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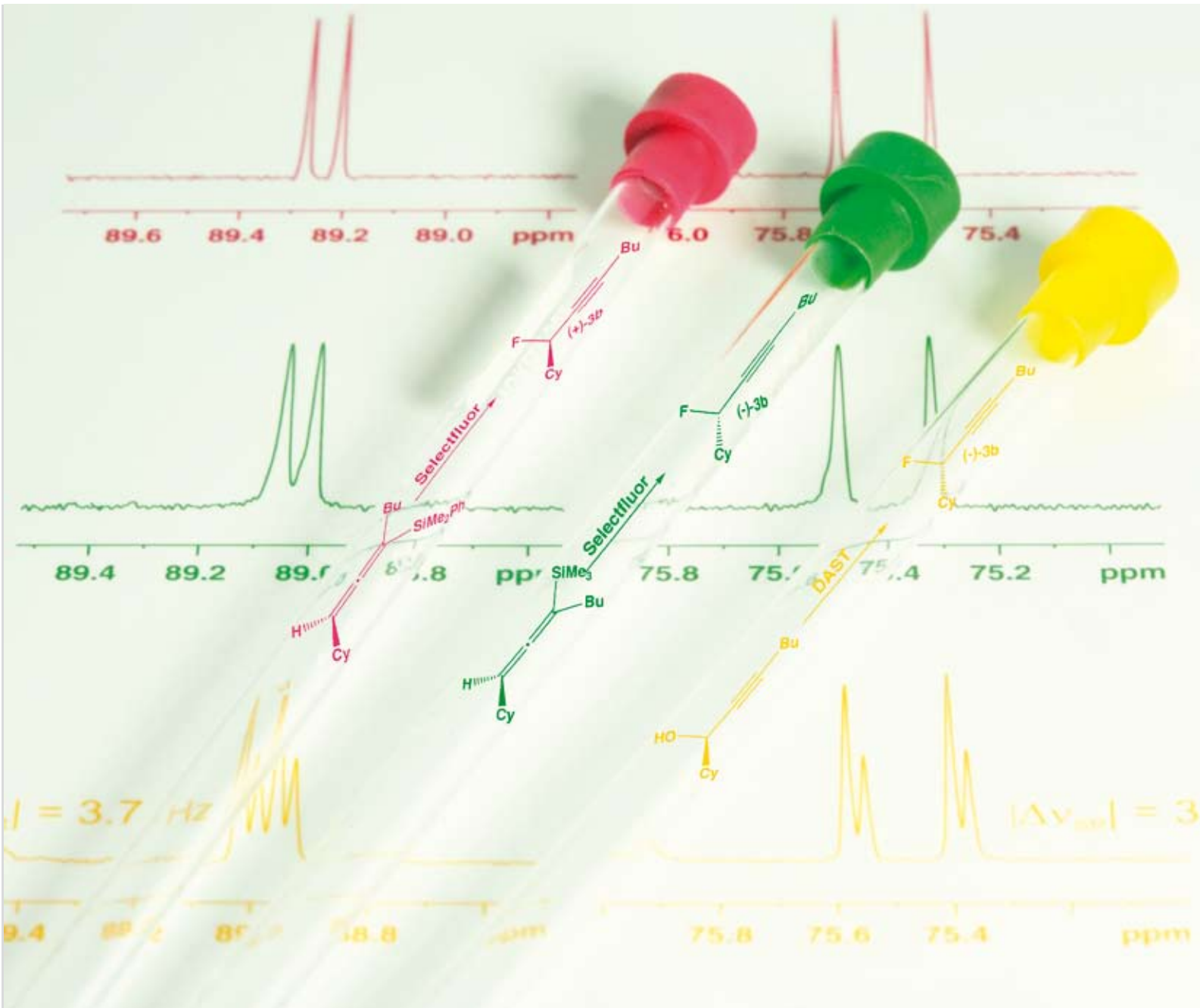

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In this issue...

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Stereospecific *anti* S_E2' fluorination of allenylsilanes: synthesis of enantioenriched propargylic fluorides†

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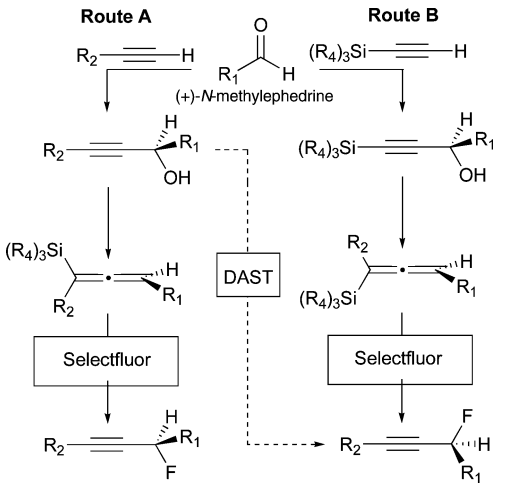
The electrophilic fluorodesilylation of enantioenriched allenylsilanes proceeds with efficient transfer of chirality. The silylation–fluorination of propargylic alcohols occurs with overall retention of stereochemistry, a result consistent with a stereospecific *anti* S_E2' mechanism for the fluorination step.

Innovative organofluorine chemistry is continuously attracting interest, owing to the unique properties that the fluorine atom can impose on a molecule.[1] In this context, propargylic monofluorides are important building blocks which can be manipulated in various ways.[2] Recently, Grée and Grée have successfully used these alkynes as dipolarophiles in 1,3-dipolar cycloadditions including Cu-catalysed azide–alkyne cycloaddition, a reaction commonly referred to as click chemistry.[3] Undoubtedly, easy access to enantioenriched propargylic fluorides can only increase the synthetic value of these underexplored compounds. The deoxyfluorination of enantioenriched propargylic alcohols reported by Grée *et al.* is based on the use of the nucleophilic fluorinating reagent diethylaminosulfur trifluoride (DAST).[4] This nucleophilic approach delivered the corresponding propargylic fluorides with moderate to excellent stereocontrol. For selected substrates, it is necessary to carry out the reaction at low temperature in order to minimise erosion of enantiomeric purity upon fluorination of enantioenriched propargylic alcohols.[4d] Recently, we reported that racemic allenylsilanes are conveniently converted into propargylic fluorides when reacted at room temperature in the presence of 1-chloro-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoro-borate) (Selectfluor), a widely used electrophilic fluorinating reagent.[5] This chemistry raised several unanswered questions for the preparation of enantioenriched propargylic fluorides, such as the efficiency of transfer of chirality upon fluorodesilylation of optically enriched allenylsilanes or the sense of stereocontrol for the fluorination step. Our mechanistic hypothesis for the fluorination step (S_E2' with *anti* approach of the fluorinating reagent with respect to the silyl group) led us to anticipate that both enantiomers of a target propargylic fluoride may be accessed from a single enantioenriched propargylic alcohol using either a *nucleophilic* or *electrophilic* fluorination approach. We describe herein the feasibility of this approach for the synthesis of enantioenriched propargylic fluorides and compare the value of the electrophilic route with the well-established nucleophilic variant. This chemistry offers a solution to the problem of erosion of ee occasionally observed upon nucleophilic fluorination and it allows for the preparation of both (+)- and (−)-propargylic fluorides using (+)-*N*-methylephedrine as the unique chiral component. Scheme 1 illustrates how this can be achieved and shows the connectivity between the nucleophilic (DAST) and electrophilic (Selectfluor) approaches.



Scheme 1 Synthesis of (+)- or (−)-propargylic fluorides.

Enantioenriched allenylsilanes are directly accessible from the corresponding propargylic alcohols. Out of the various routes available for the synthesis of enantioenriched propargylic alcohols, we selected the method developed by Carreira *et al.* featuring the addition of an *in situ* generated alkynylzinc reagent onto an aldehyde in the presence of (+)-*N*-methylephedrine.[6] This route was attractive as it allows access to both enantiomeric propargylic fluorides from a common aldehyde and (+)-*N*-methylephedrine. This can be achieved by inverting the order of introduction of the silyl group and the R_2 substituent when preparing the allenylsilane (Scheme 1, Routes A and B).

In our previous study, we validated the electrophilic fluorination of racemic allenyltrimethylsilanes.[5] These allenylsilanes were prepared from trimethylsilyl-substituted propargylic alcohols by conjugated addition of an organocopper reagent.[7,8] For our study in asymmetric series, it is necessary to prepare allenylsilanes by silylation of alkyl-substituted propargylic alcohols (Route A). This chemistry is known to be best performed with dimethylphenylsilyl lithium, a reagent easier to handle than trimethylsilyl lithium.[9] As we did not validate the fluorination of these presumably less reactive dimethylphenylsilyl-substituted allenes, we investigated first the feasibility of the silylation–fluorination of non-silylated propargylic alcohols in racemic series prior to undertaking studies with enantioenriched derivatives.

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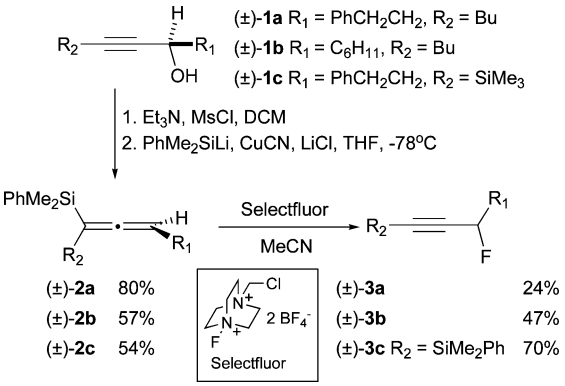
† Electronic supplementary information (ESI) available: Procedures for the preparation of all racemic and enantioenriched compounds are provided as well as full characterisation of all new compounds. See DOI: 10.1039/b803888k

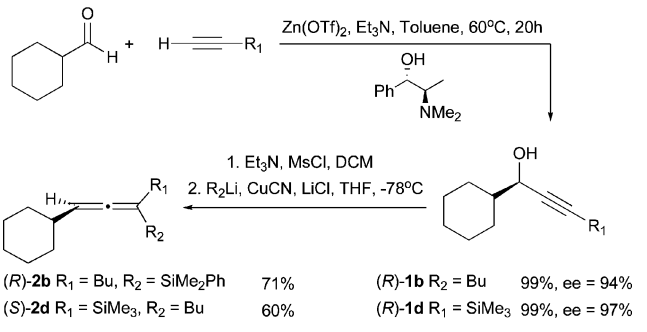
Using chemistry reported by Fleming *et al.*,[8] the alkynols (±)-**1a–c** were converted in good yields into the allenylsilanes (±)-**2a–c** upon mesylation followed by conjugate addition of dimethylphenylsilyl lithium in the presence of copper cyanide and lithium chloride in tetrahydrofuran (Scheme 2). The fluorination of (±)-**2a–c** was successfully performed at room temperature with Selectfluor in acetonitrile. The isolated yields for (±)-**3a** and (±)-**3b** do not reflect the efficiency of the fluorination process but the complications arising upon purification of the propargylic fluorides that were contaminated by dimethylphenylsilyl fluoride, a non volatile side product of the reaction. In comparison with the fluorodesilylation of trimethylsilyl allenes, longer reaction times (up to 24 hours) were necessary to fully convert (±)-**2a** and (±)-**2b** into (±)-**3a** and (±)-**3b** respectively. As anticipated, the electron withdrawing phenyl group of $SiMe_2Ph$ reduces the reactivity of the allenylsilane towards the electrophilic fluorinating reagent.[10] The fluorination of (±)-**2c** is of particular interest as it showed unambiguously that the electrophilic fluorination is accompanied by the loss of the trimethylsilyl group rather than the dimethylphenylsilyl group when these two substituents compete (Scheme 2).



Scheme 2 Synthesis and fluorodesilylation of (±)-**2a–c**.

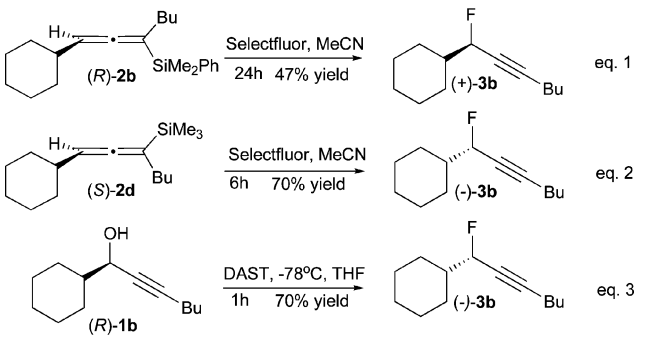
Having validated in racemic series the feasibility of the fluorination of both trimethylsilyl- and dimethylphenylsilyl-substituted allenes, we investigated next the fluorination of enantioenriched precursors. We selected the propargylic fluoride (*S*)-**3b** and its enantiomer (*R*)-**3b** as our targets. The propargylic alcohols (*R*)-**1b** and (*R*)-**1d** were prepared with high enantiomeric excesses (>94% ee) according to the methodology developed by Carreira *et al.* and revised by Rein *et al* (Scheme 3).[6,11] The conversion of the enantioenriched alkynols into the corresponding allenylsilanes (*R*)-**2b** and (*S*)-**2d** was carried out using the reaction conditions applied for the preparation of racemic samples and proved to be uneventful. Difficulty arose when attempting to determine the enantiomeric purity of the allenylsilanes. All of our attempts to measure their ee prior to fluorination failed using either chiral GC or HPLC. We assumed that, in analogy with literature data,[8] the conjugated addition of the organolithium proceeded stereospecifically *anti* to the mesylate (Scheme 3).

The electrophilic fluorodesilylation of the enantioenriched allenylsilanes (*R*)-**2b** and (*S*)-**2d** was performed using Selectfluor in acetonitrile and afforded the corresponding propargylic fluorides (*R*)-**3b** and (*S*)-**3b** in 47% and 70% yield respectively (Scheme 4, eq. 1 and 2). For comparative studies, we also performed the



Scheme 3 Synthesis of allenylsilanes (*R*)-**2b** and (*S*)-**2d**

dehydroxyfluorination of the propargylic alcohol (*R*)-**1b** using DAST in THF at −78°C. This reaction delivered (*S*)-**3b** in 70% yield (Scheme 4, eq. 3). The signs of optical rotation unambiguously confirmed that opposite enantiomers are formed for the fluorination of (*R*)-**2b** and (*S*)-**2d**. In addition, the $[\alpha]_D$ value of the propargylic fluoride prepared by nucleophilic fluorination of (*R*)-**1d** had a sign matching with the product resulting from the electrophilic fluorination of the allenylsilane (*S*)-**2d**. These data allowed us to assign the absolute configurations of all propargylic fluorides as it has been reported that the DAST-mediated fluorination of propargylic fluorides occurred with inversion of configuration (S_N2).[4d]



Scheme 4 Fluorination of (*R*)-**2b**, (*S*)-**2d** and (*R*)-**1b**.

Measurement of the enantiomeric excesses of propargylic fluorides is notoriously difficult. Standard methods such as use of chiral HPLC and chiral GC lead to elimination of HF or no separation of the enantiomers. The only method currently known for measuring the enantiomeric excess of a propargylic fluoride has been developed by Courtieu *et al.*, which involves the use of chiral liquid crystalline solvents such as poly(γ-benzyl L-glutamate) (PBLG) with chloroform.[12] We employed this approach using ^{13}C NMR spectroscopy to assess the enantiomeric purity of each fluoride *via* the resulting peak resolution of the two sp carbon centres (Fig 1; see Supporting Information for details†). Pleasingly, the propargylic fluorides resulting from electrophilic fluorination gave high enantiomeric excesses, suggesting minimal loss of enantiomeric purity for the synthesis of the allenylsilanes from the corresponding propargylic alcohol and for the fluorination step. The direct dehydroxyfluorination using DAST was less satisfactory and led to significant erosion of enantiomeric excess (ee ≈ 30%). For the propargylic fluoride (−)-**3b** prepared by fluorodesilylation of the trimethylsilylallene (*S*)-**2d**, we estimate any second minor enantiomer to be present at less than 2% of

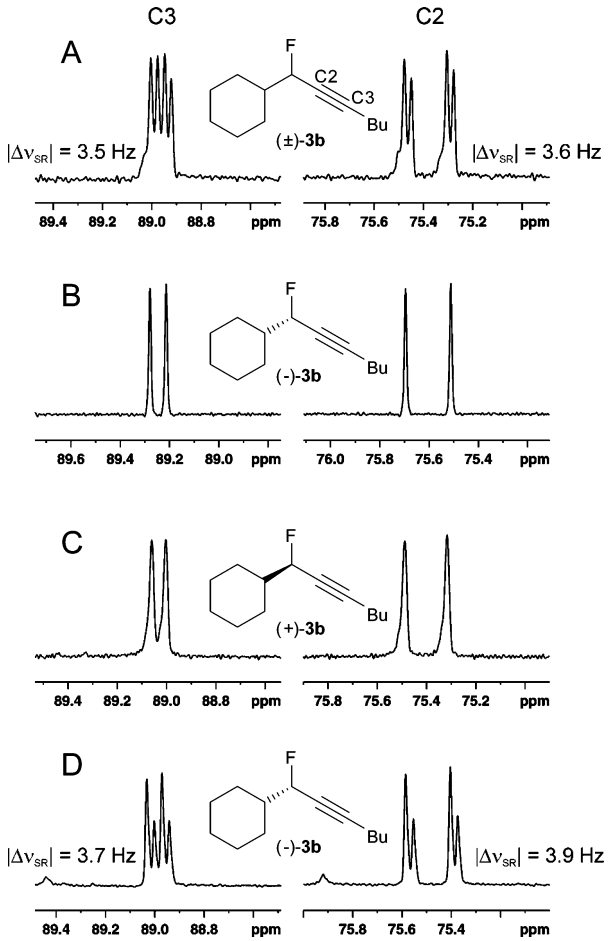
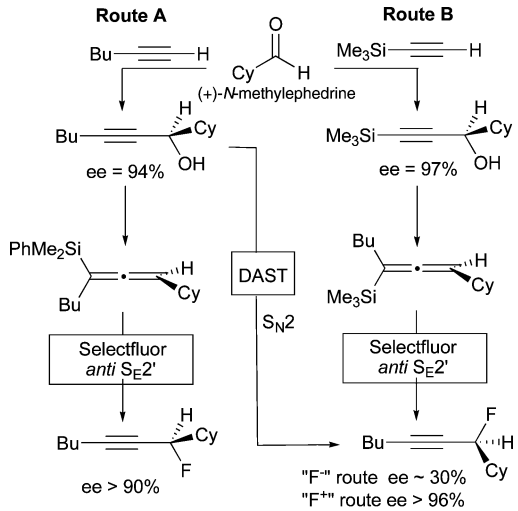


Fig. 1 Regions from ^{13}C NMR spectra recorded in chiral liquid crystalline media showing the carbon sp centres; A: racemic sample; B: sample prepared reacting (*S*)-**2d** with Selectfluor ee >96%; C: sample prepared reacting (*R*)-**2b** with Selectfluor ee > 90%; D: sample prepared treating (*R*)-**1b** with DAST ee ≈ 30%.

the major, corresponding to an ee >96%. For (+)-**3b** accessed from (*R*)-**2b**, the slight resonance shoulder leads us to take a conservative approach to estimating the ee. Whilst we believe this shoulder arises from residual lineshape distortions rather than the presence of a second resonance (the magnitude of the separation $\Delta\nu_{SR}$ would be 2.8 Hz at most which is significantly below the >3.5 Hz enantiomeric separations seen in Fig. 1), the intensity of this minor peak would represent 15% of the major at most, as judged by peak summation. This leads to a conservative estimate of the ee as being >75% for (+)-**3b**. However, since a similar and significant resonance shoulder appears in the racemic sample, we believe the ee to be >90%.

The enantiomeric excesses measured by ^{13}C NMR and the assignment of absolute configurations confirmed that the S_E2' fluorination of the allenylsilanes (*R*)-**2b**, (*S*)-**2d** occurred with efficient transfer of chirality and stereospecifically *anti* with respect to the silyl. These results suggest that the mechanistic pathway for the electrophilic fluorination of allenylsilanes is consistent with other electrophilic substitution reactions (Scheme 5).[13]

In summary, we have shown that enantioenriched propargylic fluorides can be synthesised from enantioenriched allenylsilanes. The mechanism of fluorination is a highly stereospecific *anti* S_E2'



Scheme 5 Mechanistic pathways for both nucleophilic and electrophilic fluorinations.

process. The propargylic alcohol (*R*)-**1b** could be converted to *both* enantiomeric propargylic fluorides **3b** using either the *nucleophilic* (inversion) or *electrophilic* (overall retention) approach. The ee measured for the propargylic fluoride (*S*)-**3b** prepared by nucleophilic fluorination was determined to be ~30%, suggesting significant loss of enantiomeric purity upon fluorination. This limitation was corrected by validating route B that led to (*S*)-**3b** with an enantiomeric excess estimated to be superior to 95%. Notably, the electrophilic route allowed access to both enantiomers using (+)-*N*-methylephedrine as the unique chiral non racemic component.

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