Conformational Analysis

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The Fluorine-Iminium Ion *Gauche* Effect: Proof of Principle and Application to Asymmetric Organocatalysis**

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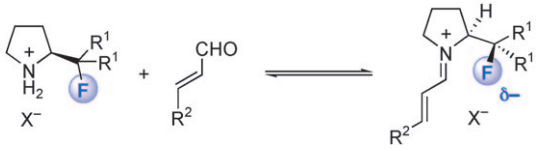
Dedicated to Professor Dr. Jack D. Dunitz

The concept of physical and electronic modulation of molecular states by the incorporation of fluorine atoms is well established in the fields of polymer and material science.[1] The propensity of highly electronegative elements, such as fluorine, to lower the energy of molecular orbitals to which they contribute has been widely exploited in the design of high performance materials; a feature that has yet to reach its full potential in the realm of catalysis. The current renaissance of catalysis mediated by small organic molecules[2] is one such area where the application of fluorinated materials may be explored. Furthermore, the predisposition of fluorinated amine derivatives to exhibit stereoelectronic and electrostatic effects lend themselves to the design of novel organocatalyst scaffolds.

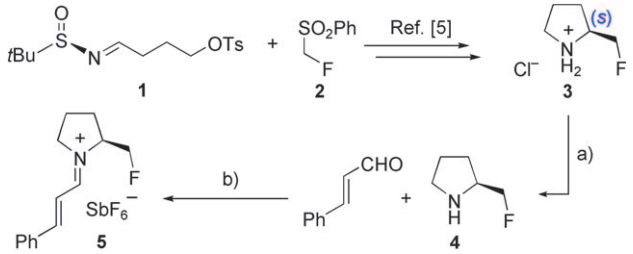
Generally, placement of fluorine beta to an electron withdrawing group leads to a preference for a *gauche* conformation—a phenomenon that is necessarily accompanied by a conformational change.[3] Hence, it was envisaged that the iminium ion, which results from the union of a secondary β-fluoroamine with an aldehyde, would assume a *gauche* conformation; an effect that would provide an extra degree of torsional rigidity and could assist induction from the secondary amine vector to the reactive centre of the π system (Scheme 1). Furthermore, the potential LUMO-lowering effect of incorporating a fluorine atom into the catalyst structure rendered this approach even more attractive.[4] Herein, we highlight the potential of the C–F bond as a valuable design element in catalysis.

Initially, we embarked upon a structural and computational study of β-fluoroiminium ions based on the pyrrolidine scaffold in order to substantiate the *gauche*-effect hypothesis.



Scheme 1. The fluorine-iminium ion *gauche* effect.

The pyrrolidinium salt **3** was selected as a starting substrate so as to minimize any steric bias on the system arising from the side chain. This salt was prepared from the sulfinyl imine **1** and sulfone **2** (Scheme 2).[5]



Scheme 2. Synthesis of β-fluoroiminium ion **5**. Reagents and conditions: a) Amberlyst A-21, MeOH; b) $HSbF_6$ (aq), MeOH (83% from **3**). Ts = 4-toluenesulfonyl.

In order to prepare suitable crystals of the parent iminium ion for X-ray crystallographic analysis, it was imperative that the salt be comprised of a large, noncoordinating counter ion; hexafluoroantimonate was the counterion of choice. Consequently, the hydrochloride salt **3** was treated with a basic ion-exchange resin in methanol, thus liberating the free amine **4**. Union of this compound with *trans*-cinnamaldehyde in a solution of hexafluoroantimonic acid and methanol furnished the desired iminium ion **5** in 83% yield (Figure 1).

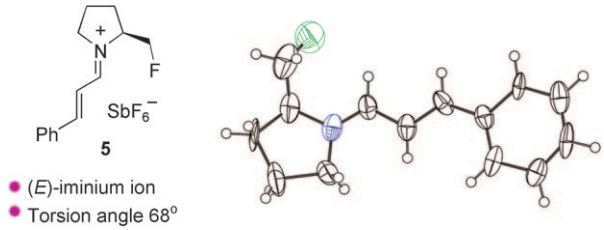


Figure 1. One of the two symmetry independent molecules of the crystal structure of iminium ion **5**. The five-membered ring shows a flexible conformation and is disordered. Thermal ellipsoids are drawn at the 50% probability level and the counterion has been omitted for clarity.

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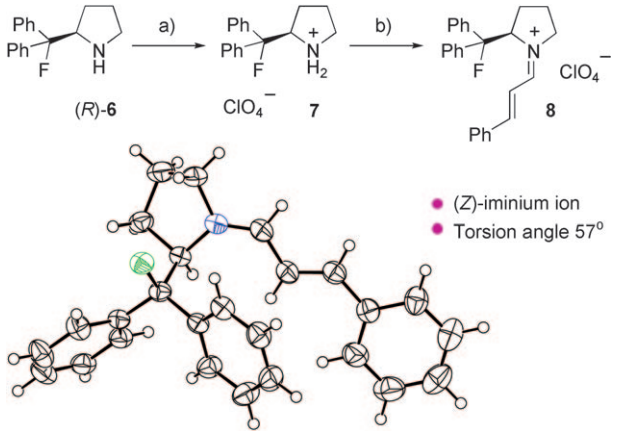
The structure of the salt **5** was unambiguously established by single crystal X-ray diffraction and confirmed the expected *E* geometry of the iminium ion **5**, which minimizes 1,3-allylic strain (Figure 1). The unit cell contained two symmetry independent molecules with torsion angles N-C-C-F of 77.8° and 68.0°, thus validating our initial hypothesis.[6] With the intention of applying this concept to asymmetric catalysis, we sought to investigate the more sterically demanding 2-(fluorodiphenylmethyl)pyrrolidine **6**, popularized by O'Hagan and co-workers.[7–9] The perchlorate salt of (*R*)-2-(fluorodiphenylmethyl) pyrrolidine **7**[10] was converted into the iminium ion **8**, and analyzed by X-ray crystallography. To our delight, a clear *gauche* orientation was observed between the nitrogen and the fluorine atoms (N-C-C-F torsion angle of 57°; Scheme 3).[11] Pertinent features of the solid state analysis



Scheme 3. Reagents and conditions: a) $HClO_4$ (aq), 77%; b) *trans*-cinnamaldehyde, 59%. Thermal ellipsoids are drawn at the 50% probability level and the counterion has been omitted for clarity.

include the *Z* configuration of the iminium ion; a factor that may be considered to be energetically unfavorable on the basis of nonbonding interactions. Initially, it was envisaged that such preorganization might give rise to a system that is complementary to the classical imidazolidinone- and prolinol-derived organocatalysts, which have been proposed to proceed through an (*E*)-iminium ion. However ^{1}H NMR analysis of **8** revealed that a 1:1 *E*:*Z* mixture is present in solution, therefore the *Z* geometry in the solid state is attributed to crystal packing forces. Interestingly, relatively few crystallographic studies of organocatalysts and their enamine/iminium ion derivatives have appeared in the literature despite the immense developments in this branch of organic chemistry.[12–14]

In order to study the conformations and electronic structures of β-fluoroiminium ions such as **8**, we undertook a density functional theory (DFT) computational study (Figure 2).[15] Calculations quickly confirmed that a *gauche* effect was significantly more pronounced with diphenylfluoromethyl derivatives (C**F**Ph$_2$), such as **8**, compared with the corresponding diphenylmethyl species (C**H**Ph$_2$). For the fluorinated derivatives, the preference for the *gauche* over the *anti* conformation was calculated to be

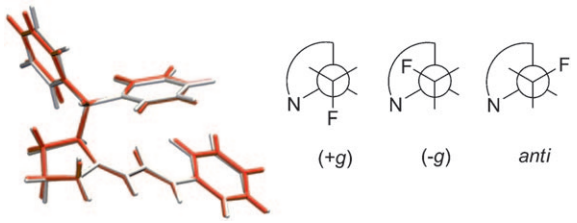
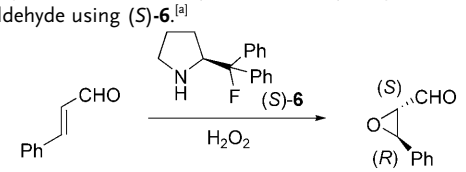


Figure 2. Structures of (*Z*-g)-(*S*)-**8**. Red: enantiomer generated from the X-ray structure of (***R***)-**8**; white: DFT-optimized structure.

16.5 kJmol^{-1} for the *E* geometry and 18.1 kJ mol^{-1} for the *Z* geometry, whereas in the nonfluorinated congeners the *gauche* conformer was favored by only 5–6 kJ mol^{-1}. The (*E*)-iminium ions were generally preferred over the corresponding (*Z*)-iminium ions by 2–7 kJ mol^{-1}; a finding that is at variance with the X-ray structure of **8**. However, computational, crystallographic (structures of **5** and **8**), and solution NMR data suggest that the *E* and *Z* forms of these iminium ions are close in energy and that the observed preference for the *E* form in the crystal structure of **8** arises from packing effects. The computational studies used to explore the effect of the fluorine substituent on the electronic structure of the iminium ion confirmed a LUMO-lowering effect, albeit small. The ε_{LUMO} of the fluorinated (*E*)-iminium ion was calculated to be 4.8 kJ mol^{-1} lower than in the parent diphenylmethyl analogue.

In an attempt to investigate the catalytic potential of β-fluoroamine derivatives, such as (*S*)/(*R*)-**6**, the Weitz–Scheffer epoxidation of α,β-unsaturated aldehydes (using hydrogen peroxide) was selected as a model reaction (Table 1).[16]

Table 1: Optimization of the asymmetric, catalytic epoxidation of *trans*-cinnamaldehyde using (*S*)-**6**.[a]



Entry	Solvent	Concentration [mmol L^{-1}]	Catalyst loading [mol%][b]	d.r.[c]	*ee* [%][d]
1	CH_2Cl_2	500	10	78:22	93
2	$CHCl_3$	500	10	82:18	96
3	THF	500	10	74:26	92
4	toluene	500	10	77:23	96
5	$CHCl_3$	5000	10	76:24	95
6	$CHCl_3$	1000	10	79:21	96
7	$CHCl_3$	100	10	77:23	95
8	$CHCl_3$	50	10	78:22	93
9	$CHCl_3$	10[e]	10	87:13	92
10	$CHCl_3$	500	20	81:19	96
11	$CHCl_3$	500	5	77:23	96
12	$CHCl_3$	500	1[e]	78:22	87

[a] Reactions were performed with aldehyde (500 μmol) and H_2O_2 (1.3 equiv) for 3 hours at room temperature. [b] (*S*)-**(6)** was purchased from Sigma–Aldrich (optical purity of 98% *ee*, determined by HPLC). [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by GC analysis on a chiral stationary phase using a Supelco β-DEX 120 column (95 °C isotherm). [e] Incomplete conversion after 3 h. THF = tetrahydrofuran.

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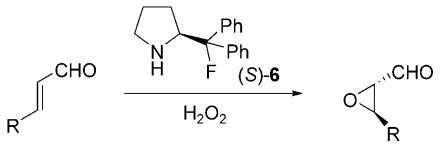
An initial screen quickly revealed $CHCl_3$ to be the solvent of choice, giving superior levels of both diastereo- and enantioselectivity in the conversion of *trans*-cinnamaldehyde into the corresponding (2*S*,3*R*)-epoxide (Table 1, entry 2). Gratifyingly, the selectivity of this transformation showed little concentration dependence (Table 1, entries 5–9). Reaction concentrations ranging from 5 mol L^{-1} to 10 mmol L^{-1} reproducibly furnished enantioselectivity in excess of 90%; a factor that is particularly attractive for scale-up. Moreover, the diastereoselectivity remained constant at about 4:1 throughout this study. Our attention was then focused on exploring the effect of catalyst loadings on the outcome of the epoxidation (Table 1, entries 10–12). Notably, catalyst loadings as low as 5 mol% continued to enforce high levels of optical enrichment (96% *ee*; Table 1, entry 11). Remarkably, elevated levels of asymmetric induction continued to be observed when reactions were performed with only 1 mol% of the catalyst (87% *ee*; Table 1, entry 12). As a control experiment, the epoxidation of *trans*-cinnamaldehyde was performed using the nonfluorinated counterpart of (*S*)-**6** (C**H**Ph$_2$). A notable loss in enantioselectivity was observed (85% *ee* compared to 96% *ee* when using (*S*)-**6**), thus illustrating the importance of the fluorine-iminium ion *gauche* effect for efficient chirality transfer.[17]

With an optimized set of reaction conditions now developed, we investigated the scope and limitations of catalyst (*S*)-**6** (Table 2). The configurations of the epoxides described herein were determined by direct comparison with literature data or by derivatization and subsequent chemical correlation.[16]

Table 2: Exploring the scope and limitations of the catalytic epoxidation reaction.[a]



Entry	Substrate	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	R = Ph	92	82:18	96
2	R = *p*-FC$_6$H$_4$	89	73:27	94
3	R = *p*-BrC$_6$H$_4$	94	81:19	94
4	R = *p*-NO$_2$C$_6$H$_4$	93	69:31	96
5	R = *p*-MeOC$_6$H$_4$	26[e]	–	–
6	R = *n*Pr	87[f]	92:8	95
7	R = *i*Pr	90[f]	>95:<5	92
8	citral[g]	91	60:40	81
9	cyclohexene-1-carboxaldehyde	68	>95:<5	97

[a] Reactions performed in $CHCl_3$ with aldehyde (500 μmol), (*S*)-**6** (10 mol%), and H_2O_2(1.3 equiv) for 3 hours at room temperature. (*S*)-**(6)** was purchased from Sigma–Aldrich (optical purity of 98% *ee*, determined by HPLC). [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by GC and HPLC analysis on a chiral stationary phase. [e] The ring opened glyoxal was isolated after 14 hours.[10] [f] After reduction using $NaBH_4$. [g] *E*/*Z* 3:2.

As highlighted in Table 2, variation in the electronic nature of the aromatic component of the starting cinnamaldehyde substrate appeared to have little influence on the inherent stereoselectivity of the epoxidation (94–96% *ee*; Table 2, entries 1–4). Notably, the reactions of aliphatic aldehydes (Table 2, entries 6 and 7) proceed with superb levels of diastereo- and enantiocontrol (>9:1 d.r., >90% *ee*). Although slightly more challenging, trisubstituted α,β-unsaturated aldehydes such as citral and cyclohexene-1-carboxaldehyde (Table 2, entries 8 and 9) were smoothly converted into their respective epoxides, thus illustrating the generality of this method for the epoxidation of α,β-unsaturated aldehydes at relatively low catalyst loadings (10 mol%). In the later case, the induction is particularly noteworthy (97% *ee* ; Table 2, entry 9) considering the optical purity of the starting catalyst (98% *ee*). The exceptional levels of enantiofacial discrimination observed in the epoxidation of *trans*-cinnamaldehyde mediated by (*S*)-**6** is consistent with the addition of H_2O_2 to the *Si* face of the transient (*E*)-iminium ion. Based on these preliminary results it is proposed that the fluorine-iminium ion *gauche* effect induces a conformational change that positions a phenyl ring across one face of the π system, thus directing the nucleophile to the less sterically congested face. This sense of asymmetric induction was found to be consistent throughout the study.

In conclusion, we have described the fluorine-iminium ion *gauche* effect and illustrated its potential as a valuable conformational tool. Subsequently, this phenomenon has been exploited in the design of a novel organocatalyst and showcased in the operationally simple, stereoselective epoxidation of α,β-unsaturated aldehydes. The *gauche* effect that is induced upon reversible formation of an iminium ion is necessarily dynamic in nature and provides a powerful method for the preorganisation of the transient intermediates that are central to secondary amine catalyzed processes. Application of this concept to other transformations is currently ongoing and will be reported in due course.

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[6] Crystallographic data for **5**: $C_{14}H_{17}F_7NSb$, $M = 454.033$, triclinic; Space group $P1$; $a = 7.4497$ (2) Å, $b = 10.7851$ (4) Å, $c = 11.2896$ (4) Å; $V = 830.54$ (5) Å^3; $Z = 2$; $\rho_{calcd} = 1.816\ Mg\,m^{-3}$; $T = 223$ K; reflections collected: 11104, independent reflections: 6517 ($R_{int} = 0.072$), $R(all) = 0.0796$. $wR(gt) = 0.1689$, Flack parameter = 0.05 (4). CCDC 716829 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[10] For the X-ray data see the Supporting Information.

[11] Crystallographic data for **8**: $C_{17}H_{19}ClFNO_4$, $M = 355.793$, orthorhombic; Space group $P2_12_12_1$; $a = 6.3518$ (2) Å, $b = 12.5281$ (5) Å, $c = 21.3780$ (8) Å; $V = 1701.18$ (11) Å^3; $Z = 4$; $\rho_{calcd} = 1.389\ Mg\,m^{-3}$; $T = 223$ K; reflections collected: 9636, independent reflections: 3794 ($R_{int} = 0.090$), $R(all) = 0.1046$. $wR(gt) = 0.1664$, Flack parameter = −0.07 (12). CCDC 716830 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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