Asymmetric C–F Activation

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Synthesis of the Smallest Axially Chiral Molecule by Asymmetric Carbon–Fluorine Bond Activation[**]

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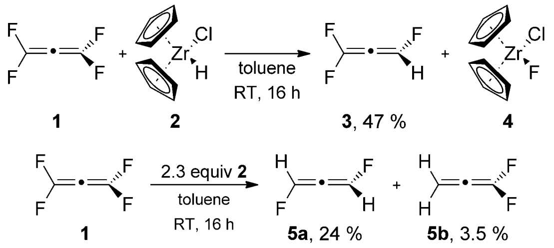
The homochirality of life's building blocks has been intriguing generations of chemists and its origin is still under considerable debate.[1] Today, asymmetric reactions represent an integral part of synthetic chemistry that has been honored with the Nobel Prize in 2001.[2] Despite substantial success, small unfunctionalized molecules generally elude enantioselective preparations. Thermodynamically stable small chiral molecules are highly sought-after targets for the experimental detection of molecular parity violation (PV).[3] Herein, one of the smallest possible C_2-symmetric molecules was synthesized by an unprecedented asymmetric carbon–fluorine bond activation.

The long atmospheric persistence of halofluorocarbons and its consequences in terms of ozone depletion and global warming[4] are contrasted by the benefits of organofluorine chemistry in controlling the lipophilicity and metabolic stability of pharmaceuticals and agrochemicals.[5] As a result, both the selective construction and deconstruction of carbon–fluorine bonds are of great interest to medicinal and environmental chemistry.[6] Fluorine forms the strongest known σ-bond to carbon; its cleavage under mild conditions is challenging but has been achieved by designing suitable reagents and catalysts.[7]

It has been established, that Group 4 hydride complexes are highly reactive towards vinylic carbon–fluorine bonds.[8] We have previously studied the organometallic chemistry of fluorinated allenes and cumulenes involving mid-to-late transition-metal complexes.[9] When tetrafluoroallene (**1**) is added to a toluene suspension of the metallocene hydride complex $[Cp_2ZrHCl]$ (**2**; $Cp = C_5H_5$), allenylic carbon–fluorine bond cleavage under formation of $[Cp_2ZrClF]$ (**4**) affords the hydrodefluorination products trifluoroallene (**3**) and difluoroallene (**5a**,**b**, Scheme 1). Although **3** and **5a** have been known for almost 40 years,[10] their chemistry has remained largely unexplored because of the limited synthetic access based on low-yield multi-step preparations starting from the now banned halofluorocarbons CF_2Br_2 and $CHFBr_2$, respectively. Depending on the stoichiometry, our new approach allowed for the isolation and characterization of **3** and **5a** in reasonable yield. In **5a**, the chemically equivalent yet magnetically inequivalent fluorine and hydrogen nuclei give rise to an AA′XX′ spin system (Figure 1). The ^{19}F NMR spectrum was analyzed by a simulation and subsequent least-squares refinement; the resulting coupling constants agree with calculated literature values.[11]



Scheme 1. Hydrodefluorination of tetrafluoroallene (**1**). Top: Synthesis of trifluoroallene (**3**); bottom: synthesis of 1,3-difluoroallene (**5a**) and 1,1-difluoroallene (**5b**).

Single-crystalline samples of **3** and **5a** suitable for X-ray structure determination were obtained in situ by maintaining sealed glass capillaries slightly below the melting points of the compounds (125 and 166 K, respectively).[12] Surprisingly, the carbon backbones of **3** and **5a** deviate by 4.4(3)° and 4.6(2)° from the linearity that would be expected based on their sp-hybridized central carbon atoms (Figure 2). Furthermore, the two terminal F-C-H planes in **5a** have a torsion angle of 91.9(2)°. The previously reported structures derived from microwave spectroscopy do not show the same distortions (Supporting Information, Table S2), because erroneously, the refinement was based on a constrained linear geometry.[13] To exclude the influence of packing effects on the observed distortions, we performed theoretical calculations at the coupled-cluster level of theory. The optimized structures of

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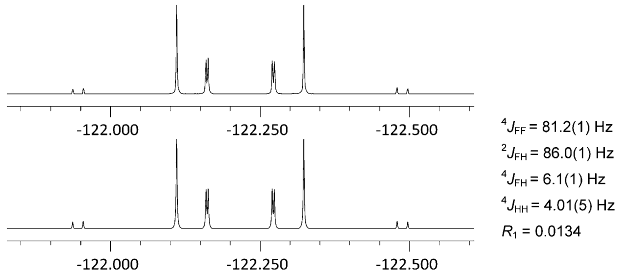


Figure 1. ^{19}F NMR spectrum of 1,3-difluoroallene (**5a**) in $CDCl_3$ solution (chemical shift in ppm, iterated coupling constants). Top: Experimental spectrum; bottom: simulation,.

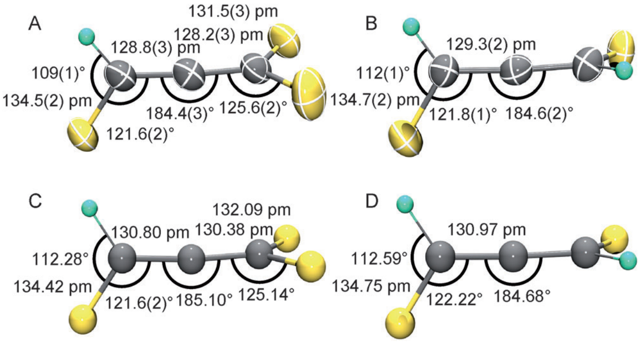
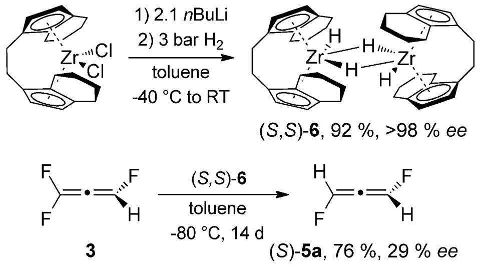


Figure 2. A,B) Experimental molecular structures of trifluoroallene (**3**) and 1,3-difluoroallene (**5a**), thermal ellipsoids set at 50% probability; C,D) CCSD(T)/aVTZ optimized structures of **3** and **5a**; C gray, F yellow, H blue.

3 and **5a** are in excellent agreement with the experimental data (Figure 2); the C-C-C angle departs slightly from linearity with the deviation becoming more prominent as the fluorine content of the molecule increases (Supporting Information, Figure S5). This deviation can be explained by the repulsive interaction of the nonbonding electrons at the fluorine atoms with the C_β–C_γ π-bonding orbitals; this π-bond is more electron-rich when more fluorine atoms are bonded to C_γ and thus the effect is more pronounced. Two perpendicular bends in **5a** result in the observed twist of the terminal F-C-H planes away from each other.

1,3-Disubstituted allenes are C_2 symmetric and therefore axially chiral. Apart from isotopologues, **5a** is the smallest possible axially chiral molecule; it is thermodynamically stable and is regarded as a promising candidate for experimental molecular parity-violation detection.[14] To perform an asymmetric synthesis of **5a**, a chiral zirconium hydride was required. Brintzinger-type *ansa*-metallocenes are well known for their rigidity and strong chiral induction;[15] we therefore chose the zirconium hydride complex **6** as a reagent. We successfully synthesized (*S,S*)-**6** and (*R,R*)-**6** from the commercially available dichloro analogues by a one-pot alkylation/hydrogenolysis reaction sequence in greater than 98% *ee* (Scheme 2); the enantiomeric purity was confirmed by derivatization with *R*-(−)-O-acetylmandelic acid. Addition of **3** to a solution of (*S,S*)-**6** at low temperatures affords **5a** in good yield. Spectroscopic discrimination of the enantiomers of **5a** is possible by forming diastereomeric inclusion compounds with the chiral solvating agent TRIMEB (Supporting Information, Figure S1).[16] This approach allowed the direct determination of the *ee* value by ^{19}F NMR spectroscopy. The *ee* values were found to be up to 30% (Supporting Information, Table S1). As expected, employing (*R,R*)-**6** reverses the enantioselectivity (Supporting Information, Figure S2).



Scheme 2. Top: Synthesis of a chiral zirconium hydride and bottom: its application for the asymmetric hydrodefluorination of **3**.

The absolute configuration of the major isomer was studied by gas-phase vibrational circular dichroism (VCD) spectroscopy (Figure 3).[17] At low concentration, only the strongest band υ_a(CF) at 1086 cm^{-1} gives rise to a detectable VCD signal, because the weaker bands are below the experimental threshold (Supporting Information, Figure S3 and S4). When **5a** is synthesized using (*S,S*)-**6**, this band exhibits a positive VCD signal. At higher concentration, negative VCD signals at 997, 1216, and 1316 cm^{-1} are detected. In agreement with our and previous theoretical calculations on the VCD spectrum of **5a**, this is unambiguously consistent with an *S*-configuration.[18] Apart from 1,3-dideuteroallene, whose optical activity has never been demonstrated experimentally,[19] *S*-**5a** represents the smallest axially chiral molecule that has been isolated in a non-racemic form.

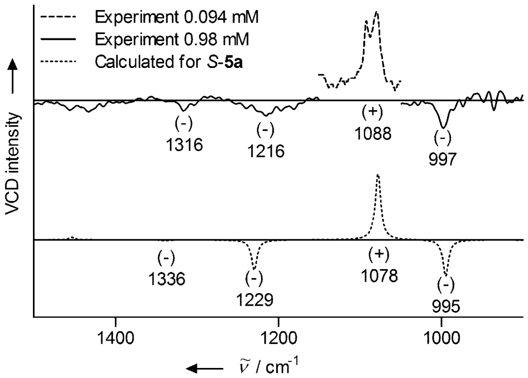


Figure 3. Gas-phase VCD spectra of **5a**. Top: Experimental spectrum of **5a** synthesized using (*S,S*)-**6** recorded at different concentrations; bottom: theoretical spectrum of *S*-**5a** at the B3LYP/6-31G** level of theory.

Our results clearly document that the combination of carbon–fluorine bond activation with asymmetric synthesis provides a new approach to chiral fluorinated molecules. This method not only offers a new strategy for the synthesis of fluorinated biologically active compounds, it also opens a new access to small chiral molecules, which are essential for studying the nature of chirality itself.

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[12] CCDC 850831 (**3**), 850830 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for **3**: C_3HF_3, $M_r = 94.04$, monoclinic, $a = 7.313(4)$, $b = 8.254(4)$, $c = 6.922(4)$ Å, $\alpha = 90.00$, $\beta = 118.038(10)$, $\gamma = 90.00°$, $V = 368.8(3)$ Å^3, $T = 123(2)$ K, space group $P2_1/c$, $Z = 4$, 1258 reflections measured, 647 independent reflections ($R_{int} = 0.1018$). The final R_1 values were 0.0461 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1271 ($I > 2\sigma(I)$). The final R_1 values were 0.0541 (all data). The final w$R(F^2)$ values were 0.1347 (all data). Crystal data for **5a**: $C_3H_2F_2$, $M_r = 76.05$, monoclinic, $a = 7.0297(14)$, $b = 6.7205(14)$, $c = 7.8245(16)$ Å, $\alpha = 90.00$, $\beta = 114.399(4)$, $\gamma = 90.00°$, $V = 336.64(12)$ Å^3, $T = 123(2)$ K, space group $P2_1/c$, $Z = 4$, 3861 reflections measured, 684 independent reflections ($R_{int} = 0.0272$). The final R_1 values were 0.0334 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1028 ($I > 2\sigma(I)$). The final R_1 values were 0.0375 (all data). The final w$R(F^2)$ values were 0.1056 (all data).

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