard to their Diels–Alder reactivity and selectivity.[27] These compounds reacted only with 1,3-diphenylisobenzofuran among the dienes studied. Some examples involving α-fluorostyrenes are given in Scheme 5A. The presence of a vinylic fluoro substituent retards the cycloaddition, as shown by comparing the experimental rate constants for **12a** and **12b** with that for *p*-fluorostyrene (**12c**) (Scheme 5B). The *endo*/*exo* selectivity depends on the position of the fluoro substituent on the alkene (Scheme 5C). The computed activation



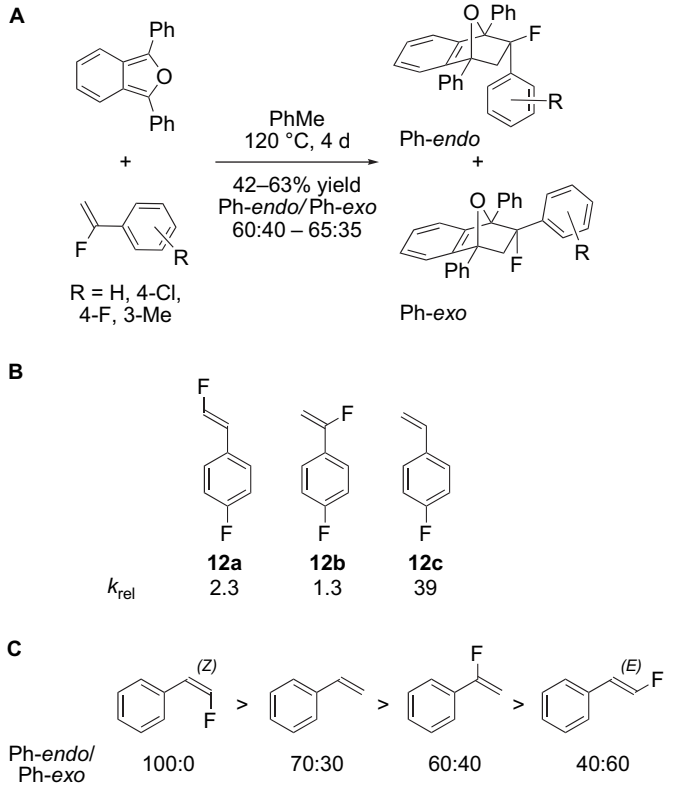
Scheme 4. (A) Diels–Alder reactions of chiral allylic fluorides **8a** and **8b** and schematic drawings of lowest-energy transition structures (B3LYP/6-31G(d)//B3LYP/6-31G(d) or B3LYP/6-31G(d)//PM3) computed using simplified allylic fluorides. Z=COPh, E=CO_2Et. (B) Relative conformational energies, in kcal/mol, (B3LYP/6-31G(d)) of model allylic fluorides **11a** and **11b**.

energies and *endo*/*exo* preferences of the cycloadditions of styrene and **12** agree qualitatively with the experimental values. The cycloadditions were found by computation to proceed with closed-shell transition states with no biradical character.

Mono- and difluorinated furan-2(5*H*)-ones **13a**–**d** react only with the reactive dienes, 1,3-diphenylisobenzofuran and cyclopentadiene, with the formation of diastereomeric 1:1 or 1:2 adducts (Fig. 1).[28] Several dienophiles **14** containing a fluoropropenoate unit have also been studied (Fig. 1).[29] These are also very unreactive compounds that react only with 1,3-diphenylisobenzofuran at 170 °C. Due to facile *E*–*Z* isomerization of the open-chain dienophiles **14a**, **14c** and **14d** at temperatures over 70 °C, their thermal Diels–Alder reactions in general occur with poor stereocontrol. The cycloaddition of the fluorinated butenolide **14b** gives the *endo*/*syn* cycloadduct cleanly.

2-Fluoronorcantharidin (**16a**) and 2-fluoroendothall (**16b**) have been prepared by a short synthetic route employing the furan Diels–Alder reactions of a monofluorinated maleic anhydride **15** (Scheme 6).[30] This approach has been extended for the synthesis of difluorinated analogues by using difluorinated maleic anhydride. The reactions proved to be highly *exo*-selective.

The dienophilic reactivities of α-fluorinated acryloyl ketone **17a** and ester **18a** have been studied and compared with their non-fluorinated analogues, **17b** and **18b** (Scheme 7).[31] The Diels–Alder



Scheme 5. (A) Diels–Alder reactions of α-fluorostyrenes. (B) Relative rate constants of Diels–Alder reactions of **12a–c** with 1,3-diphenylisobenzofuran. (C) Trend in *endo*/*exo* selectivity of styrene and α- or β-fluorostyrenes in Diels–Alder reactions with 1,3-diphenylisobenzofuran.

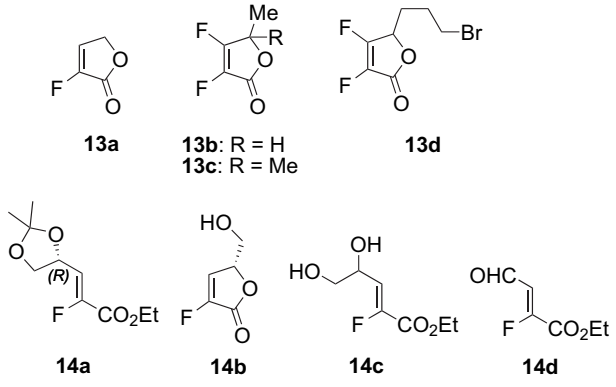
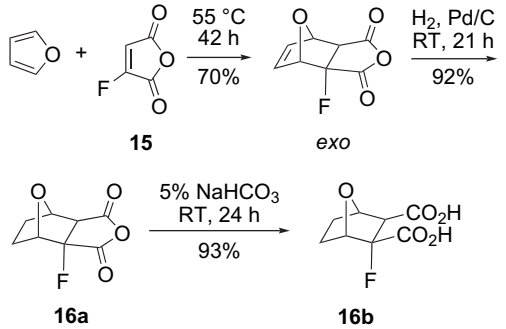
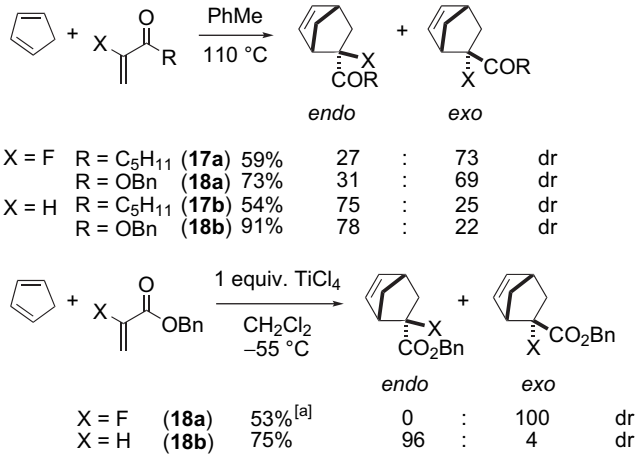


Figure 1. Fluorinated furan-2(5*H*)-ones **13** and dienophiles containing fluoropropenoate unit **14** studied as dienophiles.



Scheme 6. Concise Diels–Alder route to fluorinated norcantharidin **16a** and fluorinated endothall **16b**.



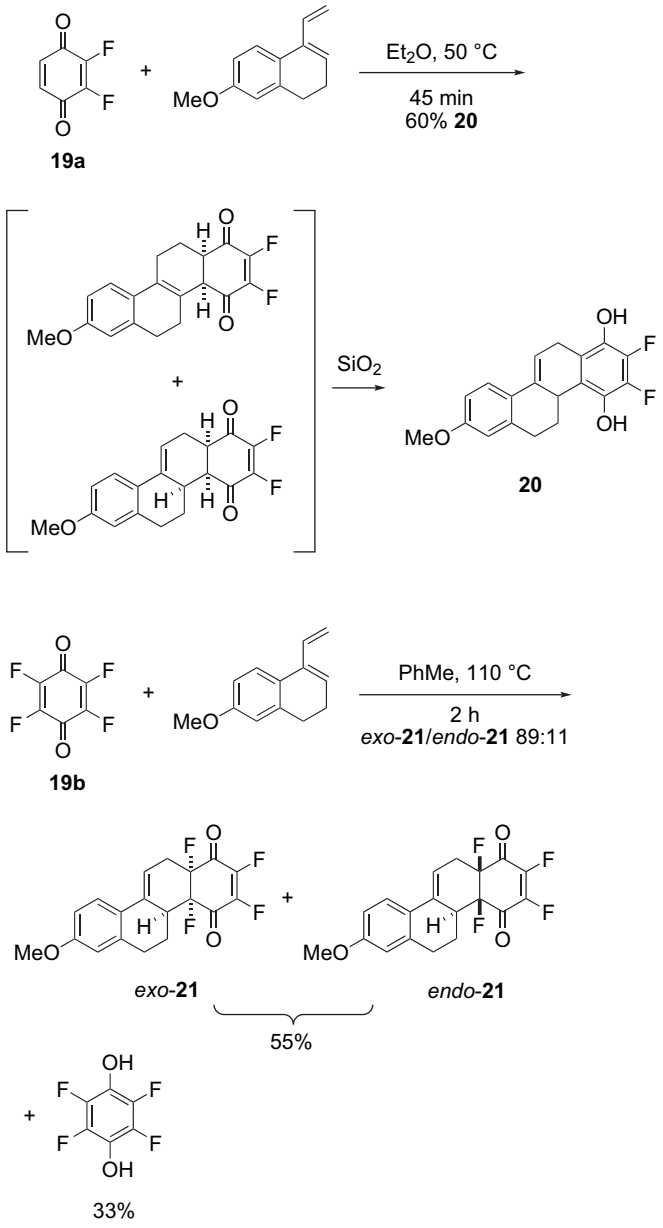
Scheme 7. (A) Thermal Diels–Alder reactions of acryloyl ketone **17b** and ester **18b**, and α-fluorinated analogues **17a** and **18a**. (B) $TiCl_4$-mediated cycloadditions of **18a** and **18b**. [a] Accompanied by 36% of two rearranged, chlorodefluorinated side products.

reactions of **17b** and **18b** with cyclopentadiene are *endo*-selective, while the fluorinated analogues **17a** and **18a** give moderate *exo*-selectivity, whether under thermal conditions or microwave activation. Use of $TiCl_4$ as a Lewis-acid promoter enhances the divergent selectivities. Computation (B3LYP/6-31G(d)) suggested that this reversal of selectivity is due to a lower activation barrier for the *exo* channel in the presence of the fluoro substituent. Attempts at an asymmetric variant of these reactions, using homochiral titanium complexes, have also been disclosed.[32]

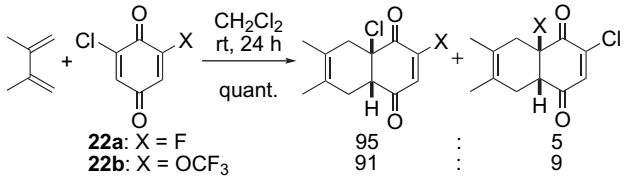
The synthesis of fluorinated D-homosteroids **20** and **21** has been achieved by the Diels–Alder reaction of a series of fluorinated benzoquinones and Dane's diene (Scheme 8).[33] The nonfluorinated double bond in the dienophile **19a** reacts preferentially. The *endo*/*exo* stereoselectivity depends on the number of fluoro substituents, with the tetrafluorobenzoquinone **19b** favouring *exo* cycloaddition. As noted by the authors, the fluoro substituents reverse the stereochemical outcome of this cycloaddition, which gives primarily an *endo* product with benzoquinone.[34]

The higher reactivity of a nonfluorinated double bond in benzoquinones, compared to a fluorinated double bond, can also be seen in the chemoselectivity of the Diels–Alder reactions of a series of 'mixed' halogenated quinones of the type **22** with symmetrical dienes (Scheme 9).[35] Thus, **22a** adds to 2,3-dimethylbutadiene primarily through its chlorinated double bond, rather than its fluorinated double bond, and **22b**, which bears a trifluoromethoxy group in place of fluorine, displays the same level and sense of selectivity as **22a**. A trifluoromethoxy group therefore exerts comparable influence in this regard to a fluoro substituent and behaves as a 'fluorine twin' in these *endo*-selective reactions. The selectivity observed is higher than would be expected solely from the electronic properties of the two substituents. The authors speculated that this 'twin relationship' occurs because the steric bulk of the trifluoromethoxy group is mainly restricted to the oxygen atom, a close isostere to fluorine, since it is known that the trifluoromethyl group in aromatic trifluoromethoxy ethers prefer to be perpendicular to the aromatic plane.[5,36]

The reactivities of mono- or difluorinated phenyl sulfoxides **23a–d**[37–40] and sulfones **24a–c**[39,41] were also investigated as dienophiles with dienes such as cyclopentadiene, furan and 1,3-diphenylisobenzofuran, under thermal or microwave activation (Fig. 2). (1-Fluorovinyl) phenyl sulfoxide (**23a**) was reported to be inert to cycloaddition with most dienes, except 1,3-diphenylisobenzofuran.[38] Notably, phenyl vinyl sulfoxide is known to take part in Diels–Alder reactions,[42–44] acting as an acetylene equivalent by elimination of sulfenic acid after the cycloaddition. Compound **23d**



Scheme 8. Synthesis of fluorinated D-homosteroids **20** and **21** by Diels–Alder reactions of Dane's diene with fluorinated benzoquinones **19**.



Scheme 9. Regiochemistry of Diels–Alder reactions of halogenated quinones **22** with 2,3-dimethylbutadiene.

reacts with cyclopentadiene smoothly, but the subsequent elimination is more difficult due to reduced basicity of the sulfinyl oxygen in the presence of electronegative fluorine atoms in the proximity.[40] α-Fluoro-β-arylvinyl sulfones **24c** react with simple dienes under thermal conditions, with the *endo*/*exo* selectivities depending on the diene structure.[41]

The dramatic effects of perfluorination can be seen in the chemistry of perfluorobicyclo[2.2.0]hex-1(4)-ene (**25**). Unlike its hydrocarbon parent, which is very labile towards dimerization and

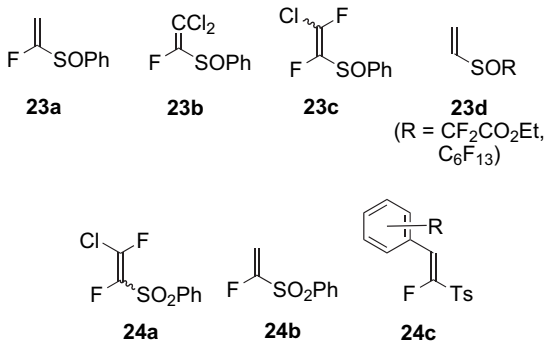
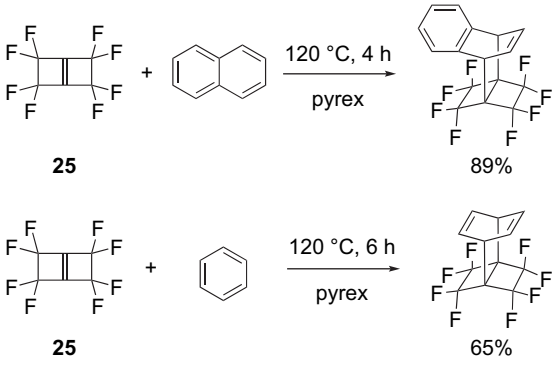


Figure 2. Sulfur-containing alkenes **23** and **24** as fluorinated dienophiles.

polymerization,[45] **25** is thermally more robust, and is an extremely reactive dienophile, adding across aromatic molecules including naphthalene, durene and even benzene (Scheme 10).[46]

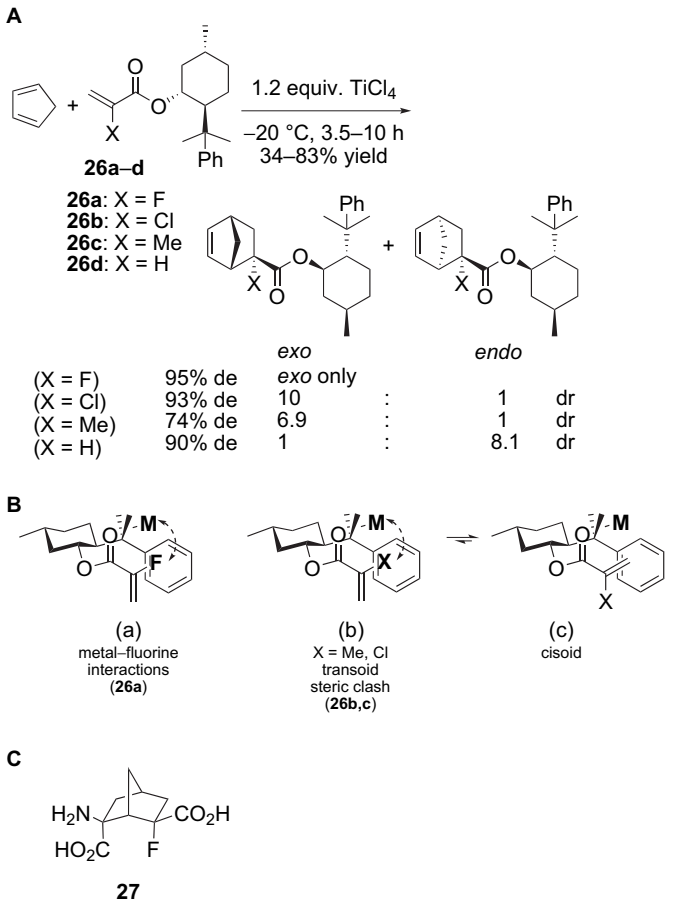


Scheme 10. Diels–Alder reactions of perfluoroalkene **25** with aromatic compounds.

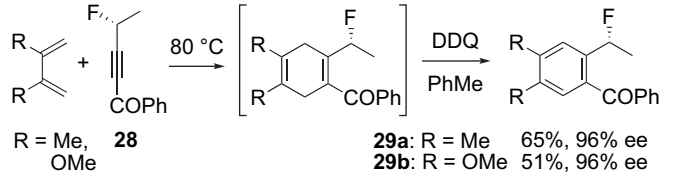
2-Fluoroacrylic ester **26a**, incorporating the 8-phenylmenthol chiral auxiliary, undergoes an asymmetric Diels–Alder reaction with cyclopentadiene in the presence of various Lewis acids (Scheme 11A).[47] The chlorinated (**26b**) or the methylated substrate (**26c**) preferentially delivers the *exo* product with high π-facial selectivity. Notably, the fluorinated substrate **26a** gives only the *exo* product, in contrast to the hydro analogue **26d**. The high facial selectivity was rationalized on the basis of stabilizing fluorine–metal interactions in the dienophile complex of **26a** (Scheme 11B, (a)), which would favour the *transoid* conformer of the acrylic acid moiety, thus rendering the *Si* face accessible to the diene. On the other hand, the *exo*-selective reactions of the methyl analogue **26c** proceed with an eroded π-facial selectivity. The bulkier methyl group in **26c** would sterically clash with the coordinating metal in the *transoid* conformer (Scheme 11B, (b)). Competition from the *cisoid* conformer (Scheme 11B, (c)) in the cycloaddition would thus lower the π-facial selectivity observed. The cycloaddition of **26a** and cyclopentadiene has found use in the synthesis of **27** (Scheme 11C), which is a fluorinated analogue of 6-aminonorbornane-2,6-carboxylic acid, a conformationally restricted analogue of glutamic acid.[48]

The asymmetric Diels–Alder reactions of 2-fluoroacrylic acid derivatives bearing an Evans-type oxazolidinone as the chiral auxiliary have also been explored.[49] These reactions are less selective than the reactions employing the menthol-based derivatives. The sense of asymmetric induction is the same as that observed with the nonfluorinated substrates.

A new method of preparing optically active benzylic fluorides starting from optically active propargylic fluorides has been disclosed (Scheme 12).[50] Cycloadducts **29a**,**b** derived from propargylic



Scheme 11. (A) Asymmetric Diels–Alder reactions of acrylic esters **26** bearing the 8-phenylmenthol chiral auxiliary. 'de' and 'dr' refer to the diastereofacial selectivity and the *endo*/*exo* selectivity, respectively. (B) Proposed rationalizations of the sense and level of diastereofacial selectivities as the α-substituent, X, is changed. (C) Structure of a fluorinated analogue of 6-aminonorbornane-2,6-carboxylic acid.

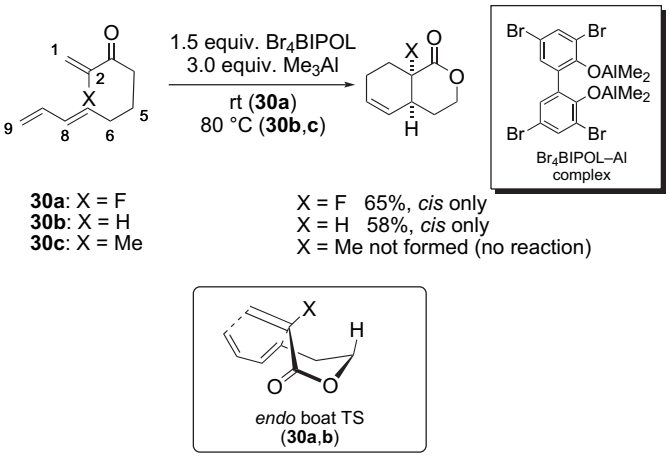


Scheme 12. Diels–Alder route to optically active benzylic fluorides.

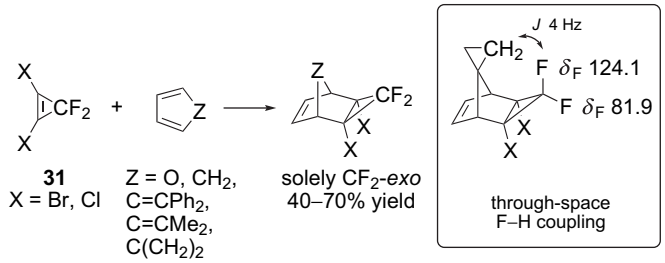
fluorides of the type **28** and symmetrical dienes undergo oxidative aromatization with no loss in optical purity.

The intramolecular Diels–Alder reaction of α-fluoroacrylate derivatives **30a** can be promoted by a bidentate aluminium complex formed from Me_3Al and 3,3′,5,5′-tetrabromo-2,2′-biphenyl-1,10-diol (Br_4BIPOL) (Scheme 13).[51] In most cases, complete cis selectivity was observed. This was rationalized by an *endo*-boat TS. Compound **30b** with a hydrogen atom instead of fluorine furnishes the cis cycloadduct exclusively in the presence of the aluminium complex at a higher temperature, but the chloro analogue and the methyl analogue **30c** do not react under the same conditions.

The thermal Diels–Alder reactions of dihalodifluorocyclopropenes **31** with furan or a series of cyclopentadienes are exclusively CF_2-*exo*-selective (Scheme 14).[52] The stereochemical assignment is supported by a through-space coupling observed in the spirodiene adduct ($Z{=}C(CH_2)_2$) and its similar ^{19}F chemical shifts to other adducts in the series.

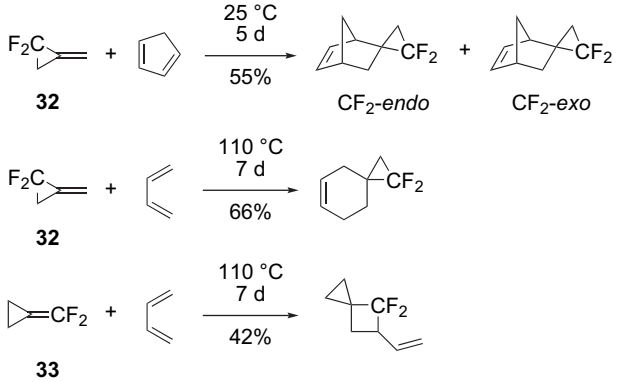


Scheme 13. Intramolecular Diels–Alder reactions of **30** promoted by bidentate aluminium complex.



Scheme 14. *exo*-Selective cycloadditions with cyclopropenes **31** and stereochemical assignments of the cycloadducts on the basis of through-space coupling between *endo* fluorine and *syn* apical cyclopropyl proton spins.

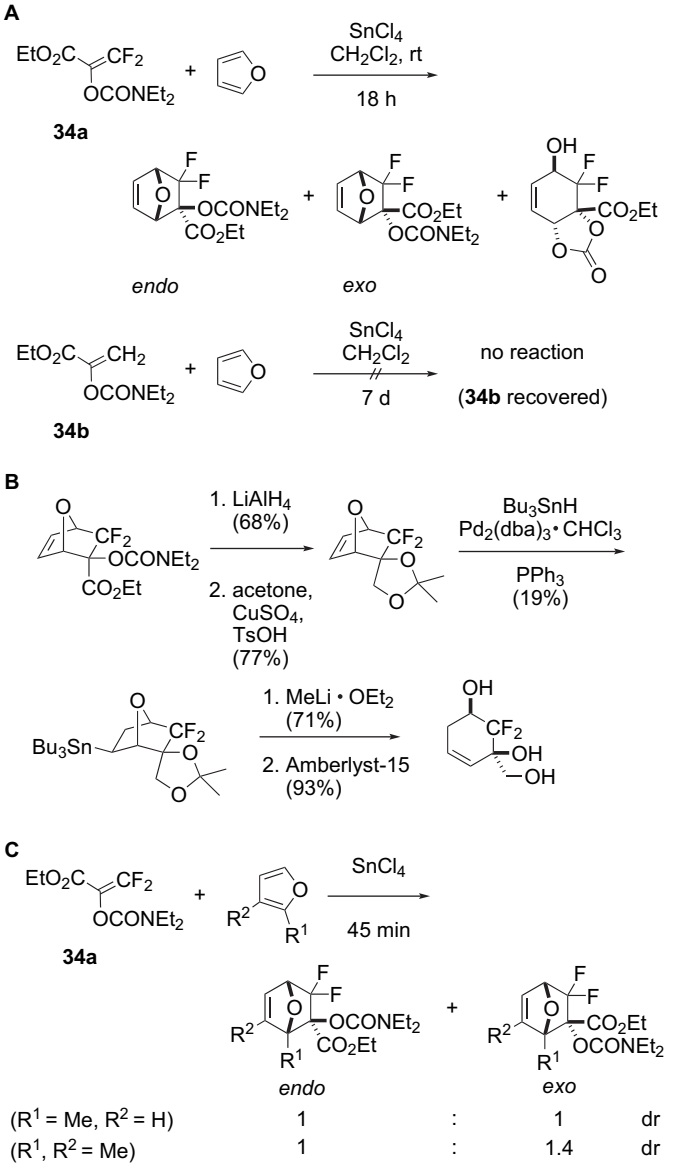
The contrasting cycloaddition reactivities of difluoromethylenecyclopropanes **32** and **33**[53] were first reported by Dolbier and Smart in the 1980s (Scheme 15).[54] Compound **32** adds to dienes in a [4+2] manner with good CF_2-*endo*-selectivity, while **33** preferentially undergoes [2+2] cycloadditions. The dienophilicity of **32** relative to its nonfluorinated parent, which primarily reacts as a [2+2] substrate, was attributed to the allylic fluoro substituents, which lower the LUMO energy of the substrate. As the authors noted, the [2+2] reactivity of **33** is consistent with the general observation that fluorinated alkenes are reactive [2+2] reactants and poor dienophiles. Other substituted difluoromethylenecyclopropanes related to **32** have also been shown to be good dienophiles with high *endo* selectivities.[55]



Scheme 15. Cycloadditions of fluorinated methylenecyclopropenes **32** and **33**.

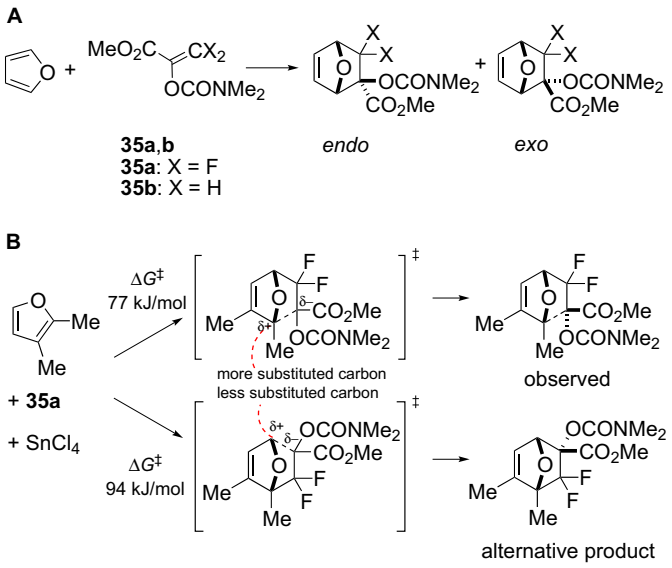
The *gem*-difluorinated dienophile **34a** was synthesized by Percy and its Diels–Alder reaction with different furans systematically

studied (Scheme 16A).[56] The cycloadducts so formed can be ring opened, in some cases in situ, without aromatization. Further transformations from these products into difluorinated cyclohexene or cyclohexene polyols were validated (Scheme 16B).[56,57] When methylated furans are used, the additions are faster and completely regioselective, although the stereoselectivity is not high (Scheme 16C).



Scheme 16. (A) Cycloaddition of **34a** to furan with in situ ring opening, and the lack of cycloaddition of **34b**. (B) Further transformations of a bicyclic cycloadduct into a stereodefined, polyhydroxylated fluorinated six-membered ring compound. (C) Cycloadditions of **34a** with methylated furans.

Various issues of the reactivity and regio- and stereoselectivity of the Diels–Alder reactions of fluorinated **34a** and its non-fluorinated counterpart **34b** were addressed experimentally and computationally by Hillier, Percy and co-workers.[58] While **34a** is a reactive dienophile in the presence of a tin(IV) catalyst, **34b** remains unchanged, even after prolonged reaction (Scheme 16A).[56] To explain the differing reactivities of **34a** and **34b**, the simplified molecules **35a** and **35b** were used in computations (Scheme 17A). With furan as the diene component, the uncatalyzed cycloadditions of **35a** and **35b** have equal free energies of activation (Table 1). The overall reaction of **35a** is exergonic, but that of **35b** is



Scheme 17. Model Diels–Alder reaction using simplified dienophiles **35a** and **35b** for computation of activation and reaction free energies. (B) Rationalization of regiochemistry of Diels–Alder reactions involving 2,3-dimethylfuran.

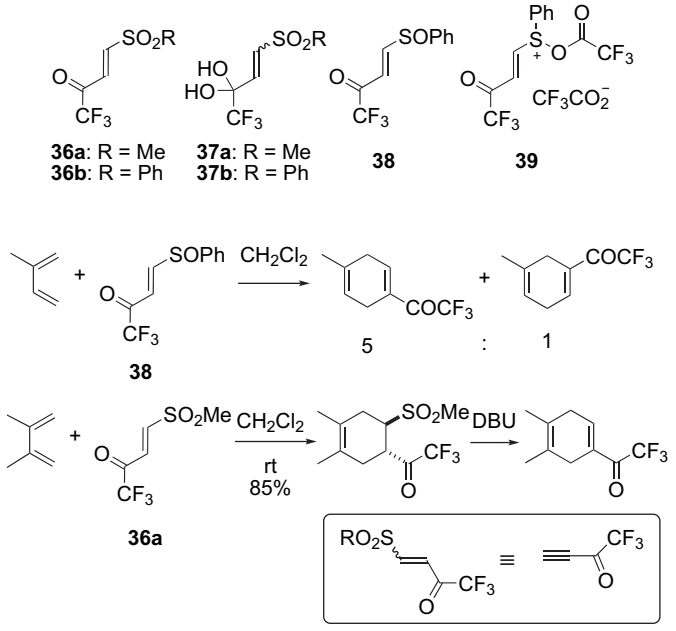
Table 1
Activation free energies and enthalpies at 298 K (kJ/mol) for the cycloadditions of **35a** and **35b** with furan (Scheme 17) in vacuum, computed at the B3LYP/6-31G(d,p) level of theory

Entry	Dienophile	Catalyst	$\Delta G^{\ddagger}_{endo}$ ($\Delta H^{\ddagger}_{endo}$)	$\Delta G^{\ddagger}_{exo}$ ($\Delta H^{\ddagger}_{exo}$)
1	**35a**	None	134 (106)	133 (105)
2	**35b**	None	139 (115)	133 (110)
3	**35a**	SnCl4	106 (82)	113 (87)
4	**35b**	SnCl4	111 (85)	107 (79)

ergonically neutral. Therefore, the *gem*-difluoro substituents in **35a** facilitate the cycloaddition by the thermodynamic advantage of the difluoromethylene carbon to be sp^3-hybridized (as in the cycloadduct), compared to sp^2-hybridized. The computed mechanism is concerted and highly asynchronous in the absence or presence of $SnCl_4$ in a vacuum, or in the absence of the catalyst when solvation effects are included, but, in the presence of both solvent and catalyst, a two-step mechanism was found. A zwitterionic intermediate could be located along the reaction coordinate between the two transition structures, which are close in energy. The accelerating effect of methyl substituents on furan (Scheme 16C) was explained in terms of their stabilization of the partial positive charge on the diene fragment in the charge-separated transition state. The high regioselectivities were rationalized in similar terms. For example, two regioisomeric transition states are possible for the 2,3-dimethylfuran/**35a** cycloaddition (Scheme 17B). The transition state in which a partial positive charge builds up on the more-substituted carbon was computed to have the lower energy (77 kJ/mol) and give the experimental regioisomer. As computations revealed a highly polar nature of these Diels–Alder reactions in which the diene reacts like a nucleophile, the authors attempted to draw structure–reactivity relationships involving Mayr's π-nucleophilicity parameter (*N*),[59,60] which had been obtained for a range of cyclic and acyclic dienes. A linear fit was obtained between the experimental rate constants of three furans and their *N* values. This reflects the importance of the diene π-nucleophilicity for the success of these cycloadditions. However, a survey of a wider range of dienes revealed that there is no simple relationship between *N* and the reaction outcome, as factors such as conformational freedom and possible ligation by a Lewis acid also need to be considered.

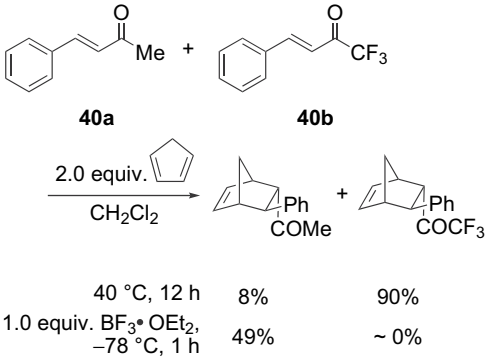
2.1.2. Trifluoromethylated and related dienophiles. Alkenes bearing a trifluoromethyl group have been extensively used in cycloadditions to prepare trifluoromethylated rings. As this area was reviewed in 2000,[61] this section will cover progress reported since then.

β-Trifluoroacetylvinyl sulfones **36a**,**b**, their hydrates **37a**,**b**,[62] and the analogous phenyl sulfoxide **38** and its sulfonium salt **39**[63] have been studied as dienophiles (Scheme 18). These species are reactive towards simple dienes under thermal conditions with moderate regio- and stereoselectivities. Sulfinyl or sulfonyl elimination occurred in situ or mediated by DBU. In Diels–Alder reactions, these compounds can therefore be considered as equivalent to the 1,1,1-trifluorobutynone synthon.



Scheme 18. Trifluoromethylated ketones incorporating sulfur-based functional group investigated as dienophiles in thermal Diels–Alder reactions, and some examples illustrating synthetic equivalence to 1,1,1-trifluorobutynone synthon.

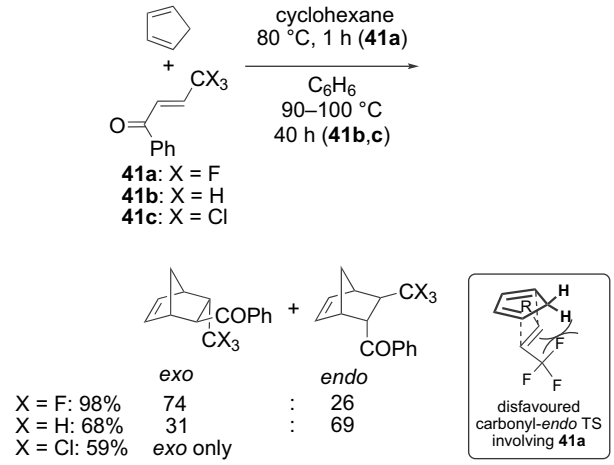
The chemoselectivity of a trifluoromethylated compound versus its methyl congener was demonstrated through a judicious choice of either thermal or Lewis-acidic conditions for a range of transformations, including the Diels–Alder reaction. When a 1:1 mixture of (*E*)-4-phenylbut-3-en-2-one (**40a**) and (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (**40b**) is treated with cyclopentadiene under thermal conditions, cycloaddition of the more electrophilic dienophile **40b** prevails (Scheme 19). However, in the presence of a boron Lewis acid, the sole product is the cycloadduct derived from



Scheme 19. Competition experiments between trifluoromethylated ketone **40b** and nonfluorinated parent **40a** using Diels–Alder reaction.

the nonfluorinated **40a**.[64] It was proposed that boron coordination to **40a** is more energetically profitable than to the electron-poor **40b**, resulting in the preferential reaction of the former compound. This was confirmed by calculations (MP2/6-31G(d)) and ^{13}C NMR spectroscopy of model compounds.

β-Fluoroalkylated enones such as **41a** are reactive dienophiles under thermal conditions, furnishing the carbonyl-*exo* adducts with consistently moderate stereoselectivities (Scheme 20).[65] As the authors noted, these species are more reactive towards cyclopentadiene in the Diels–Alder reaction than the analogous enones with a methyl or trichloromethyl group.[66] This was explained by a smaller energy gap between the HOMO of cyclopentadiene and the LUMO of **41a**, compared to that of the nonfluorinated counterparts **41b** and **41c** (Table 2). The carbonyl-*exo* selectivity observed in the cycloadditions of **41a** with cyclopentadiene is opposite to that involving the methyl ketone **41b**. The *endo*-selectivity has been explained in terms of the steric repulsion that would occur between a cyclopentadiene bridging hydrogen and the trifluoromethyl group in the alternative transition state.

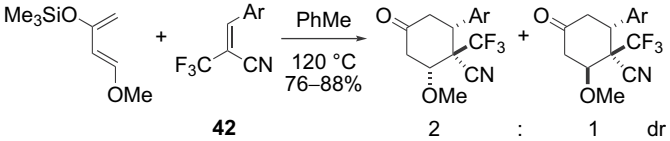


Scheme 20. Cycloadditions of β-trifluoromethylated enone (**41a**), and methyl (**41b**) and trichloromethyl (**41c**) analogues with cyclopentadiene.

Table 2
Energy differences (eV) between HOMO of cyclopentadiene and LUMO of **41a–c**

Entry	Method	ΔE ($LUMO_{41}-HOMO_{cyclopentadiene}$)		
		41a	**41b**	**41c**
1	AM1	7.9828	8.6265	8.0462
2	PM3	8.0691	8.7104	8.1983

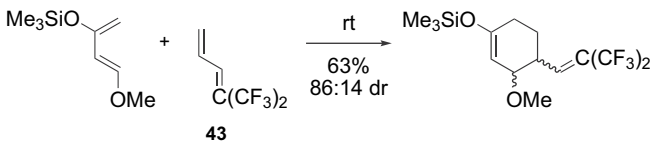
α-Trifluoromethylacrylonitriles of the type **42** react as dienophiles in the *E*-configuration with reactive dienes including cyclopentadiene, 2,3-dimethylbutadiene and Danishefsky's diene, with the nitrile-*endo*/*exo* selectivity up to 2:1.[67] The α-fluorinated derivatives of **42** are not useful as dienophiles as a result of inseparable product mixtures (Scheme 21).



Scheme 21. Diels–Alder reactions of α-trifluoromethylacrylonitriles **42**.

The chemistry of 1,1-bis(trifluoromethyl)buta-1,3-diene **43** was systematically studied.[68] In normal electron-demand Diels–Alder

reactions with compounds such as cyclopentadiene or Danishefsky's diene, it reacts primarily as a dienophile through its nonfluorinated terminus (Scheme 22).



43

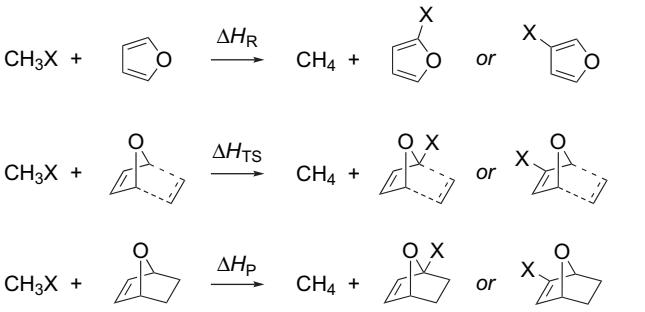
Scheme 22. Diels–Alder reaction of 1,1-bis(trifluoromethyl)buta-1,3-diene **43**.

2.1.3. Fluorinated dienes. The presence of a fluoro or a trifluoromethyl substituent within a furan or hydrocarbon diene system is beneficial to the energetics of intermolecular Diels–Alder reactions, according to high-accuracy CBS-QB3 results reported by Houk and Pieniazek.[69] As Table 3 shows, these substituents and other halogens were found to lower the activation enthalpies, while increasing the exothermicities. In other words, the facilitations are both kinetic and thermodynamic in nature. The potency of these effects increases with the electronegativity of the halogen, although fluorine and chlorine are sometimes reversed. The technique of isodesmic equations was employed to reveal the origin of the increase in exothermicity. These are given for fluorine in Table 4 and Scheme 23. The higher exothermicities were found to correspond with a larger stabilization of the product than that of the diene. For example, a stabilization of 5.3 kcal/mol results for fluorination at the 2-position of furan (entry 2; Table 4), but 14.0 kcal/mol of stabilization is derived from the cycloadduct formed from 2-fluorofuran. As the isodesmic equations in Scheme 23 show, the greater product stabilization was traced to a preference of the electronegative halogen to be attached to a more highly alkylated carbon framework in the cycloadduct (Eqs. 1–3). This propensity overrides the relatively weak preference of a halogen to be bonded to an sp^2 carbon as found in the 2-substituted furan over an sp^3 carbon as found in the product (Eq. 4).

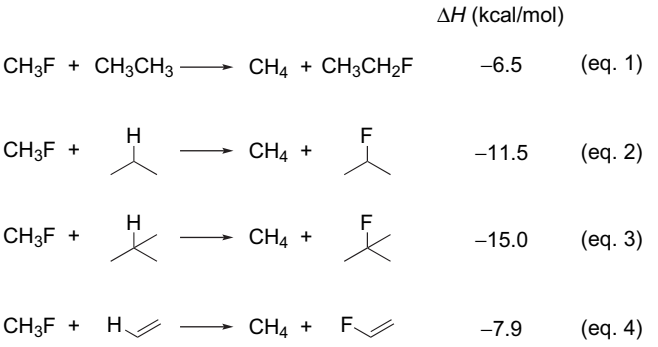
Table 3
Activation and reaction enthalpies (kcal/mol) for Diels–Alder reactions of furan or 2- or 3-substituted furan with ethene, computed at CBS-QB3 level of theory

Entry	X	Diene	$\Delta H^{\ddagger}$	Product	ΔH_{rxn}
1	H		20.5		−12.2
2	F	X	17.1	O X	−20.9
3	Cl		18.4		−17.1
4	Br		18.3		−17.3
5	CF3		18.1		−16.9
6	F		18.6		−16.2
7	Cl	X'	18.1	O	−16.0
8	Br		18.0	X'	−16.0
9	CF3		19.4		−14.1

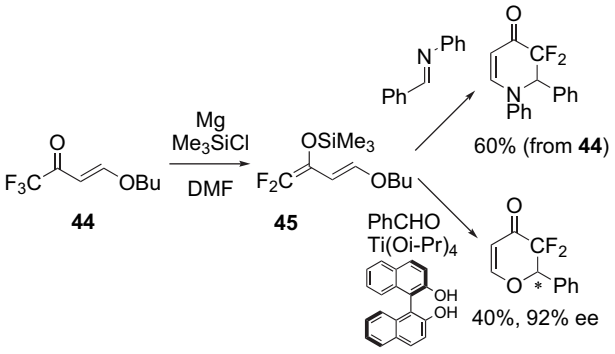
Table 4
Isodesmic equations that reveal reactant, transition structure and product stabilization induced by fluorine. All energies in kcal/mol



Entry	X	Diene	ΔH_R	ΔH_{TS}	Product	ΔH_P
1	H	X	0	0	O X	0
2	F	O	−5.3	−8.8		−14.0
3	H	X	0	0	O	0
4	F	O	−1.9	−3.7	X	−5.9



Scheme 23. Isodesmic equations that reveal magnitude of stabilization upon fluorine substitution at carbons of different extents of alkylation (Eqs. 1–3) or hybridization state (Eq. 4).

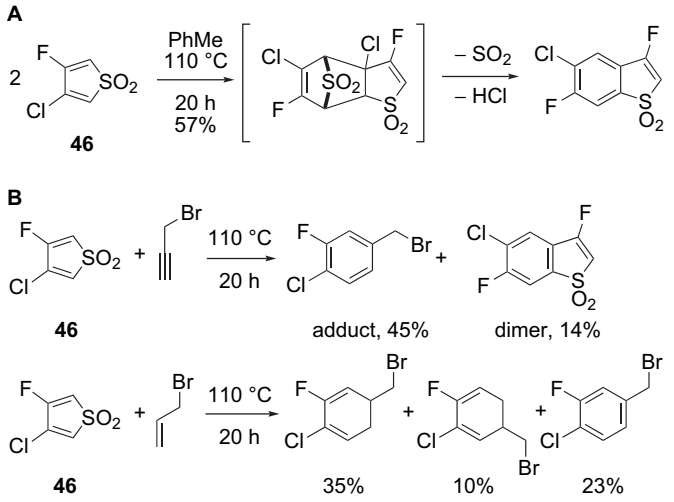


Scheme 24. *Hetero* Diels–Alder reactions of difluorinated Danishefsky's diene **45**.

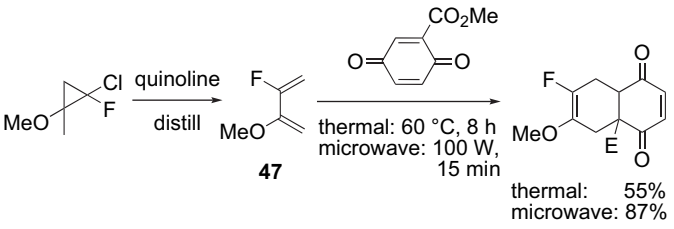
The difluorinated Danishefsky's diene **45** has been prepared from **44** and demonstrated to be a versatile building block for the synthesis of difluorinated dihydropyranones and dihydropyridones via a *hetero* Diels–Alder reaction.[70] A catalytic asymmetric variant has also been validated (Scheme 24).

3-Chloro-4-fluorothiophene-1,1-dioxide (**46**) is an effective reactant in Diels–Alder reactions acting as either a diene or a dienophile.[71] In the absence of an external dienophile, it condenses upon itself, with the chlorinated, rather than the fluorinated, double bond participating as the dienophilic component. The primary adduct undergoes aromatization with the elimination of sulfur dioxide and hydrogen chloride (Scheme 25A). The cycloadditions with alkynes as dienophiles are completely regioselective; those with alkenes proceed with moderate regioselectivities, accompanied with in situ aromatization in some cases (Scheme 25B).

2-Fluoro-3-alkoxy-1,3-butadienes such as **47** have been prepared using a cyclopropane ring-opening reaction.[72] Microwave-assisted Diels–Alder reactions of **47** with a range of symmetrical and unsymmetrical dienophiles give superior results than under thermal conditions (Scheme 26).[73]

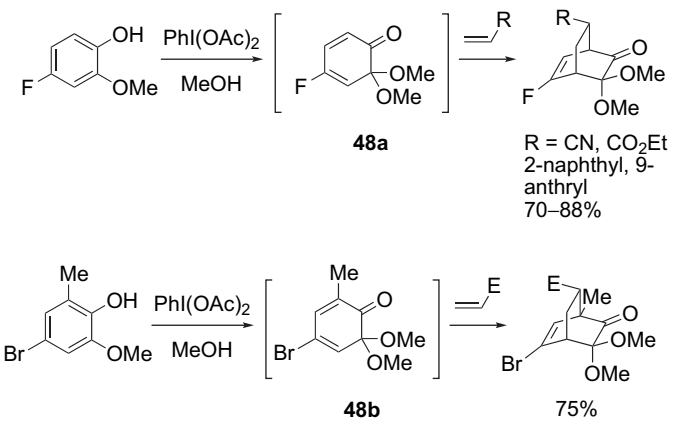


Scheme 25. (A) Dimerization of **46** in absence of external dienophile. (B) Reaction of **46** as fluorinated diene equivalent.



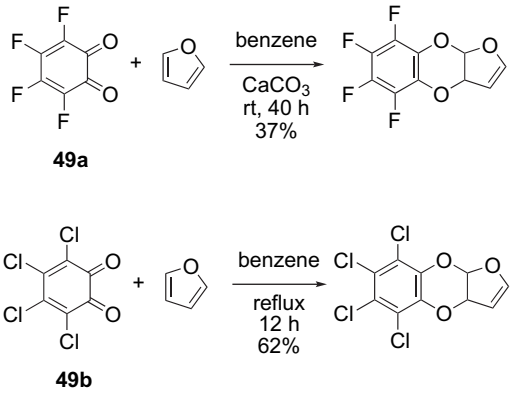
Scheme 26. Preparation of monofluorinated diene **47** and Diels–Alder reaction. E=CO_2Me.

A fluorinated masked *o*-benzoquinone **48a** has been prepared in situ from the oxidation of 4-fluoro-2-methoxyphenol and reacted with a range of dienophiles in normal electron-demand Diels–Alder reactions (Scheme 27).[74] The regio- and stereoselectivities are high. The impact of the fluoro substituent on the efficacy of the reaction is minimal, as the reaction of **48b** containing a bromo substituent proceeds with a similar yield.[75]



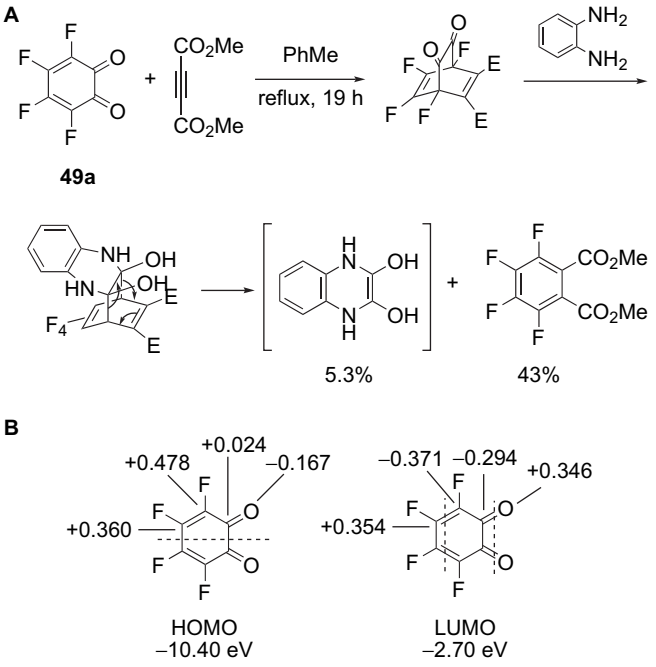
Scheme 27. Generation and Diels–Alder reactions of fluorinated (**48a**) and brominated (**48b**) masked *o*-benzoquinone. E=CO_2Me.

In their cycloadditions with dienophiles, *o*-benzoquinones can participate as a diene through its carbon termini or as a *hetero* diene through its carbonyl oxygens. With furan as the dienophile component, the fluorinated **49a**[76] and chlorinated **49b**[77] react as a *hetero* diene, and give the corresponding benzodioxins (Scheme 28), but the parent *o*-quinone leads to an intractable mixture.



Scheme 28. *Hetero*-Diels–Alder reactions of tetrafluorinated (**49a**) and tetrachlorinated (**49b**) *o*-benzoquinones.

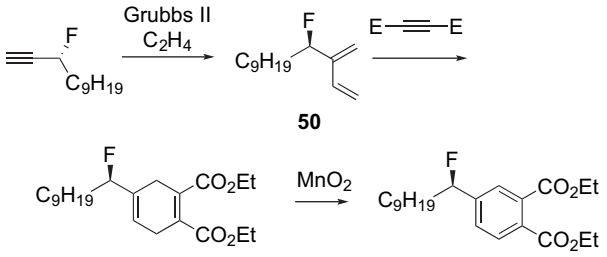
The relative preference for the competing *carbo* and *hetero* Diels–Alder pathways as the dienophile component is changed was examined by Lemal experimentally and computationally (Schemes 28 and 29).[76] The *hetero* Diels–Alder pathway was computed to be thermodynamically favoured in all of the cases studied, because it generates an aromatic ring in the product. As shown in Scheme 28, this was borne out by the cycloaddition of **49** and furan. However, the Diels–Alder products were obtained with all of the alkyne dienophiles and a number of alkene dienophiles studied. For example, the cycloaddition of **49a** with dimethyl acetylenedicarboxylate (DMAD) furnishes the *carbo* Diels–Alder adduct, which leads to dimethyl tetrafluorophthlate as the major product upon attempted derivatization by *o*-phenylenediamine (Scheme 29A). This Diels–Alder preference is kinetic in nature, and several factors were put forward by Lemal for its explanation. Filled-orbital repulsion at the electron-rich oxygen atoms would increase the activation barrier for the *hetero* pathway, while the Diels–Alder route would be favoured by the kinetic advantage of rehybridization at carbon of the C–F bonds from sp^2 to sp^3 and by the larger orbital coefficients at the carbon termini than at the oxygens (Scheme 29B). In the case of the cycloaddition using DMAD, the frontier orbital interaction



Scheme 29. (A) Diels–Alder reaction of **49a**. E=CO_2Me. (B) AM1 frontier orbital energies and coefficients of **49a**.

HOMO(**49a**)–LUMO(DMAD) is of a similar magnitude to the HOMO(DMAD)–LUMO(**49a**) interaction.

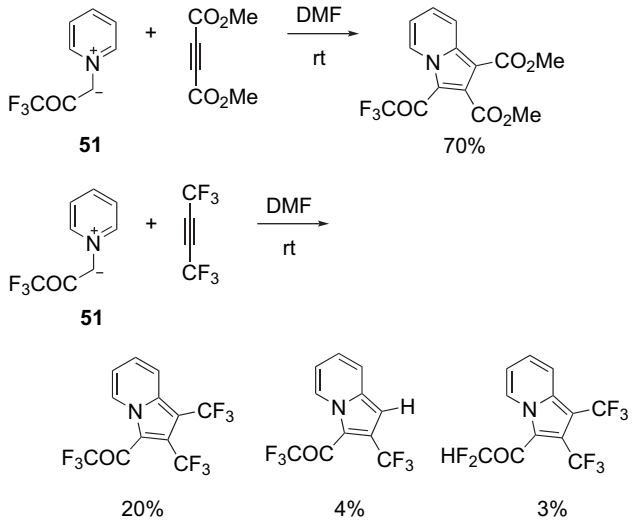
Optically active dienes with allylic monofluoro or *gem*-difluoro substituents on the side chain such as **50** can be accessed from the corresponding enantioenriched propargylic mono- or difluoride by enyne metathesis (Scheme 30).[78] These compounds react as the diene component in thermal Diels–Alder reactions, giving multi-substituted benzylic fluorides after aromatization.



Scheme 30. Preparation and Diels–Alder reaction of **50** and subsequent oxidation of the cycloadduct. Grubbs II=second-generation Grubbs' catalyst, E=CO_2Et.

2.2. [3+2] Cycloadditions

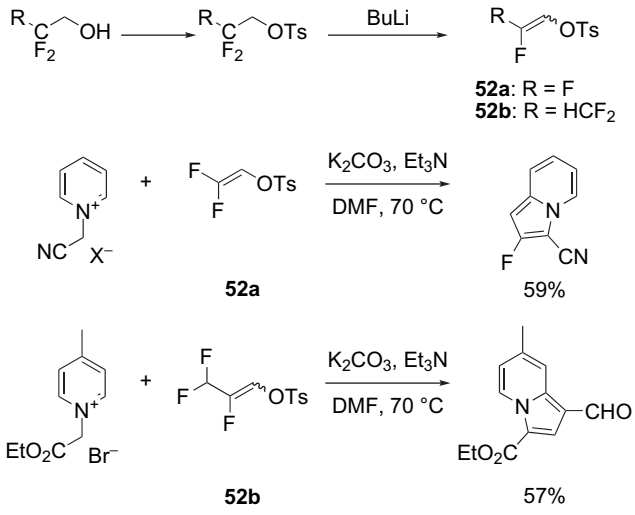
2.2.1. Additions to N-heterocyclic ylides. The addition of *N*-heterocyclic ylides and dipolarophiles gives rise to a variety of nitrogen-based heterocycles. Initial efforts by Banks to adapt this cycloaddition to synthesize fluorine-containing analogues of these nitrogenated heterocycles, using either a fluorinated dipolarophile or dipole, often resulted in complex product mixtures.[79–83] For instance, in the cycloaddition of the trifluoromethylated pyridinium *N*-ylide **51**, the use of DMAD as the dipolarophile gives good yields in the desired reaction, but with perfluoro-2-butyne a more complex product distribution was observed (Scheme 31).[80]



Scheme 31. Banks' initial efforts using trifluoromethylated reactants in [3+2] cycloadditions.

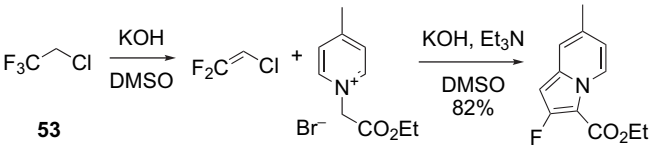
More recently, several industrially available fluorinated compounds were tested as precursors to a broader range of fluorinated dipolarophiles. Fluorinated alkenyl tosylates **52a**,**b**, prepared from fluorinated alcohols,[84] have been engaged as dipolarophiles in the cycloadditions with *N*-ylides to give mono- or nonfluorinated indolizines and their derivatives after elimination of HF and/or TsOH (Scheme 32).[85]

The commercially available hydrofluorocarbons, HCFC-133a (1-chloro-2,2,2-trifluoroethane, **53**) and HFC-134a (1,1,1,2-tetrafluoro-



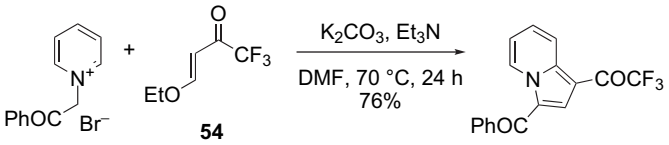
Scheme 32. Preparation of fluorinated alkenyl tosylates **52** and [3+2] cycloadditions.

ethane), furnish, upon base-induced elimination of HF, difluoroohaloethene intermediates, which react with *N*-heterocyclic ylides, giving 2-fluoroindolizines and related compounds (Scheme 33).[86] Other light-weight fluoroalkenes have also been used as fluorinated dipolarophiles.[87,88]



Scheme 33. [3+2] Cycloaddition of chlorodifluoroethene, derived from **53**, with *N*-ylide.

Trifluoroacetyl-substituted indolizines were regiospecifically accessible by the same methodology using fluorinated push–pull alkenes such as **54** as dipolarophiles (Scheme 34).[89]

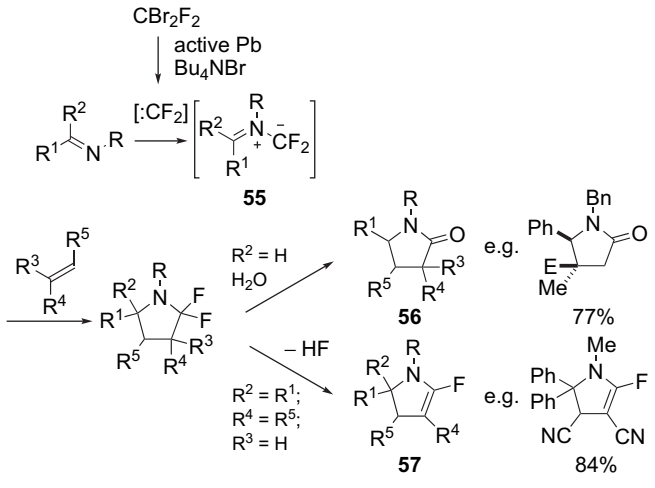


Scheme 34. [3+2] Cycloadditions using push–pull fluorinated alkene **54**.

The use of dipolarophiles bearing a polyfluorinated fluoroalkyl chain has also been described.[90–92]

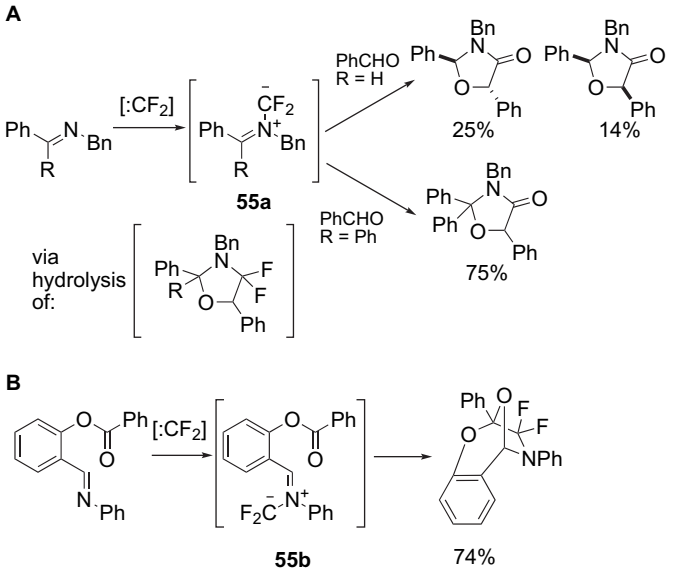
2.2.2. Additions to azomethine ylides. The chemistry of fluorine-containing azomethine ylides has been systematically studied by Khlebnikov and co-workers. Difluorocarbene can be generated by the reduction of dibromodifluoromethane with active lead in the presence of tetrabutylammonium bromide. Fluorinated azomethine ylides **55** are formed from the addition of difluorocarbene and various imines (Scheme 35).[93] Intermediates of the type **55** react as useful 1,3-dipoles towards electron-deficient alkenes in stereospecific [3+2] cycloadditions. The primary cycloadducts, difluorinated pyrrolidines, can be transformed into multiply substituted 2-pyrrolidinones **56**[93] or fluoropyrrolines **57**,[94] depending on the starting materials.

Aldehydes are also suitable dipolarophiles in [3+2] cycloadditions towards ylides **55a** derived from acyclic aldimines or



Scheme 35. Generation of difluorinated azomethine ylides **55** and [3+2] cycloadditions yielding as final products nitrogen-based heterocycles **56** and **57**. E=CO_2Me.

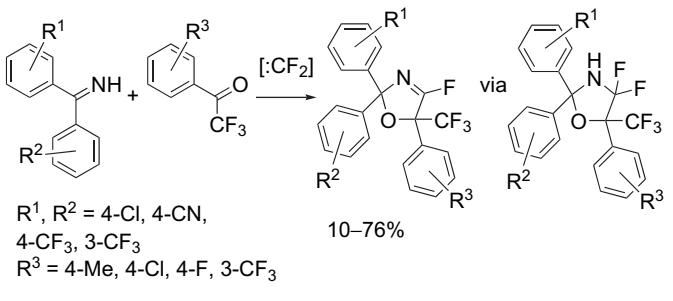
ketimines (Scheme 36A). Oxazolidinones are formed after hydrolysis of the *gem*-difluorinated oxazoline adduct.[95] The cycloadditions provide only one regioisomer, although the *endo*/*exo* selectivity is low when aldimines are used. Ester carbonyls were also engaged in intramolecular 1,3-dipolar cycloadditions of **55b** with complete regioselectivity (Scheme 36B).[96]



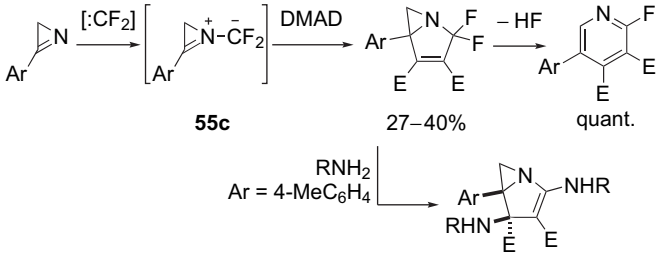
Scheme 36. [3+2] Cycloadditions of difluorinated azomethine ylides with (A) aldehydes and (B) esters.

This method has provided entry to a new class of fluorinated heterocycles, 4-fluoro-3-oxazolines, starting from difluorinated *NH*-azomethine ylides and trifluoroacetophenones (Scheme 37).[97]

Azomethine ylides **55c** with the C–N bond constrained in an aziridinum ring can also be generated from the appropriate 3-aryl-2*H*-azirines (Scheme 38).[98] These reactive intermediates react with DMAD and benzaldehyde regioselectively, giving difluorinated [5,3]-fused heterocycles as cycloadducts, which are amenable to transformations in which the aziridine ring can be preserved. By the same method, monofluorinated azomethine ylides can be generated from imines and dibromofluoromethane.[99,100] These species can be trapped by electron-poor alkenes or alkynes in a [3+2] cycloaddition, yielding pyrroles or their derivatives after in situ elimination of HF.

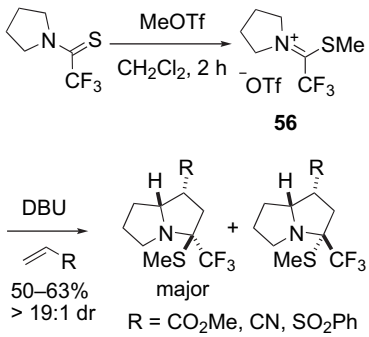


Scheme 37. Access to 4-fluoro-3-oxazolines by [3+2] cycloadditions of difluorinated azomethine ylides.



Scheme 38. [3+2] Cycloaddition of difluorinated azomethine ylide with C–N bond constrained in aziridinum ring, and further transformations of cycloadduct. E=CO_2Me.

Azomethine ylides such as those derived from **56** react with electron-poor alkenes in a highly diastereoselective manner (Scheme 39).[101]



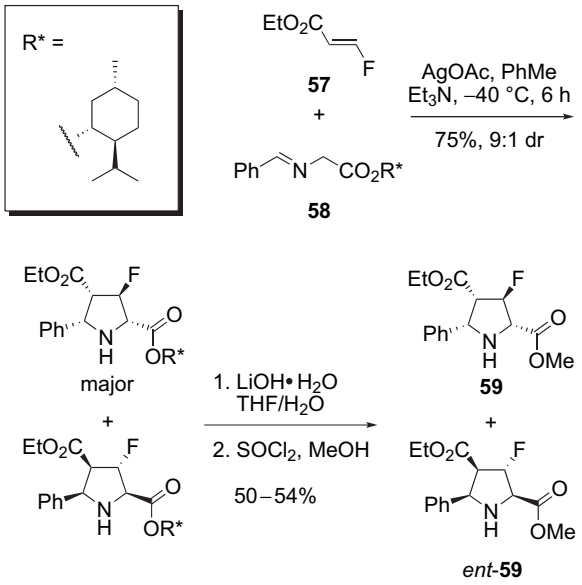
Scheme 39. Generation of trifluoromethylated azomethine ylide **56** and diastereoselective [3+2] cycloaddition with alkenes.

Enantioenriched fluorinated proline derivatives such as **59** can be directly constructed by 1,3-dipolar cycloadditions of fluoroalkene **57** with an azomethine ylide (**58**) bearing a menthol-based chiral auxiliary (Scheme 40).[102]

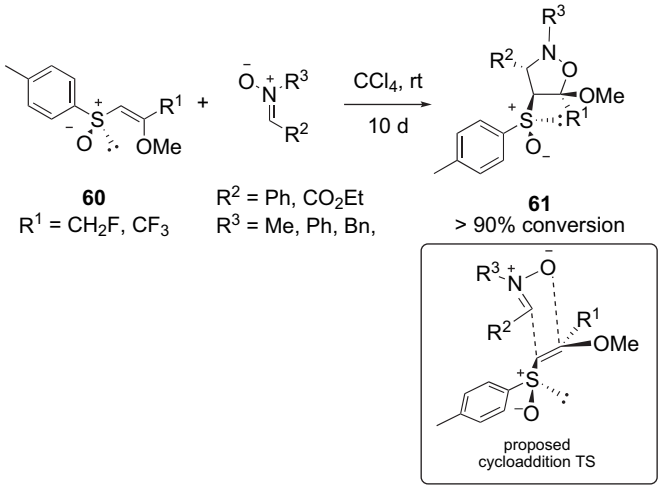
2.2.3. Additions to nitrones. The enantiopure *S*-chiral compounds **60** containing an allylic fluoride or a trifluoromethyl group display very high π-facial selectivities in their 1,3-dipolar cycloadditions to nitrones, giving the chiral fluorinated isoxazolidines **61** as the sole products in high conversion (Scheme 41).[103]

Homochiral allylic fluorides can also be engaged in 1,3-dipolar cycloadditions with nitrones to give isoxazolidines with high *endo*/*exo* selectivity, the sense of which depends on the structure of the allylic fluoride.[104] Reductive N–O bond cleavage, which affords fluorinated enantiopure amino polyols, has also been demonstrated.

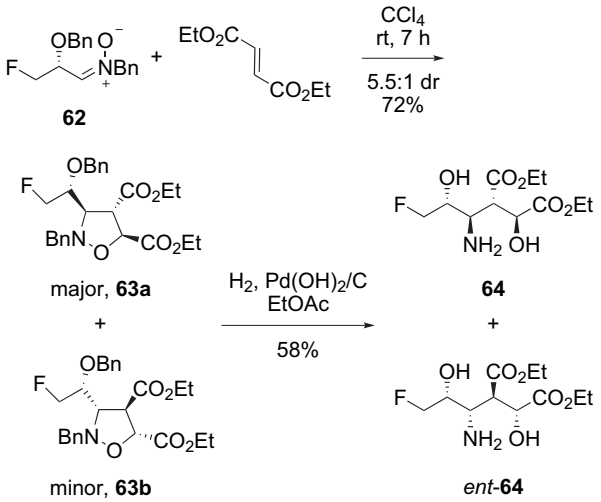
Enantiopure fluorinated isoxazolidines **63** and their derivatives can also be accessed by placing the fluoro substituent on a homochiral nitrone such as **62** (Scheme 42).[105] These reactions are



Scheme 40. Auxiliary-mediated asymmetric [3+2] cycloaddition of **58** to construct enantioenriched fluorinated proline derivatives. 'dr' refers to diastereofacial selectivity of cycloaddition.



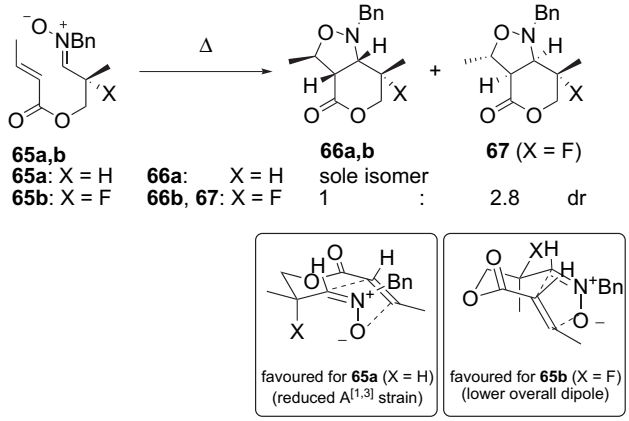
Scheme 41. Highly facial-selective [3+2] cycloadditions of homochiral fluorinated alkenyl sulfoxides **60** to form enantioenriched fluorinated isoxazolidines **61**.



Scheme 42. Cycloaddition route to enantiomerically pure fluorinated amino alcohols.

completely *endo*-selective, with moderate π-facial selectivities that were rationalized by invoking Felkin–Anh-based transition-state models on the nitrone. Reductive cleavage of **63** gives the highly functionalized and enantioenriched open-chain fluorinated amino alcohols **64**.

In their intramolecular 1,3-dipolar cycloadditions, the non-fluorinated nitrone **65a** and its 2-fluorinated counterpart **65b** give opposite diastereoselectivities. The intramolecular reaction of **65a** is highly stereoselective for the bicyclic isoxazolidine **66a**, while the reaction of the corresponding fluorinated nitrone **65b** moderately favours the formation of the diastereomer **67** over **66b** (Scheme 43).[106] The reversal in diastereoselectivity was explained by considering the reactive conformations. For the nonfluorinated substrate **65a**, the favoured conformer is the one in which the allylic-1,3 strain induced by the methyl substituent is lower. This conformer was thought to be disfavoured in the presence of a fluoro substituent, due to dipole repulsion between the fluorine and the nitrone oxygen atoms. This leads to the ring-flipped conformer reacting preferentially, giving the observed diastereomer **67**. The same effect was postulated to account for the diastereochemical outcome of the intermolecular cycloadditions of 2-hydro- and 2-fluoronitrones with ethyl vinyl ether.[107]

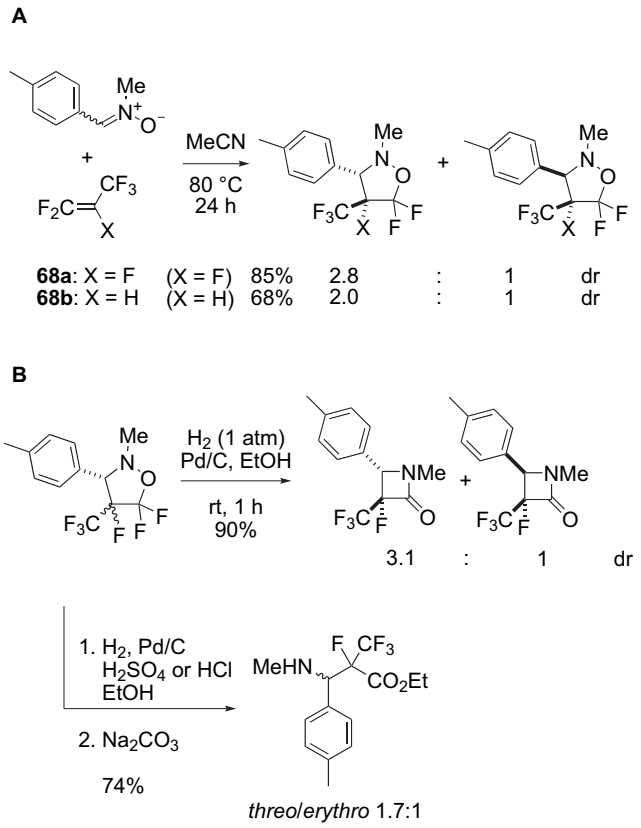


Scheme 43. Diastereoselectivities of intramolecular 1,3-dipolar cycloadditions involving nonfluorinated (**65a**) or fluorinated nitrone (**65b**).

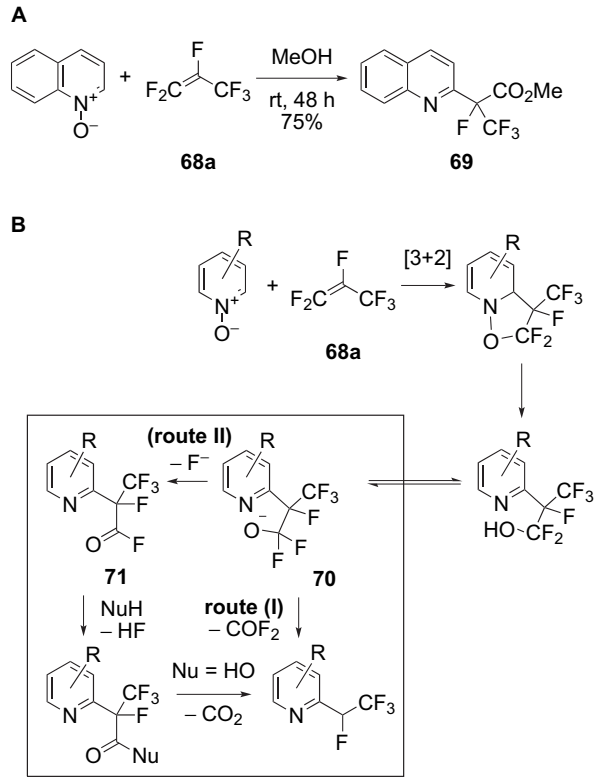
The 1,3-dipolar cycloadditions of nitrones and polyfluoroalkenes **68a**,**b** proceed with complete regiocontrol and moderate *endo* stereoselectivities (Scheme 44A), except when the nitrone is cyclic, in which case complete *exo*-selectivity was observed. Fluorinated β-lactams and β-amino acids can be prepared by scission of the N–O bond within the isoxazolidine cycloadducts under mild conditions (Scheme 44B).[108]

The cycloadditions of *N*-heterocyclic *N*-oxides and hexafluoropropene **68a** have been re-investigated and its synthetic scope expanded.[109] The cycloaddition of quinoline *N*-oxide and **68a** in the protic solvent, methanol, gives exclusively the methyl ester **69** (Scheme 45A). The authors noted that this observation is not consistent with the mechanism previously proposed by Banks and co-workers,[110] who suggested a direct collapse of **70** into the end product with elimination of difluorophosgene (Scheme 45B, route I). A modified mechanism has thus been put forward,[109] which involves the elimination of fluoride to form the acid fluoride **71** (route II), instead of expulsion of difluorophosgene. Facile hydrolysis and decarboxylation in situ afford the final product, as observed by Banks. The synthetic implications of the revised mechanism were exemplified by a 3-component reaction for a broad variety of *N*-heterocyclic *N*-oxides, fluorinated dipolarophiles and nucleophilic quenches.[109]

The thermal cycloadditions of the difluoromethylenecyclopropane **72** with nitrones give spiro heterocycloadducts, which

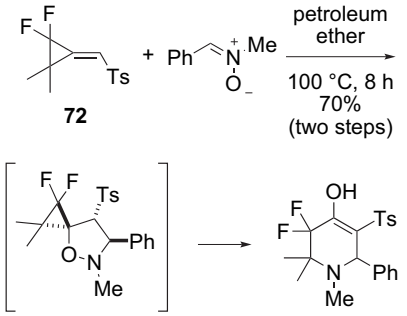


Scheme 44. (A) 1,3-Dipolar cycloadditions of fluorinated alkenes **68** to nitrone. (B) Scission of N–O bond in [3+2] cycloadducts yielding fluorinated β-lactams and β-amino acids.



Scheme 45. (A) Synthesis of quinolinyl perfluoropropionic ester by [3+2] cycloaddition. (B) Banks' mechanism (route I) and revised mechanism (route II) showing different proposed routes from **70** to final product.

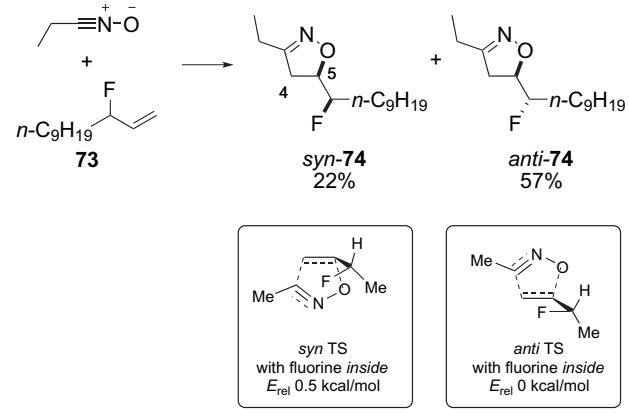
can rearrange, in one pot, into highly substituted difluorinated tetrahydropyridinols (Scheme 46).[111]



Scheme 46. Highly substituted difluorinated tetrahydropyridinols by [3+2] cycloadditions of difluoromethylenecyclopropane **72**.

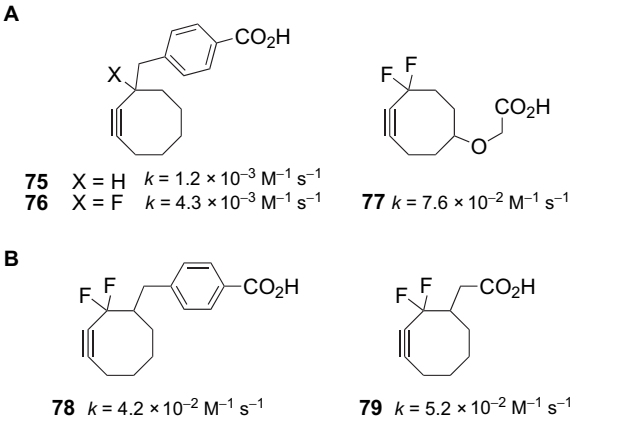
2.2.4. Additions to nitrile oxides. Optically active propargylic fluorides of the type **28** prepared by Grée react with nitrile oxides as 1,3-dipoles with high regioselectivity.[50]

The [3+2] cycloadditions of nitrile oxides to chiral allylic fluorides were studied regarding their regio- and stereoselectivity.[112] The reactions of propionitrile oxide to allylic fluorides **8** and **73** were examined. These reactions consistently favour the 5-substituted cycloadducts. For **73**, only *syn*-**74** and *anti*-**74** were obtained as a 1:2 mixture (Scheme 47). Computational modelling of the cycloaddition transition states revealed the '*inside* fluoro effect', as the fluorine and the alkyl group prefer to occupy the *inside* and the *anti* positions, respectively. As noted by the authors, these results are fully consistent with previous conclusions based on nitrile oxide cycloadditions with 3-alkoxy-1-butenes.[113]



Scheme 47. Experimental results of cycloaddition of **73** to propionitrile oxide, and corresponding computational transition structures.

2.2.5. Additions to azides (click chemistry). The Huisgen 1,3-dipolar cycloaddition of azides and alkynes to form triazoles has received revived attention in recent years.[114,115] In chemical biology, the possibility of using strained cyclooctynes to effect metal-free cycloadditions has been explored. The effects of fluorine incorporation into the alkyne component on the efficacy of tagging azide-containing target biomolecules have been studied recently. Model reactions of **75**–**77** and benzyl azide revealed an enhanced reactivity with increasing number of propargylic fluoro substituents (Scheme 48A).[116,117] In particular, the difluoromethylene group in **77** has been featured as a biocompatible electron-withdrawing group that activates its neighbouring alkyne towards cycloaddition without promoting Michael-type alkylations, as would be expected from a conjugating carbonyl group. Specific protein labelling, live cell labelling and dynamic in vivo imaging have been demonstrated.[117] A couple of synthetically more accessible,

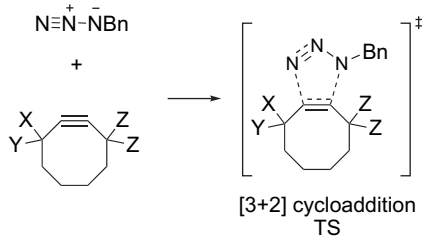


Scheme 48. (A) Second-order rate constants for cycloadditions of **75**–**77** with benzyl azide in deuterated acetonitrile. (B) Second-order rate constants for cycloadditions of second-generation difluorinated cyclooctynes **78** and **79** with benzyl azide in deuterated acetonitrile.

second-generation difluorinated cyclooctynes **78** and **79** also performed efficiently as copper-free click reagents (Scheme 48B).[118]

Different aspects concerning the energetics of these so-called 'strain-promoted' click reactions were computationally analyzed by Houk and co-workers.[119] The reactivity differences observed in general for this series of reactions as the structures of the azide or alkyne component varied were found to be more closely related to the differences in distortion energies than to the amount of strain relief upon product formation. Among other substituents including methoxy, chloro and cyano, it should be noted that fluoro substituents adjacent to the triple bond in cyclooctyne bring about the largest activating effect in the cycloaddition with benzyl azide, as shown by computed free energies of activation in Table 5.[120] The magnitude of this effect increases with the number of fluoro substituents. By considering the distortion/interaction model,[121] these results were explained in terms of lower distortion energies, primarily of the 1,3-dipole, as the transition states become earlier when fluorinated reactants are employed. Upon fluorination of the dipolarophile, the HOMO is lowered the most, while the LUMO is lowered to a lesser extent.[120]

Table 5
Free energies of activation ($\Delta G^{\ddagger}$), activation barriers ($\Delta E^{\ddagger}$) and dissection into distortion ($\Delta E_d^{\ddagger}$) and interaction energies ($\Delta E_i^{\ddagger}$) (all in kcal/mol) for 1,4-regioisomeric transition states of cycloaddition of benzyl azide to cyclooctynes



Entry	X	Y	Z	$\Delta G^{\ddagger}$[a]	$\Delta E^{\ddagger}$[b]	$\Delta E_d^{\ddagger}$[b] (dipole)	$\Delta E_d^{\ddagger}$[b] (alkyne)	$\Delta E_i^{\ddagger}$[b]
1	H	H	H	24.9	11.6	17.5	1.6	−7.5
2	H	CN	H	23.9	9.5	16.7	1.7	−8.9
3	Cl	Cl	H	24.7	9.8	16.1	2.7	−8.9
4	H	F	H	23.7	10.0	15.9	1.8	−7.7
5	F	F	H	23.0	10.2	15.4	1.8	−8.1
6	F	F	F	20.9[c]	—	12.7	1.6	—

[a] Computed at SCS-MP2/6-31G(d)//B3LYP/6-31G(d) level of theory for 298 K, including solvation corrections in acetonitrile computed by CPCM at B3LYP/6-31G(d) level, unless otherwise stated.
[b] Computed by SCS-MP2/6-31G(d)//B3LYP/6-31G(d).
[c] Computed by B3LYP/6-31+G(d,p) for 298 K with solvation corrections in water computed by CPCM at B3LYP/6-31+G(d,p) level of theory.

The cycloadditions of azide or alkyne components containing fluorine, especially the fluorine-18 isotope widely used in positron emission tomography, constitute an active area of biomedical research beyond the scope of this review.[122–125] Click chemistry employing perfluoroalkylated azides has also been featured in polymer sciences very recently.[126]

3. Sigmatropic rearrangements

3.1. Cope rearrangements and variants

The mechanistic impact of fluoro substitution on the Cope rearrangement has been extensively studied. Table 6 lists the activation parameters for various Cope rearranging systems **80a**,**b**–**88a**,**b** obtained by experiment or computation. It is well recognized that, for a difluoromethylene group, the rehybridization of carbon from sp^2 to sp^3 is thermodynamically favoured.[127] By experimentally determining the activation parameters of various fluorinated 1,5-hexadienes, Dolbier showed that such a transformation is also kinetically favoured, as the activation enthalpies decrease with increasing geminal fluoro substitution (compare entry 1 with entries 2 and 3). A 3-fluoro substituent (entry 4) has little kinetic effect on the Cope rearrangement, and the product distribution is largely dictated by thermodynamic stability.[128]

The concerted transition state of a generic Cope rearrangement can adopt the chair or the boat as limiting conformations. The deuterated or fluorinated 1,4-bis(methylene)cyclohexenes **84a**, **85a** and **86a** were designed to rearrange through a boat-like transition state. Their activation parameters have been measured (entries 5–7, Table 6).[132]

In another experimental study, the 2,2′-bis(methylene)cyclopentane system was devised as an ideal mechanistic probe for the Cope rearrangement, as the *dl* and the *meso* isomers are constrained to rearrange unambiguously via, respectively, a chair- and a boat-like transition state (Scheme 49).[133]

The terminal *gem*-difluorinated analogues of this system, *dl*- and *meso*-**88a**, were used by Dolbier to delineate the impact of fluoro substitution on these two mechanistic scenarios.[130] The activation enthalpy for *dl*-**88a** (22.4 kcal/mol; entry 9, Table 6) proceeding through a chair-like transition state is lower than that for the parent compound *dl*-**87a** (28.0 kcal/mol; entry 8, Table 6), as expected from the perturbation by fluoro substitution in open-chain 1,5-hexadienes. However, in the *meso* series where a boat-like transition state is enforced, fluorine substitution has an inhibitory kinetic effect on the rearrangement, reflected in the increased enthalpy of activation of *meso*-**88a** (49.5 kcal/mol; entry 11, Table 6), compared to *meso*-**87a** (41.8 kcal/mol; entry 10, Table 6). As asserted by the authors, the contrasting reactivities of the pair of fluorinated *dl* and *meso* isomers are due to the steric and electrostatic effects of the *cis* fluoro substituents on C1 and C6 in the stringent environment imposed by the *meso* system. The positive entropy of activation of *meso*-**88a** (8.1 eu) is remarkable for a Cope rearrangement, as this indicates that fluorine substitution at the rearranging termini causes the transition state to become more dissociative than pericyclic in character.

Scheme 50 outlines the three limiting cases of the mechanism of a Cope rearrangement. The rearrangement can proceed through a concerted transition state involving delocalization across all of the six carbon atoms (**II**) or two alternative radical intermediates involving either two non-interacting allyl radicals (**I**) or a cyclohexane-1,4-diyl radical (**III**).[135]

The distinction and assignment of the possible mechanisms have been addressed computationally,[135] and the effects of fluoro substitution on the Cope rearrangement have been examined by Houk and co-workers.[134] The energetics of the rearrangements of **80**–**82a** and *dl*-**87**–**88a** can be modelled by the restricted B3LYP

Table 6
Experimental and computed activation parameters for Cope rearrangements of various deuterated or fluorinated 1,5-hexadienes (**80**–**88**)

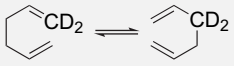
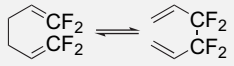
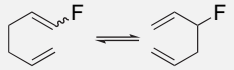
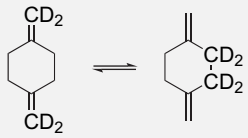
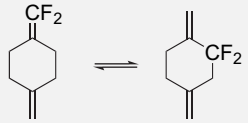
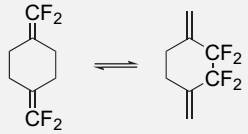
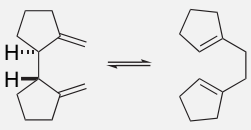
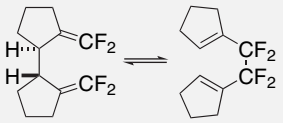
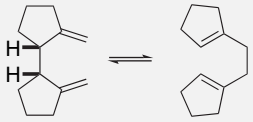
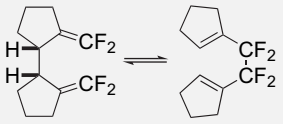
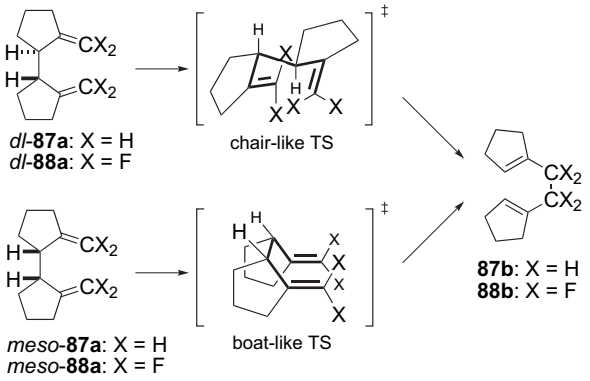
Entry		Experimental values $\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Computed values [a] $\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Ref.
Open-chain 1,5-hexadienes						
1	 **80a** **80b**	33.5±0.5	−13.8±1	34.0, 34.8[b] (chair TS); 41.2, 41.1[b] (boat TS)	−8.1, −8.6[b] (chair TS); −6.1, −6.6[b] (boat TS)	129
2	 **81a** **81b**	32.0±0.7	−12.1±1.4	31.2, 33.0[b] (chair TS); 40.6, 41.2[b] (boat TS)	−10.8, −10.9[b] (chair TS); −8.0, −8.2[b] (boat TS)	130
3	 **82a** **82b**	29.9±0.2	−18.5±0.5	32.1, 34.2[b] (chair TS); 43.9, 44.3[b] (boat TS)	−14.0, −12.8[b] (chair TS) −8.8, −9.7[b] (boat TS)	130
4	 **83a** **83b**	33.8 (*E*); 33.9 (*Z*)	−14.1 (*E*); −14.0 (*Z*)	Not reported (*E*); 35.2 (chair TS) (*Z*);[b] 41.6 (boat TS) (*Z*)[b]	Not reported (*E*); −10.1 (chair TS) (*Z*);[b] −7.7 (boat TS) (*Z*)[b]	128
1,4-Bis(methylene)cyclohexanes						
5	 **84a** **84b**	44.4±1.8	−3.7±3.2	47.9 (boat TS)[b]	−2.2 (boat TS)[b]	131
6	 **85a** **85b**	40.8±0.5	−6.1±0.9	44.7 (boat TS)[b]	−5.9 (boat TS)[b]	132
7	 **86a** **86b**	40.7±0.5	−10.1±0.8	46.5 (boat TS)[b]	−3.6 (boat TS)[b]	132
2,2′-Bis(methylene)cyclopentanes						
8	 *dl*-**87a** **87b**	28.0±1.1	−11.4±2.6	27.0 (chair TS)	−5.6 (chair TS)	133

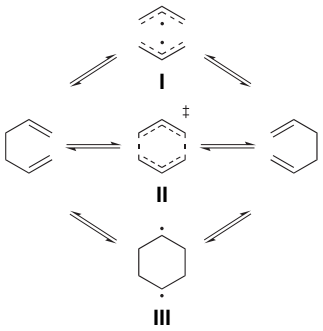
Table 6 (*continued*)

Entry		Experimental values $\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Computed values [a] $\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Ref.
9	 *dl*-**88a** **88b**	22.4±0.2	−17.5±0.4	24.2 (chair TS)	−8.5 (chair TS)	[130]
10	 *meso*-**87a** **87b**	41.8±0.5	−0.4±1.0	35.3 (boat TS)	−4.3 (boat TS)	[133]
11	 *meso*-**88a** **88b**	49.5±1.0	+8.1±1.7	39.8 (boat TS)	−3.6 (boat TS)	[130]

[a] Computed at B3LYP/6-31+G(d,p),[134] unless otherwise stated.
[b] Computed at B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d).[132]



Scheme 49. *dl* and *meso* isomers of fluorinated and nonfluorinated 2,2′-bis(methylene)cyclopentanes as mechanistic probes for Cope rearrangement.



Scheme 50. Canonical mechanistic descriptions of Cope rearrangement.

method. The activation enthalpies computed for the concerted pathway via a chair-like transition structure agree closely with the experimental values (entries 1–3, 8 and 9, Table 6). This confirms the reaction mechanism and demonstrates the enthalpic stabilization of the *gem*-difluoro substituents in these substrates. The hypothetical boat-like transition structure in the rearrangement of **82a** displays very close fluorine–fluorine contacts across the reacting bond, confirming Dolbier's conclusion[130] that this factor is significantly destabilizing to boat-like transition structures. The boat-like transition structures involving *meso*-**87**–**88a** cannot be adequately modelled using DFT, as substantially lower enthalpies of activation and more negative activation entropies were computed than measured experimentally (entries 10 and 11, Table 6). Dolbier modelled the Cope rearrangements of the open-chain 1,5-hexadienes and 1,4-bis(methylene)cyclohexenes (entries 1–7, Table 6),[132] using B3LYP with a more extended basis set. The activation enthalpies and entropies computed were similar to the results of Houk.

The effects of fluoro substituents on the reaction mechanism and energetics of the Cope rearrangement were found by Houk to depend on the position and extent of substitution. The more heavily fluorinated derivatives **89a**,**b** of hexa-1,5-diene (Fig. 3) favour radical pathways through cyclohexane-1,4-diyl radical intermediates (form **III** in Scheme 50). This was attributed to the preference of the fluorines to be attached to sp^3 carbons, as opposed to sp^2.

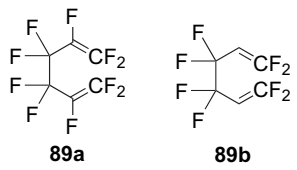
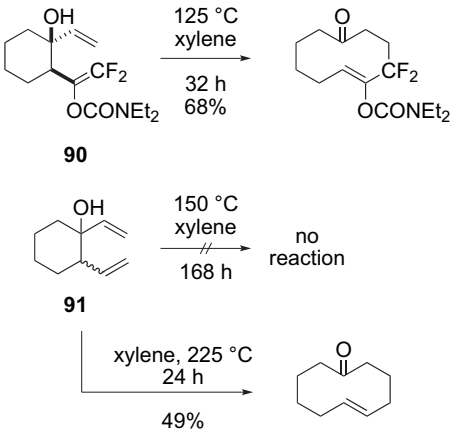


Figure 3. More heavily fluorinated hexa-1,5-dienes **89** for which Cope rearrangement mechanisms were computationally modelled.

The oxy-Cope rearrangement of *gem*-difluorinated divinylcyclohexanols such as **90** has been used to access selectively fluorinated cyclodecenones (Scheme 51).[136] The conversion of an sp^2-CF_2 group into an sp^3-CF_2 group provides the driving force necessary, as the nonfluorinated substrate **91** needs a higher temperature for the transformation.[137]



Scheme 51. Oxy-Cope rearrangements of *gem*-difluorinated divinylcyclohexanol **90** and nonfluorinated **91**.

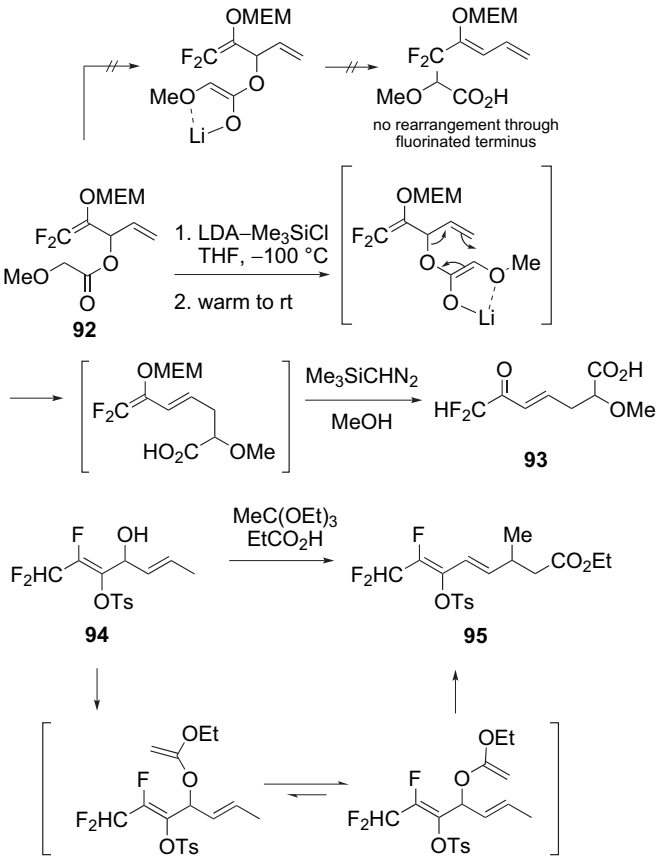
3.2. Claisen rearrangements and variants

The Claisen rearrangement and its variants constitute another synthetically significant class of pericyclic processes involving fluorinated building blocks. Two reviews published in the 1990s by leading practitioners in the field contain a substantial coverage of these transformations.[138–140] We therefore focus here on the recent progress reported since then.

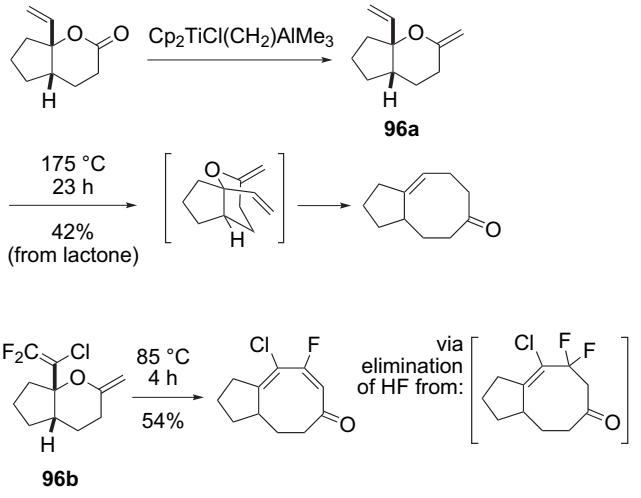
3.2.1. Systems containing fluoro substituents. As mentioned above, the advantage derived from the rehybridization of carbon in a difluoromethylene group from sp^2 to sp^3 serves to facilitate [3,3]-sigmatropic rearrangements of some substrates containing this group. In Claisen rearrangements, *gem*-difluorination on the double bond of the *vinylic* terminus exerts an accelerative effect, but at the *allylic* terminus its effect on the reaction rates is minimal.[139] The latter observation was reinforced by the chemical behaviour of **92**, which bears a difluoromethylene group at its allylic end. Two rearrangement pathways are possible for **92**, involving either the *gem*-difluorinated or the nonfluorinated terminus (Scheme 52).[141] Under ester-enolate Claisen conditions, no product expected from the former route occurs; the rearrangement takes place exclusively through the nonfluorinated terminus, giving **93** after deprotection. The Johnson–Claisen rearrangement of **94** (Scheme 52), which could similarly follow two chemodistinct pathways, was found to proceed exclusively through the nonfluorinated allylic terminus, giving the rearranged product **95**.[142]

An instance where difluorination on the allylic terminus results in a more facile Claisen rearrangement was documented by Percy and Dimartino.[143] The difluorinated substrate **96b** rearranges smoothly with concomitant HF elimination at 85 °C within 4 h, whereas the nonfluorinated substrate **96a** is much less reactive and requires a temperature 90 °C higher and a longer reaction time (Scheme 53).

Advances in Claisen rearrangements of fluoro-substituted substrates continue to exploit the sp^3-hybridization preference of carbon in a difluoromethylene group.[144] The Claisen rearrangements of a series of difluorovinyl allyl ethers were featured as a key step in a short route to access direct precursors to carbocyclic analogues of saccharides in which the endocyclic oxygen is replaced by a difluoromethylene group (Scheme 54).[145] The trifluoromethylated precursor **97** was conveniently prepared from trifluoroethanol. The Claisen substrate **98** was formed by dehydrofluorination/lithiation of **97**, followed by quenching with acrolein. The Claisen rearrangement took place in refluxing chloroform. Reduction of the rearranged product to form **99**, followed by ring-closing metathesis, furnished **100a**,**b**, which are advanced precursors to fluorinated carbasugars.

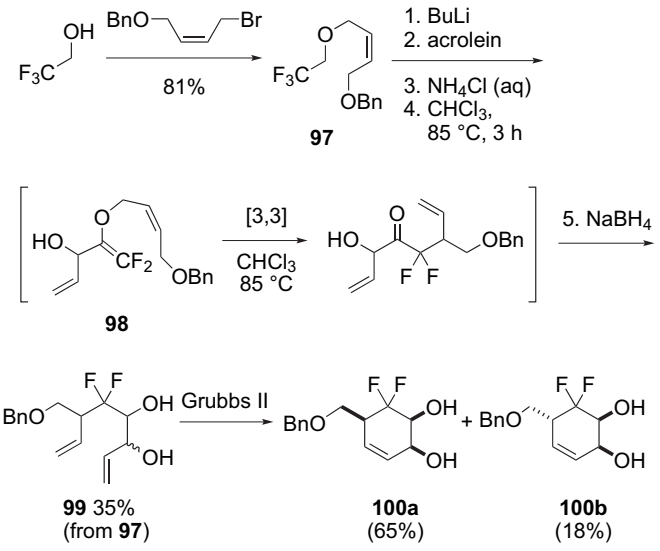


Scheme 52. Chemoselectivities of **92** and **94** both favouring rearrangements through nonfluorinated allylic terminus.

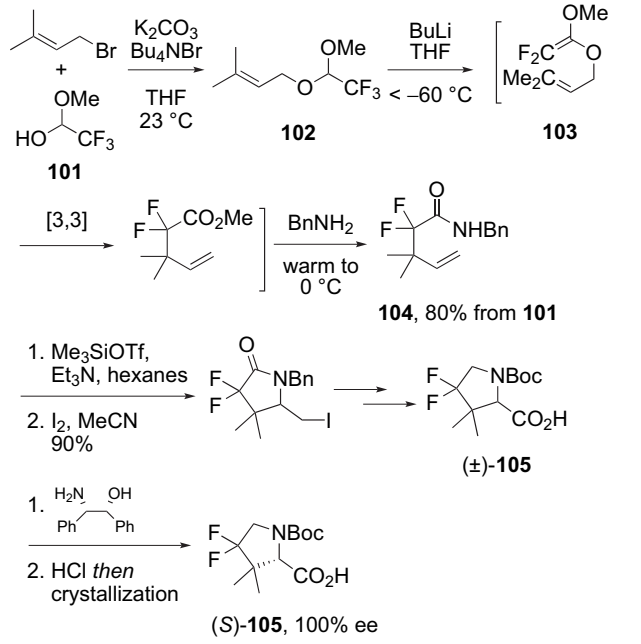


Scheme 53. Rapid Claisen rearrangement of fluorinated **96b** involving ring expansion.

An *N*-protected 4,4-difluoro-3,3-dimethylproline derivative (*S*)-**105**, a key building block for several second-generation HIV protease inhibitors, was made available through a concise and industrially scalable sequence with a Claisen rearrangement and an iodolactamization as the key steps (Scheme 55).[146] The precursor to the Claisen substrate **102** was easily assembled using trifluoroacetaldehyde methyl hemiacetal (**101**) as the source of fluorine. The rearranging system **103** was generated by basic dehydrofluorination of **102**. The methoxy group in **102** is essential, since it suppresses side reactions by blocking a potential lithiation site during dehydrofluorination. Iodolactamization of the amide **104** formed from the rearranged product delivered the



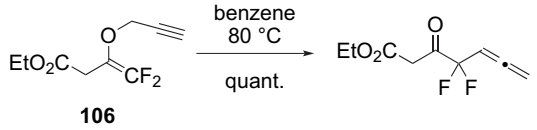
Scheme 54. Concise preparation of compounds **100a**,**b**, precursors to carbasugars, upon Claisen rearrangement of **98**. Grubbs II=second-generation Grubbs' catalyst.



Scheme 55. Synthesis of difluorinated proline derivative (*S*)-**105**.

difluorinated pyrrolidine ring. Further functional-group changes, followed by a classical chemical resolution, afforded the enantiopure product (*S*)-**105**.

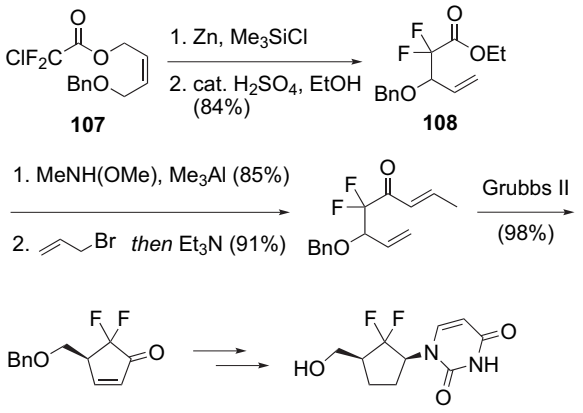
The Claisen rearrangement of the 1,1-difluorovinyl propargyl ether **106** furnishes an allenylic β-ketoester with a *gem*-difluoromethylene unit (Scheme 56).[147]



Scheme 56. Claisen rearrangement of **106** yielding difluoromethylenated allene.

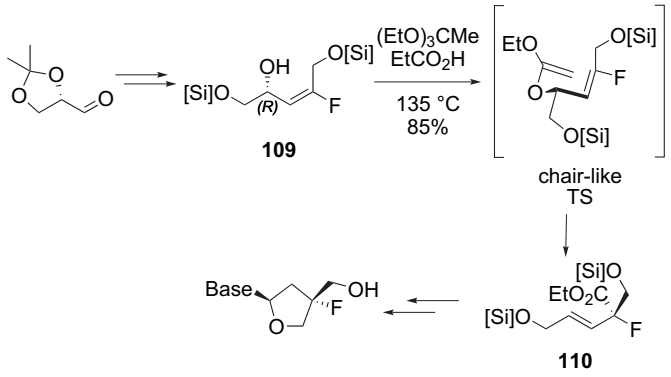
A direct and rapid route to α,α-difluoroacylsilanes by Claisen rearrangement has also been demonstrated.[148]

A Reformatsky–Claisen rearrangement of **107** was used to introduce a *gem*-difluoromethylene group regiospecifically. The product **108** was then elaborated to prepare a difluorinated sugar analogue used in the construction of 2′,3′-dideoxycarbocyclic nucleosides (Scheme 57).[149]



Scheme 57. Use of Claisen rearrangement in synthesis of fluorinated nucleoside analogues. Grubbs II=second-generation Grubbs' catalyst.

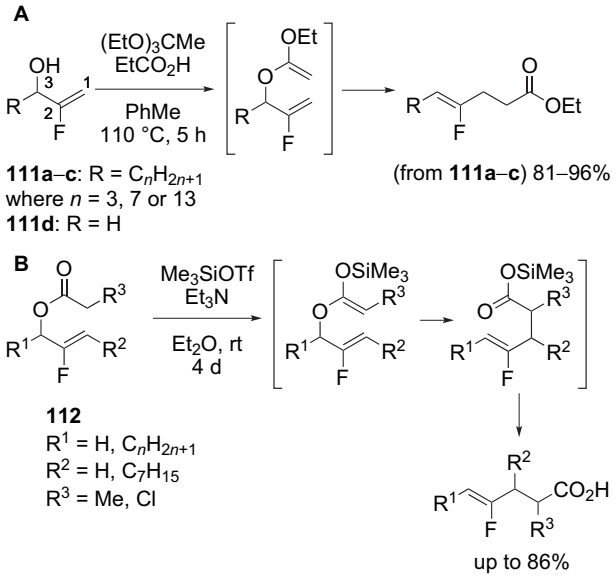
The Claisen rearrangement is also capable of installing a tertiary fluorinated stereocentre by virtue of its highly ordered chair-like transition state. For instance, effective 1,3-chirality transfer can be achieved from the starting allylic alcohol **109** to the resultant allylic fluoride **110** in the course of the preparation of homochiral fluoroapionucleosides from enantiopure starting materials (Scheme 58).[150,151]



Scheme 58. Efficient chirality transfer in Claisen rearrangement of **109** to form **110** proceeding through chair-like transition state. [Si]=*tert*-butyldimethylsilyl.

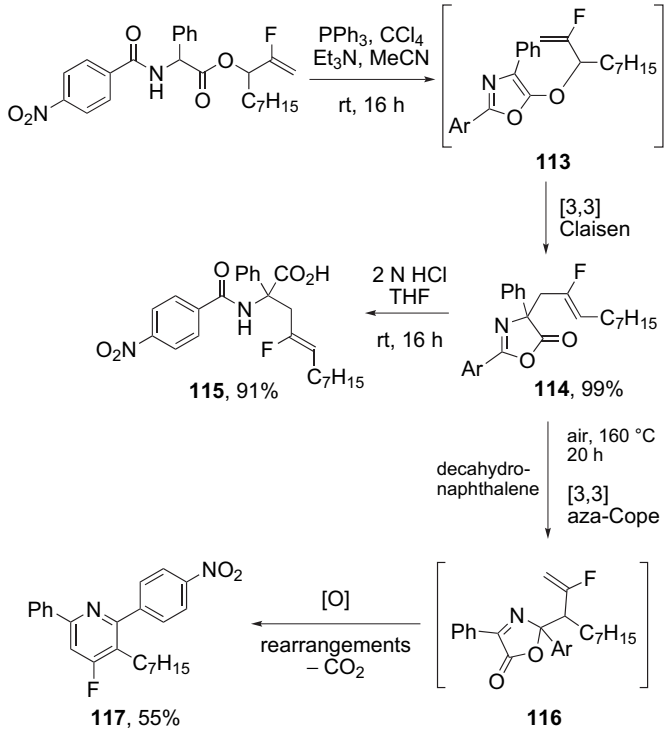
Alicyclic vinylic fluorides such as **111** have been subjected to the Johnson and Ireland variants of the Claisen rearrangement.[152] Structural constraints on the efficacy of this transformation were identified. Thus, under Johnson–Claisen conditions, **111a–c** substituted at C3 react, but not the C3-unsubstituted substrate **111d** (Scheme 59A). Allylic esters possessing a terminal or internal vinylic fluoride fragment **112** undergo the Ireland–Claisen rearrangement in which the stereochemical outcome is consistent with a chair-like transition state (Scheme 59B). The synthesis of γ-fluoro-α-amino acids by a Claisen rearrangement has also been reported.[153]

The analogous Claisen rearrangements of vinylic fluorides involving an aromatic oxazole derivative **113** have also been demonstrated.[154] The rearranged product **114** can be hydrolyzed to give **115**. In some cases, **114** can be subjected to a cascade process



Scheme 59. Claisen rearrangements of alicyclic vinylic fluorides.

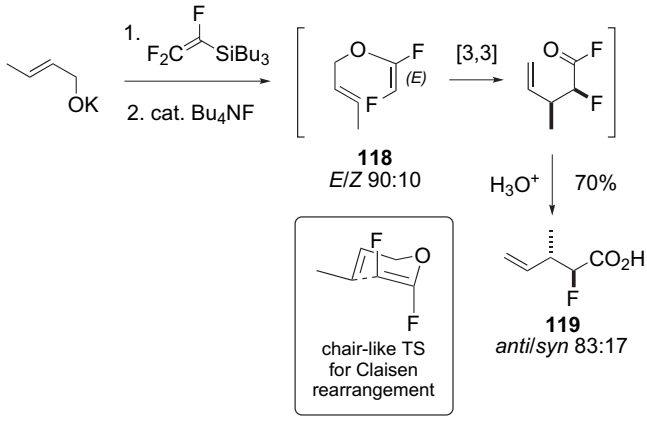
starting with an aza-Cope rearrangement to give **116**, which further rearranges to 2,6-diaryl-4-fluoropyridines **117** as final products (Scheme 60).



Scheme 60. [3,3]-Rearrangements of **113**. Ar=4-nitrophenyl.

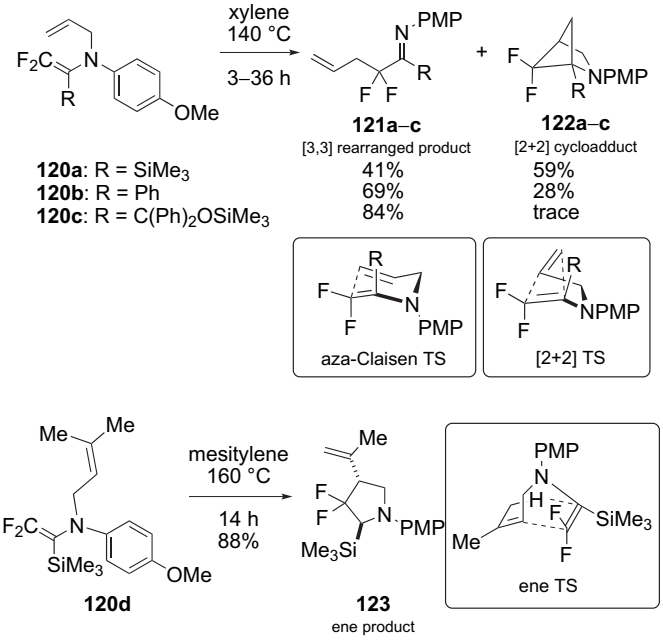
Allyl fluorovinyl ethers of the type **118** are precursors to α-fluoro β-substituted γ,δ-unsaturated carboxylic acids such as **119** using the Claisen rearrangement as the key step (Scheme 61).[155] The formation of **118**, and its rearrangement and subsequent hydrolysis can be carried out in one pot. The sequence can be extended to the synthesis of α-trifluoromethyl unsaturated acids and derivatives by using a suitable substrate.

While fluorinated allyl vinyl ethers are good substrates for the Claisen rearrangement, the corresponding amines are open to additional reaction paths. Under thermal conditions, depending on



Scheme 61. Claisen rearrangement of **118** as key step to form α-fluorinated unsaturated carboxylic acid **119**.

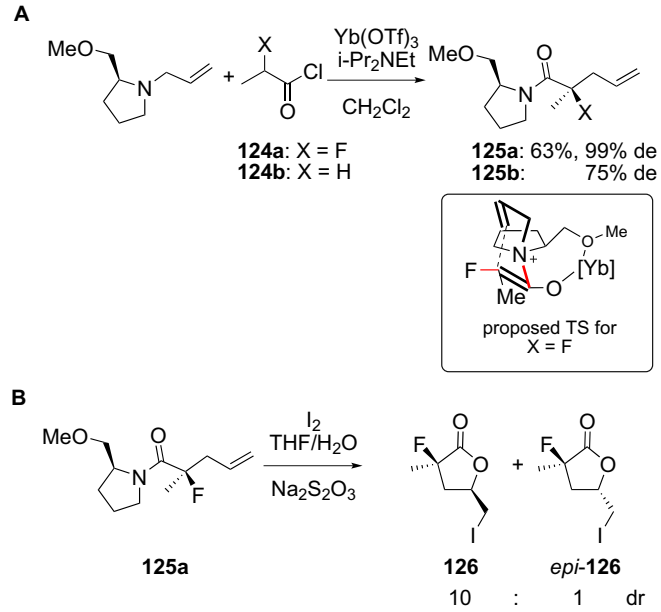
the substituents, *N*-allylic difluoroenamines **120** could afford the aza-Claisen product **121** and [2+2] cycloadducts **122** or, in one case (**120d**), an ene product **123** (Scheme 62).[156]



Scheme 62. Substituent-dependent reactivities of *N*-allylic difluoroenamines **120**. PMP=*p*-methoxyphenyl.

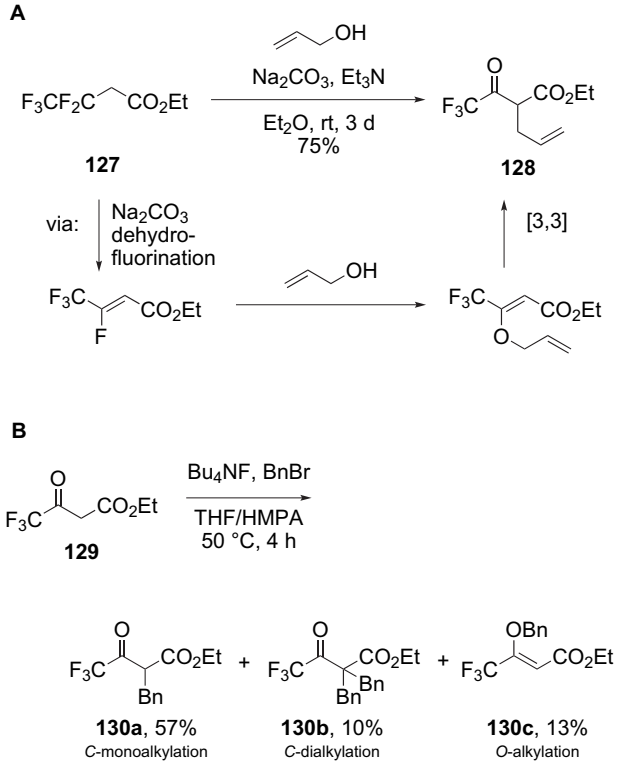
An asymmetric zwitterionic aza-Claisen rearrangement mediated by a chiral auxiliary has been used as the key step to prepare stereodefined α-fluoroamides and α-fluoro-γ-lactones.[157] The formation of the requisite Claisen substrate and its rearrangement took place in the presence of an ytterbium Lewis acid (Scheme 63A). The rearrangement of the Claisen substrate bearing (*S*)-2-(methoxymethyl)pyrrolidine as the chiral auxiliary proceeded with a virtually complete diastereoselectivity when fluorine is present (**124a**). The selectivity was lower for the nonfluorinated analogue derived from **124b**, which afforded **125b** with a diastereomeric excess of 75%. The asymmetric induction was rationalized by bidentate ytterbium chelation to both oxygens in the rearranging substrate, and the higher level of diastereoselectivity in the presence of fluorine was explained by a chair-like conformation that preferentially places the C–F and C–N^+ bonds *gauche* to each other, as this arrangement is known[158] to be stabilized by the charge–dipole interactions associated with these two linkages.

Iodolactonization of **125a** afforded the α-fluorinated lactones **126** and *epi*-**126** with a high diastereoselectivity (Scheme 63B).



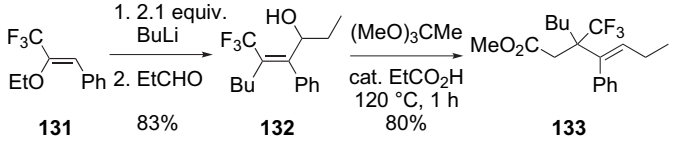
Scheme 63. (A) Auxiliary-mediated asymmetric aza-Claisen rearrangements using fluorinated (**124a**) or nonfluorinated (**124b**) starting materials. (B) Highly diastereoselective iodolactamization of fluorinated rearranged product **125a**.

3.2.2. Systems containing fluoroalkylated and/or fluoro substituents. Substituted β-ketoesters **128** featuring a trifluoromethylated ketone can be accessed by a tandem reaction employing a Claisen rearrangement, starting from **127** (Scheme 64A).[159] These are valuable building blocks in fluorinated heterocyclic chemistry. Compound **128** corresponds to the product of direct allylation of ethyl 4,4,4-trifluoroacetoacetate (**129**), a process which, as the authors noted, is not trivial owing to reversible O-alkylation[160] and other issues[161] arising from the presence of the electron-withdrawing trifluoromethyl group (Scheme 64B).



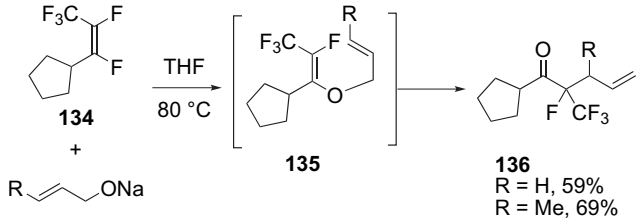
Scheme 64. (A) Conversion of **127** to **128** via dehydrofluorination and Claisen rearrangement. (B) Results of direct alkylation of unsubstituted trifluoromethylated β-ketoester **129**.

A short stereoselective route to access trifluoromethylated allylic alcohols **132** bearing a tetrasubstituted, functionalized double bond has been reported (Scheme 65). The route involves carbolithiation of **131** followed by trapping by an aldehyde. The Claisen rearrangement of the hindered **132** gives **133** bearing a quaternary trifluoromethyl-substituted carbon and a trisubstituted alkene with complete stereoselectivity.[162]



Scheme 65. Claisen rearrangement of sterically congested **132** to form **133** featuring trisubstituted double bond and quaternary trifluoromethyl-substituted carbon.

The one-pot procedure for the Claisen rearrangement of fluoro-substituted allyl vinyl ethers (see Scheme 61) has been adapted to the synthesis of α-trifluoromethyl unsaturated acids and derivatives.[163] Molecules possessing a fluoro- and trifluoromethyl-substituted stereogenic centre are also accessible by the Claisen rearrangement of suitably substituted substrates.[164] Thus, **135**, prepared via the nucleophilic substitution of **134** by the sodium alkoxide of an allylic (or a propargylic) alcohol, undergoes facile rearrangement to give **136** (Scheme 66).



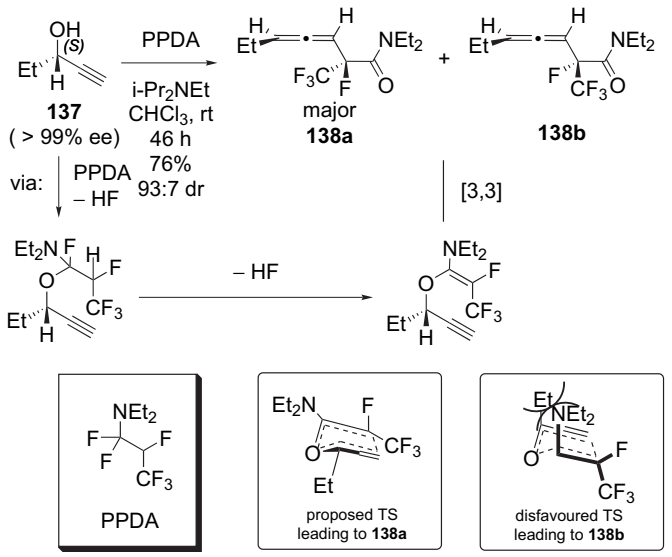
Scheme 66. Claisen rearrangement of **135** to access **136** bearing quaternary carbon simultaneously substituted with fluoro and trifluoromethyl substituents.

An analogous Eschenmoser-type propargyl–allenyl Claisen rearrangement has been demonstrated for both terminal and internal alkyne substrates, installing a simultaneously fluoro- and trifluoromethyl-substituted stereogenic centre adjacent to the resulting allene (Scheme 67).[165] The reaction proved to favour **138a** over the alternative product **138b**, due to efficient chirality transfer from the propargylic alcohol **137** to the chiral allene and the fluorinated stereocentre in the product. The stereoselectivity was rationalized by considering the steric congestion in the two alternative transition states.

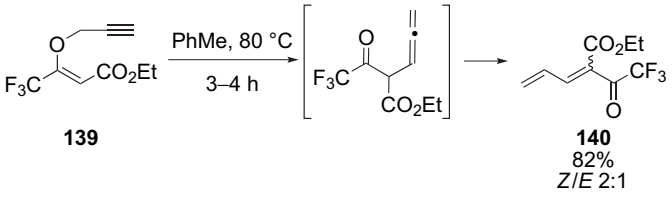
Propargyl vinyl ethers with a trifluoromethyl group on the 2-position such as **139** also rearrange easily, giving conjugated dienes **140** with modest *Z*/*E* selectivity via the allenylic intermediate as the primary rearranged product (Scheme 68).[147]

α-Amino acid derivatives[166] and other multifunctionalized molecules[167] featuring a trifluoromethyl or other fluoroalkylated groups on a stereogenic centre can be prepared by a one-pot sequence combining palladium-catalyzed nucleophilic substitution and the Ireland–Claisen rearrangement. A substrate-controlled asymmetric variant of this sequence starting from **141** is shown in Scheme 69.

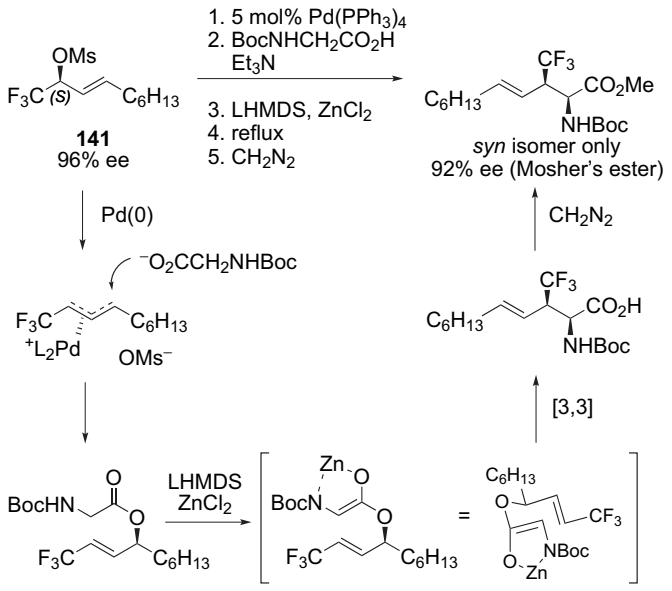
Trifluoromethyl-substituted butenolides are accessible by a domino Claisen–Cope rearrangement, starting from a fluorine-



Scheme 67. Eschenmoser–Claisen rearrangement of **137** with high level of chirality transfer. PPDA=hexafluoropropene–diethylamine adduct.

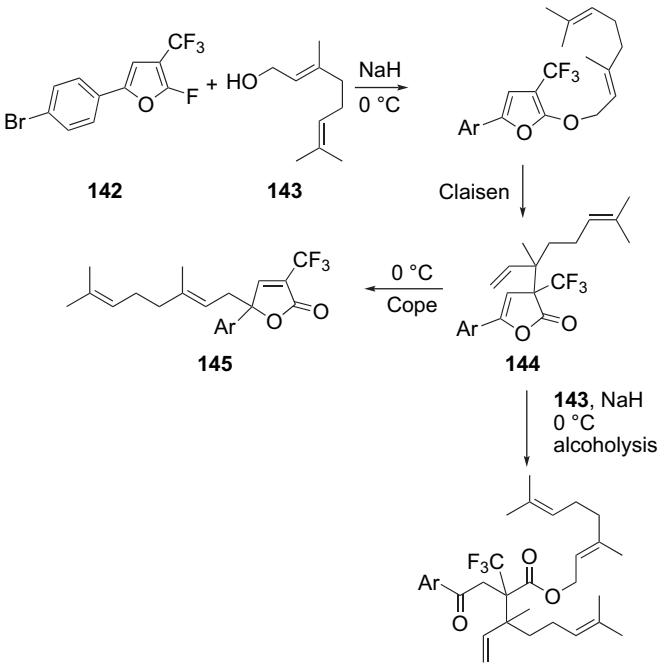


Scheme 68. Claisen rearrangement of propargyl vinyl ether **139** to give conjugated diene **140** after tautomerization of rearranged product.



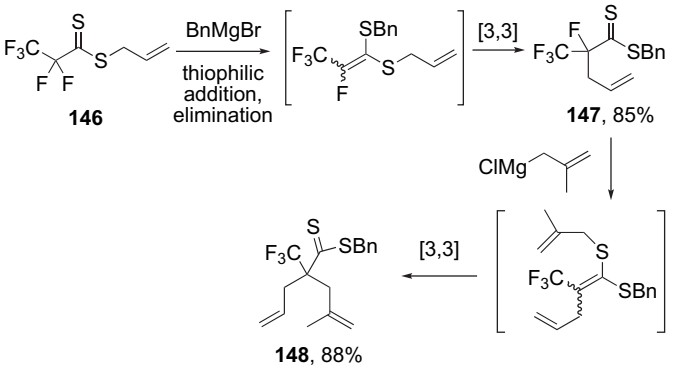
Scheme 69. Synthesis of enantioenriched amino acid derivative bearing trifluoromethylated side chain with good control of relative stereochemistry starting from homochiral starting material **141**.

containing thiophene or furan **142**, and an allylic alcohol such as **143** (Scheme 70).[168,169] This methodology has been applied for the incorporation of lipidic anchors into biologically relevant compounds such as **145**. Alternatively, the reaction can be interrupted after the Claisen rearrangement step by alcoholysis of **144** using the allylic alcohol component. The methodology has been applied to the synthesis of α-trifluoromethyl-substituted α-amino acids.[170]



Scheme 70. Access of trifluoromethylated butenolide **145** using domino Claisen–Cope rearrangement.

A three-step domino reaction composed of a thiophilic addition, β-fluoride elimination and a thio-Claisen rearrangement, starting from substrates such as **146**, was used to synthesize dithioesters such as **147** with a simultaneously fluoro- and trifluoromethyl-substituted stereogenic centre adjacent to the thiocarbonyl group. The unsaturated dithioesters produced could optionally be subjected to this sequence once more, yielding symmetrical or unsymmetrical bis(unsaturated) dithioesters such as **148** with a quaternary, trifluoromethylated carbon (Scheme 71).[171]

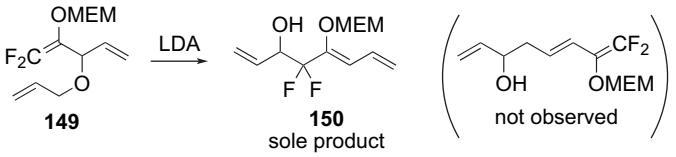


Scheme 71. Preparation of unsymmetrical α-trifluoromethylated dithioester **148** by using three-step domino reaction with thio-Claisen rearrangement as key step.

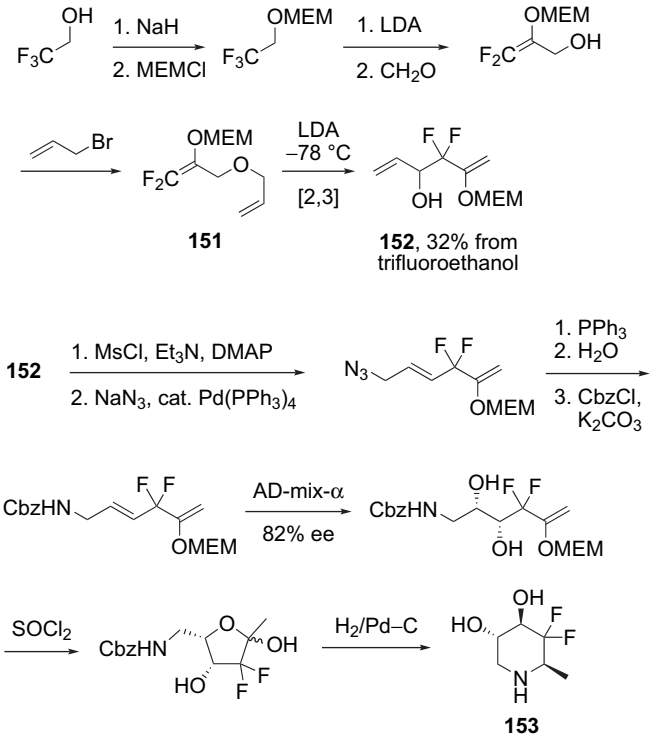
3.3. [2,3]-Wittig rearrangements

The [2,3]-Wittig rearrangement of difluoroallylic ethers, developed by Percy and co-workers,[172] is useful for accessing molecules with a difluoromethylene group in a mid-chain position. When the substrate has a choice to rearrange through a vinyl or a difluorovinyl terminus, the latter was found to react exclusively, as the rearrangement of **149** gives **150** as the sole product (Scheme 72).[172] As the authors noted,[172] this

result is in line with the expectation from the LUMO-lowering effect of the fluoro substituents on the rearranging olefinic system. This rearrangement has been used in the highly stereocontrolled syntheses of a number of selectively difluorinated azasugars[173] and other sugar mimics.[174,175] Scheme 73 shows how the difluorinated azasugar analogue **153** was accessed starting from 2,2,2-trifluoroethanol and using the [2,3]-Wittig rearrangement of **151** to give **152** as a key step.[173] Optically active fluorinated allylic alcohols are also accessible by this reaction coupled with enzymatic resolution.[176]

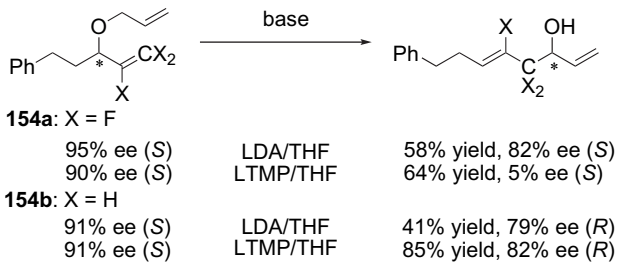


Scheme 72. Chemoselectivity in the Wittig rearrangement of **149** favouring exclusively the participation of the difluorinated terminus, giving **150** as the sole product.



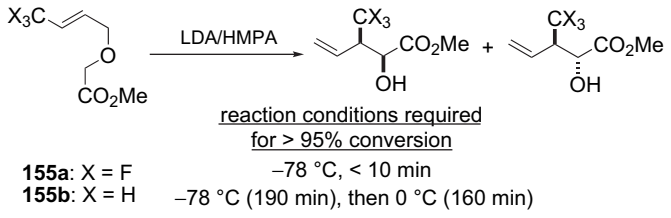
Scheme 73. Wittig rearrangement of **151** into **152**, and outline of further transformations of **152** into D-1,4,6-trideoxy-4,4-difluoronojirimycin (**153**).

An interesting dependence of the extent of chirality transfer of the [2,3]-Wittig rearrangement of enantioenriched 1,1,2-trifluoroallylic ethers on the counterion of the lithium base has been observed.[166] As shown in Scheme 74, the enantiopurity of the fluorinated substrate **154a** substantially erodes when LTMP is used as the base; with LDA, the erosion is slight. However, with the nonfluorinated substrate **154b**, similar results were obtained, regardless of the counterion.



Scheme 74. Base dependence of chirality transfer in Wittig rearrangements of **154**. LTMP=lithium tetramethylpiperidide.

A trifluoromethyl group on the allylic portion of the starting material accelerates the rearrangement substantially. Thus, the fluorinated substrate **155a** requires less than 10 min to achieve >95% conversion, while the nonfluorinated **155b** takes a longer time and requires a higher temperature (Scheme 75).[177] This difference was thought to arise from the decrease of the LUMO energy level of the alkene, due to the electron-withdrawing trifluoromethyl substituent.[178]

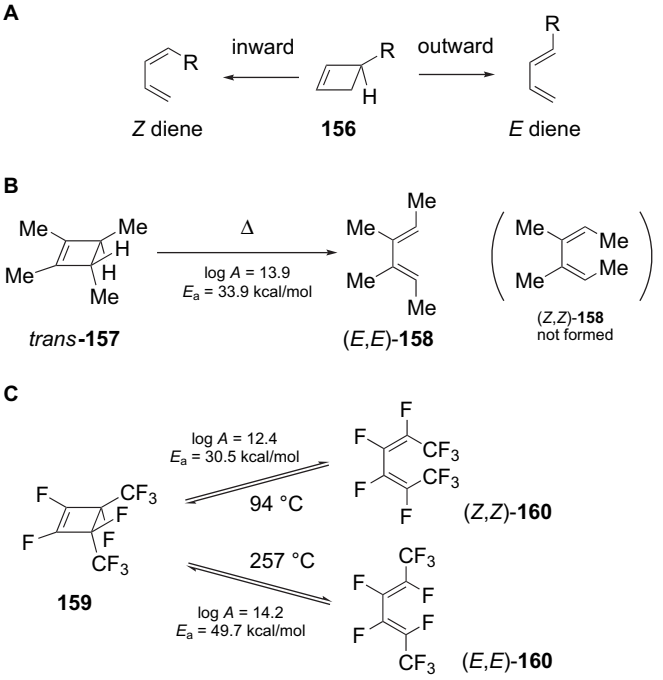


Scheme 75. Acceleratory effect of trifluoromethyl group on Wittig rearrangements.

4. Electrocyclic reactions

4.1. Fluoroorganic compounds in theoretical studies

Historically, the use of fluoroorganic molecules contributed considerably to our mechanistic understanding of electrocyclic reactions in general. An electrocyclic reaction following either a conrotatory or disrotatory path could occur in two opposite 'directions'. This is illustrated for the conrotatory ring opening of a cyclobutene in Scheme 76A, in which the 'inward' and 'outward' rotations about the breaking σ-bond, respectively, lead to the stereospecific formation of a *Z* and an *E* diene. Torquoselectivity is the preference of one of these 'twists' over the other, where 'torquo-' refers to the twist of the σ-bond in the transition state for reaction.



Scheme 76. (A) 'Inward' and 'outward' torquoselectivities in electrocyclic opening of cyclobutene **156**. (B) Outcome of ring opening of cyclobutene *trans*-**157**. (C) Ring opening of fluorocarbon **159** favouring sterically more congested diene (*Z*,*Z*)-**160**.

The sense of this selectivity depends on the identity of the substituents. Early torquoselective results were rationalized on steric grounds. Thus, the exclusive formation of the (*E*,*E*) isomer of **158** from the trans isomer of 1,2,3,4-tetramethylcyclobutene **157** (Scheme 76B) was thought to be the result of the steric stress in the transition state for the formation of the alternative, *Z*,*Z*-diene as the two methyl groups on the breaking σ-bond simultaneously rotate inwards.

Dolbier and Burton demonstrated in the 1980s that the torquoselectivities of the electrocyclic ring openings of fluorinated cyclobutenes run contrary to steric arguments.[179–181] Compound **159**, for example, was found to favour rotation of the much bulkier trifluoromethyl groups inwards and that of the smaller fluoro substituents outwards, giving preferentially the sterically more congested diene (*Z*,*Z*)-**160** as product (Scheme 76C).[180] In these systems, the small size of a fluoro substituent, coupled to its potent electronic effects, made it unambiguous that the observed torquoselectivities in electrocyclic reactions are stereoelectronic rather than steric in origin. Experiments had shown that, in the electrocyclic ring openings of substituted cyclobutenes, π-donors prefer to rotate away from the breaking bond, while strong acceptors rotate inwards. By means of computation,[182–184] Houk showed how these preferred directions of rotation result from interactions between the orbital on the substituent, including the fluoro substituent, and the transition state's frontier molecular orbitals. An elegant account of the torquoselectivity model was published by Dolbier and Houk in 1996.[185]

Ab initio computations showed that the HOMO of the transition state for cyclobutene ring opening is the σ-orbital of the cleaving C–C bond, while the LUMO is the corresponding σ*-orbital. In the torquoselectivity model, the substituent is considered to contribute a π-type orbital that is either full (for a donor substituent) or empty (for an acceptor) (Fig. 4). Upon inward rotation, the filled orbital of a donor substituent experiences unfavourable closed-shell repulsion against the cleaving σ-bond of the cyclobutene. Therefore, the substituent prefers to rotate outwards (Fig. 4B). An acceptor substituent rotates inwards to maximize the interactions between its vacant π*-orbital and the breaking σ-bond (Fig. 4B). Fluorine, with its lone pairs of electrons, is treated as a donor substituent in the context of this model,[183] which explains why (*Z*,*Z*)-**160** featuring all of the fluorines 'outside' is preferentially formed from the ring opening of **159** (Scheme 76C).[180] More recently, Houk showed that a low-lying σ*-orbital such as that associated with a Si–C bond in a trialkylsilyl group can also mix with the σ-type frontier molecular orbitals of the transition state and influence torquoselectivities (Fig. 4C).[184]

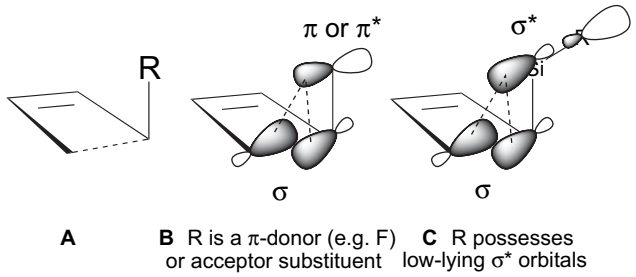


Figure 4. Houk's torquoselectivity model of ring opening of cyclobutenes.

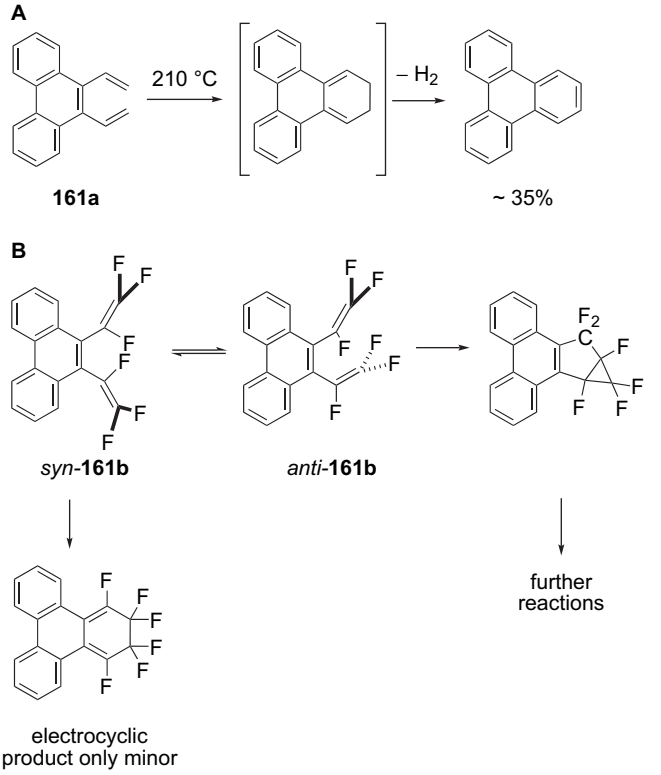
The energetics computed for the inward and outward electrocyclic ring openings of a series of 3-fluoromethylated cyclobutenes **156b–d** are consistent with the picture of orbital mixing outlined above (Table 7).[184] The outward ring-opening barrier ($\Delta H^{\ddagger}_{out}$) increases with the number of fluoro substituents on the methyl group, from 31.4 kcal/mol for **156a** to 34.5 kcal/mol for **156d**. This is due to the reduced hyperconjugative ability of the fluorinated substituents and reduced mixing with the breaking σ-bond at the transition state. On the other hand, the barrier for the inward path ($\Delta H^{\ddagger}_{in}$) is progressively lower from **156a** to **156b** and **156c** as the acceptor character of the substituent increases, due to the electronegative fluorine. As the authors noted, for the trifluoromethylated cyclobutene **156d**, the inward activation energy is larger than the mono- and difluorinated cases, because of electrostatic repulsion between the fluorinated substituent and the π-system of the cyclobutene.

Table 7
Activation energies (kcal/mol) for outward and inward electrocyclic ring openings of 3-substituted cyclobutenes **156** (Scheme 76A)

Entry	R	$\Delta H^{\ddagger}_{out}$ [exp]	$\Delta H^{\ddagger}_{out}$ [a] [comp]	$\Delta H^{\ddagger}_{in}$ [a] [comp]	$\Delta\Delta H^{\ddagger}$ [a,b] [comp]	$\Delta\Delta H^{\ddagger}$ [b] [exp]
1	Me (**156a**)	31.6	31.4	37.3	5.9	>4
2	CH_2F (**156b**)	—	32.2	34.2	2.0	—
3	CHF_2 (**156c**)	—	34.0	34.3	0.3	—
4	CF_3 (**156d**)	35.5	34.5	36.8	2.3	>2.3

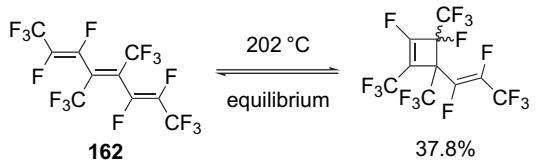
[a] Computed at B3LYP/6-31G(d) level of theory.
[b] $\Delta\Delta H^{\ddagger}=\Delta H^{\ddagger}_{in}-\Delta H^{\ddagger}_{out}$.

While the electrocyclic ring closure of 9,10-divinylphenanthrene **161a** is known (Scheme 77A),[186] the corresponding 9,10-bis(trifluorovinyl) derivative **161b** was found by Dolbier to be surprisingly resistant to the expected rearrangement (Scheme 77B).[130] A radical pathway competes effectively with the electrocyclic reaction, giving a bicyclo[3.1.0]hexane, which is open to further reactions. Compound **161b** exists as a mixture of atropisomers, with the two trifluorovinyl groups either *syn* or *anti* relative to the plane of the aromatic nucleus. The inhibition of the electrocyclic process of **161b** was ascribed to the substantial steric and electrostatic repulsion between the *cis* fluoro substituents in the requisite 6π-electrocyclic, disrotatory boat-like transition state.



Scheme 77. Different ease with which nonfluorinated **161a** and fluorinated **161b** undergo 6π-electrocyclizations.

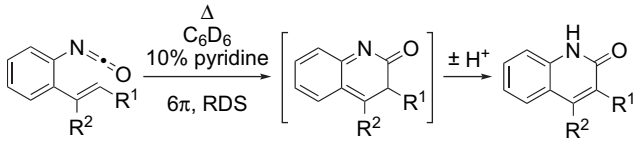
The inhibition of cyclization by fluorinated substituents was also observed on an acyclic substrate. The fluorinated 1,3,5-hexatriene **162** is resistant to 6π-electrocyclization at temperatures up to 200 °C (Scheme 78),[130] while an analogous hydrocarbon system cyclizes readily at 160 °C.[187]



162

Scheme 78. Resistance of **162** towards 6π-electrocyclization, even at high temperatures, giving 4π-cyclization product in equilibrium with itself instead.

To study the influence of fluorine on the torquoselectivity of 6π-cyclizations, Dolbier turned to the *o*-vinylphenyl isocyanate system **163**,[188] which is devoid of a cis (or a trans) substituent that sterically impedes the desired 6π-cyclization (Scheme 79). The transformation of the parent system **163a** (R^1, R^2=H) into 2-quinolinone was shown to proceed via an endothermic rate-determining electrocyclization followed by a bimolecular proton transfer.



163a–g

Scheme 79. 6π-Electrocyclization of **163** and subsequent proton transfer to form 2-quinolinones (Table 8). RDS=rate-determining step.

A series of α- and β-substituted systems **163b–g** was examined with regard to their experimental kinetics and computed transition structures (Table 8). Fluorinated substituents consistently increase the free energies of activation of the cyclizations.

Table 8
Experimental rate constants and free energies of activation for electrocyclic rearrangements of (*E*)-**163** (Scheme 79)

Entry		R^1	R^2	T (°C)	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
1	(**163a**)	H	H	109.4	9.8×10^{-5}	29.8
2	(**163b**)	H	F	178.9	2.0×10^{-6}	38.6
3	(**163c**)	H	CH_3	112.6	7.3×10^{-5}	30.1
4	(**163d**)	H	CF_3	182.3	9.0×10^{-5}	35.5
5	(**163e**)	CH_3	H	35	2.4×10^{-4}	23.2
6	(**163f**)	CH_3	F	101.6	3.80×10^{-4}	28.0
7	(**163g**)	CF_3	H	149.3	6.9×10^{-5}	33.0

The computed transition structures show that these cyclizations are pseudopericyclic in nature.[189–192] The effects of fluorine-containing substituents upon the torquoselectivity in the monorotatory process during these reactions can be seen through the relative rates of electrocyclizations of the *E* and the *Z* isomers of **163c**,**d** and **163f** (Table 9).[188] The ratios show that the torquoselectivities are not steric in origin, since the largest effect originates from the smallest, fluoro substituent, whereas the smallest kinetic effect is seen from a large trifluoromethyl group. The authors thus confirmed the stereoelectronic nature of torquoselectivities in 6π-electrocyclizations.

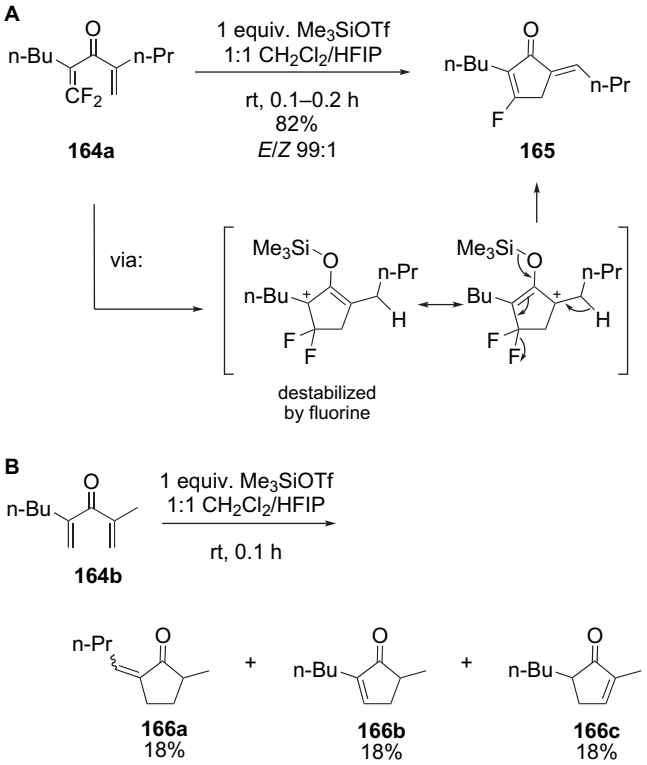
Table 9
Relative rate constants for electrocyclizations of *E* and *Z* isomers of nonfluorinated (**163c**) and fluorinated (**163d** and **163f**) *o*-vinylphenyl isocyanates, and differences in experimental activation free energies and in computed activation barriers (in kcal/mol) (Scheme 79)

Entry		R^1	R^2	T/°C	k_E/k_Z	$\Delta\Delta G^{\ddagger}$ [exp]	$\Delta\Delta E_a$ [comp][a]
1	(**163c**)	H	CH_3	112.6	11.7	−1.9	−2.0
2	(**163d**)	H	CF_3	182.3	3.2	−1.0	−0.9
3	(**163f**)	CH_3	F	101.6	82.1	−3.3	−7.4

[a] Computed at MP2/6-31G(d)//RHF/6-31G(d) level of theory including zero-point energies.

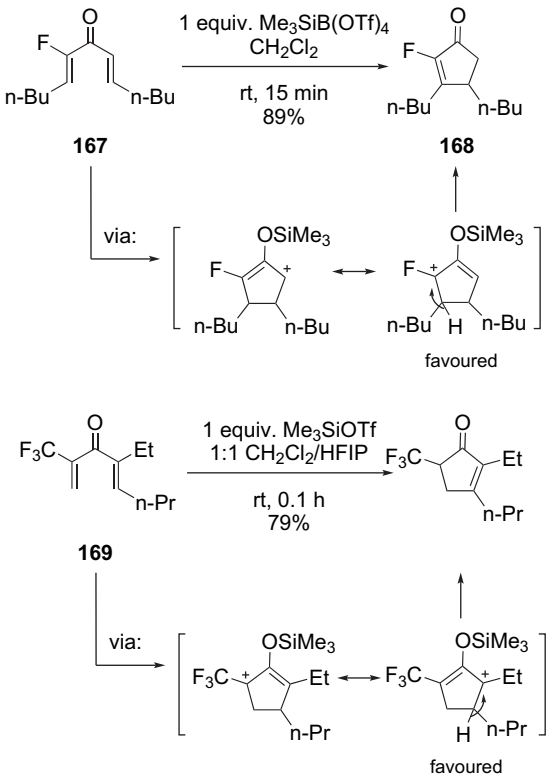
4.2. Nazarov cyclizations

The Nazarov cyclization is widely used for cyclopentenone construction. Key to its utility is the control over the position of the double bond in the product. The fluoro and the trifluoromethyl substituents can be used as regiocontrol elements in this transformation by virtue of their electronic influence towards the intermediate cation. This was first illustrated by Ichikawa using the cyclization of 2,2-difluorovinyl vinyl ketones such as **164a** (Scheme 80A) to give fluorinated cyclopentenones such as **165**.[193] The *gem*-difluoromethylene group disfavours the build up of positive charge on its adjacent carbon and serves to direct the position of the endocyclic double bond, regardless of the substitution pattern of the substrate. The critical role of this group in achieving regioselective ring closure can be highlighted by the Nazarov cyclization of nonfluorinated **164b** under analogous conditions, which unselectively affords a mixture of isomers **166a–c** arising from various modes of proton abstraction from the intermediate cyclopentenylic cation (Scheme 80B).



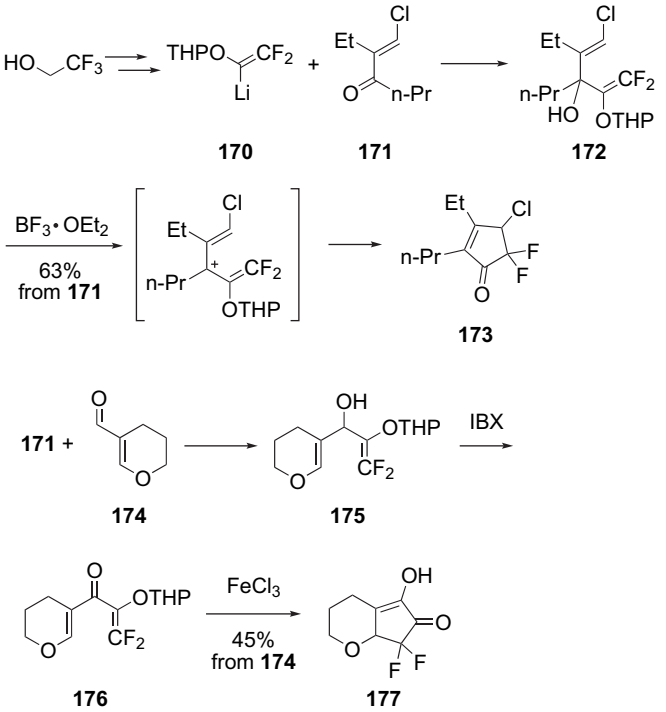
Scheme 80. (A) Nazarov cyclizations directed by fluoro substituents illustrated by **164a**. HFIP=1,1,1,3,3,3-hexafluoroisopropanol. (B) Control experiment using nonfluorinated divinyl ketone **164b**.

The α-cation-stabilizing effect of a fluoro substituent was also used in defining the placement of the double bond in the Nazarov product, as shown by the reaction of **167**, which gives **168** selectively.[194] A suitably positioned trifluoromethyl group in the substrate **169** directs the Nazarov cyclization by its cation-destabilizing effect (Scheme 81).[195]



Scheme 81. Other fluorine-directed Nazarov cyclizations.

α,α-Difluorocyclopentenones such as **173** can be prepared by Nazarov cyclization of substrates such as **172** assembled by the nucleophilic addition of the protected difluorovinyllithium species **170** to various α-substituted α,β-unsaturated enals or enones such as **171** (Scheme 82).[196] Compound **170** can be derived from 2,2,2-trifluoroethanol. The requisite 4π-carbocation for the cyclization is formed from **172** by a Lewis-acid-induced ionization. Alternatively, **175** derived from enal **174** can be oxidized to a difluorovinyl vinyl ketone **176** and cyclized, giving α-hydroxy-α′,α′-difluorocyclopentenone **177** as product.



Scheme 82. Difluorocyclopentenone syntheses using Nazarov cyclization. IBX=2-iodoxybenzoic acid.

5. Conclusions and outlook

The manifold modifications of fluorine-containing substituents on the pericyclic chemistry of organic molecules have been illustrated by recent experimental and theoretical studies. Through these examples, we can see that the principles by which these substituents exert regio- and/or stereocontrol in polar reactions often apply in pericyclic reactions. In some pericyclic systems, however, fluorine substitution is understood to play a more peculiar and sometimes surprising role. For example, the preponderance for the carbon in a difluoromethylene group to adopt the sp^3 hybridization as opposed to sp^2 is a recurring theme in the sigmatropic rearrangements of fluorinated building blocks. The incorporation of fluorine, by virtue of its unique combination of small size and high electronegativity, and the trifluoromethyl group in cyclobutenes has provided revealing results that helped to establish the electronic nature of torquoselectivity in 4π-electrocyclizations. We have also seen how fluorine unexpectedly inhibits the 6π-electrocyclization of some fluorinated hexa-1,3,5-trienes. Recent high-level computational studies have improved our understanding of some of these 'fluorine effects'. From a synthetic point of view, pericyclic reactions provide an expedient, atom-economical approach for constructing structurally complex compounds. As only a few effective asymmetric variants using fluorinated starting materials are known, there is considerable scope for the development of enantioselective, preferably catalytic, pericyclic reactions to access these compounds.

Acknowledgements

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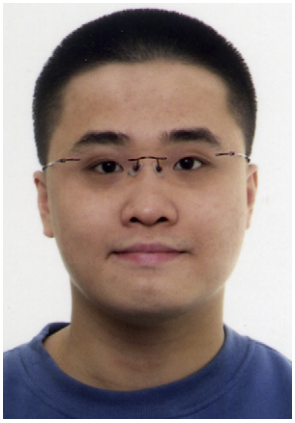
Biographical sketch



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