Conformational Analysis

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Fluoro-Organocatalysts: Conformer Equivalents as a Tool for Mechanistic Studies**

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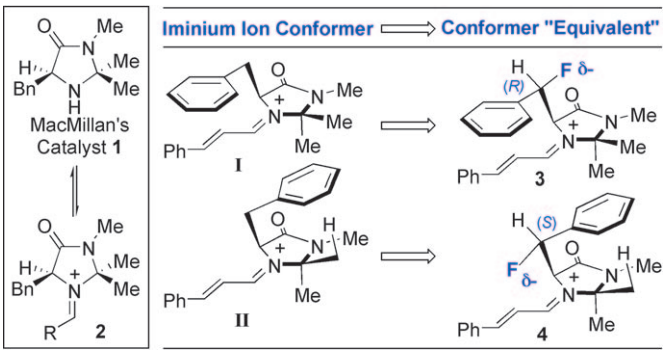
Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

Enantioselective organocatalysis has revolutionized the field of asymmetric synthesis, transforming rudimentary considerations of enamine and iminium ion reactivity into powerful strategies for stereoselective reaction design. This renaissance of catalysis mediated by low-molecular-weight organic amine derivatives not only compliments existing organometallic and enzymatic strategies for enantioinduction, but confers a number of advantages ranging from ease of catalyst preparation through to simplicity of reaction execution. Unsurprisingly a colossal number of innovative, often bioinspired, organocatalytic processes have been reported.[1] While this constantly expanding repertoire is impetus enough for further development, interplay between preparative and mechanistic studies is imperative in order to sustain innovation. The improvement of existing catalyst topologies and the de novo design of unique architectures require an intimate appreciation of the decisive interactions involved in orchestrating asymmetric amplification. Conformational analysis is therefore of fundamental importance.

MacMillan's seminal reports of Diels–Alder,[2] 1,3-dipolar cycloaddition,[3] and Friedel–Crafts reactions[4] of α,β-unsaturated aldehydes catalyzed by imidazolidinone **1** remain landmark developments in this field. Catalytic efficiency is principally due to several design features that take effect upon intramolecularization to form a transient iminium ion intermediate (**2;** Scheme 1). In particular the three sp^2 hybridized centers create a highly strained core, while the *gem*-dimethyl motif imparts geometric control by virtue of 1,3-allylic ($A^{1,3}$) strain. Enantioinduction is conferred by a directing phenyl group, however, the prevailing conformation responsible for amplification of chirality has yet to be firmly established. Models incorporating π–π interactions, CH–π interactions, and the oscillatory motion of the phenyl ring have been described.[2–5] However, to the best of our knowledge no "tool" to study the contributions of individual conformations, separated by minimal steric bias, has been described. We therefore envisaged that the fluorine–iminium ion *gauche* effect[6] reported earlier by our research group could be exploited in the design of conformational probes for organocatalysis. Stabilizing hyperconjugative [$\sigma_{C-H} \rightarrow \sigma^*_{C-F}$] and/or electrostatic [$N^+ \cdots F^{\delta-}$] interactions render the C–F bond an excellent steering group for controlling molecular topology without introducing additional steric constraints. The predetermined configuration of the benzylic fluorine center would encode for a given topology, hence diastereoisomers **3** and **4** were envisioned to be "conformer equivalents" of **I** and **II**, respectively (Scheme 1).



Scheme 1. Iminium ion conformer equivalents.

Synthesis of iminium salt **3** commenced with the methylation and subsequent amidation of L-*threo*-phenylserine **5** (Scheme 2). Diastereoselective fluorination by treatment with DAST in CH_2Cl_2 proceeded with retention of configuration to furnish the desired fluoride **8** in good yield (d.r. = 4.2:1). The stereoselectivity observed in this transformation may be rationalized by minimization of 1,3-allylic strain in the transient chiral benzylic cation in accordance with the models proposed by Bach and co-workers.[7] Subsequent formation of the imidazolidinone ring system furnished the target *R*,*R*-catalyst structure **9** which was then processed to the iminium ion **3** for conformational analysis and mechanistic studies. Iminium salt **4** was prepared from the fluorophenylalanine derivative **11** by an analogous reaction sequence.[8] Again, the diastereoselectivity of the fluorination reaction is dictated by $A^{1,3}$ strain, to furnish the *R*,*S*-diastereoisomer **11** in a concise, highly selective manner (d.r. = 120:1).

Initially, fluoroimidazolidinone salts **9** and **13** were analyzed by ^{1}H NMR spectroscopy and single-crystal X-ray

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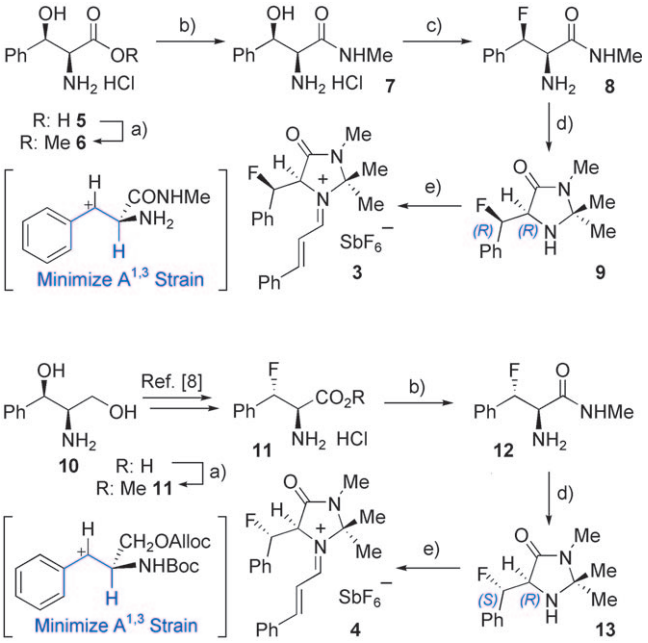


Scheme 2. Synthesis of fluoroiminium ions (*R*,*R*)-**3** and (*R*,*S*)-**4**. Reagents and conditions: a) $SOCl_2$, MeOH; b) $MeNH_2$, EtOH (**12**, 70%, 2 steps); c) DAST, CH_2Cl_2 (**8**, 43%, 3 steps); d) Me_2CO, *p*-TsOH (**9**, 68%; **13**, 79%), e) 1. $HSbF_6$, MeOH, 2. (*E*)-cinnamaldehyde, Et_3N, EtOH (**3**, 73%; **4**, 70%). Alloc = allyloxycarbonyl, Boc = *tert*-butoxycarbonyl, DAST = diethylaminosulfur trifluoride, *p*-TsOH = *para*-toluenesulfonic acid.

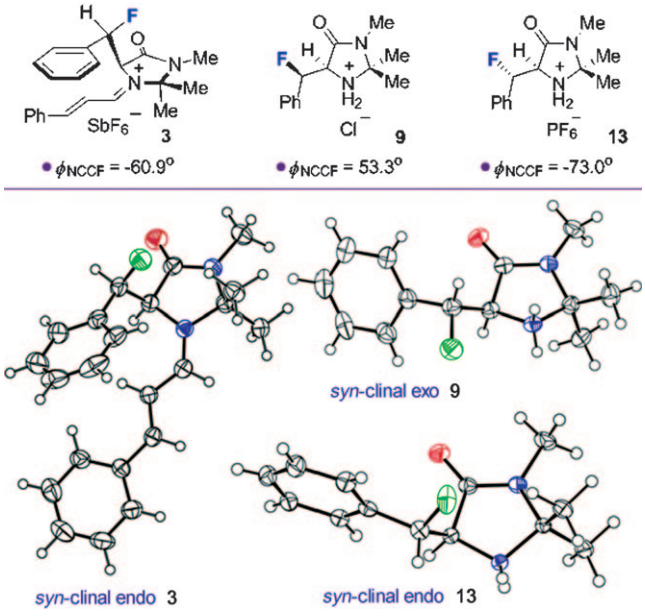


Figure 1. Solid-state analysis of β-fluoroiminium salt **3**, and fluoroimidazolidinones **9** and **13**. Thermal ellipsoids are drawn at the 50% probability level. The counterions have been omitted for clarity.[9]

diffraction methods to determine which of two possible *gauche* conformations was favored (*syn*-clinal *endo* vs. *syn*-clinal *exo*).[9] In both cases, an open *gauche* conformation was established with the phenyl ring being positioned away from the catalyst core (Figure 1). While the *R*-configured fluoride **9** adopted a *syn*-clinal *exo* topology ($\phi_{NCCF} = 53.3°$), the analogous *S*-configured system **13** resided in the *syn*-clinal *endo* conformation ($\phi_{NCCF} = -73.0°$).

Intriguingly, intramolecularization with *trans*-cinnamaldehyde elicited a conformational response with the *R*,*R*-configured fluoroiminium ion **3** selecting the *syn*-clinal *endo* topology in which the phenyl ring is placed over the π system. X-ray analysis of this material revealed a dihedral angle of $\phi_{NCCF} = -60.9°$ (an equivalent of conformer **I**). The dynamic nature of this topological change triggered by intramolecularization was confirmed by ^1H and ^{13}C NMR spectroscopy. Figure 2 shows the upfield shift of the β-iminium proton of **3** ($\delta_H = 5.80$ ppm vs. $\delta_H = 7.50$ ppm for **4**) consistent with the shielding influence exerted by the proximal phenyl ring.[5d,e] The noticeable shifts of the α and γ protons, albeit to a lesser extent, are also attributable to this conformation ($\Delta\delta_H$(**4**α-**3**α) = 0.19 ppm; $\Delta\delta_H$(**4**γ-**3**γ) = 0.55 ppm). A conformational change was also observed when the *R*,*S*-configured fluoroimidazolidinone **13** was converted into iminium ion **4** with the phenyl ring being placed in proximity to the adjacent methyl group. Although this compound proved to be recalcitrant to crystallization, it was possible to grow microcrystalline material: frustratingly, this was unsuitable for X-ray analysis. However, ^1H NMR studies confirmed that the *syn*-clinal *exo* conformer predominates (an equivalent of conformer **II**) in solution by virtue of the significant up-field shift of the *syn*-methyl group ($\delta_H = 0.57$ ppm, Me′; $\Delta\delta_H$(**4**$_{Me''}$-**4**$_{Me'}$) = 1.08 ppm).[10]

Further validation came from ^{13}C NMR studies as shown in Figure 2 (upper). The spectrum of iminium salt **3** shows a weak scalar coupling ("through-space") between the fluorine atom and the *syn*-methyl group (Me′; $^5J_{CF} = 6.7$ Hz). This effect is only possible if the carbon and fluorine atoms are within van der Waals contact:[11] this distance is around 3 Å in the solid state. Furthermore, the ^{13}C NMR spectrum of iminium ion **4** also showed a clear scalar coupling with the β carbon of the pendant iminium chain ($^5J_{CF} = 15.3$ Hz). Collectively, these NMR data indicate that the iminium ion conformers present in the solid state are also dominant in solution.

Having completed this conformational study we investigated the potential usefulness of "conformer equivalents" in understanding enantioinduction in organocatalytic transformations. As a representative reaction, we initially elected to study Friedel–Crafts-type addition reactions to *trans*-cinnamaldehyde under MacMillan's previously reported conditions using **1**, **9**, and **13**.[4a] However, in some reactions mediated by **9** and **13**, inversion of the sense of enantioselectivity was observed. We attribute these findings to selective formation of the *Z*-iminium ion as the kinetic product,[12] and under these conditions addition of the nucleophile occurs prior to preequilibration to the *E*-iminium ion. Optimistic that these initial findings might give an insight into the conformational requirements of the phenyl group for efficient geometric control during iminium ion formation, the thermodynamically more stable *E*-iminium ions (**3** and **4**) were preformed and isolated prior to conjugate addition. From ^1H and ^{19}F NMR analyses of these iminium ions, we measured similar *E*/*Z*

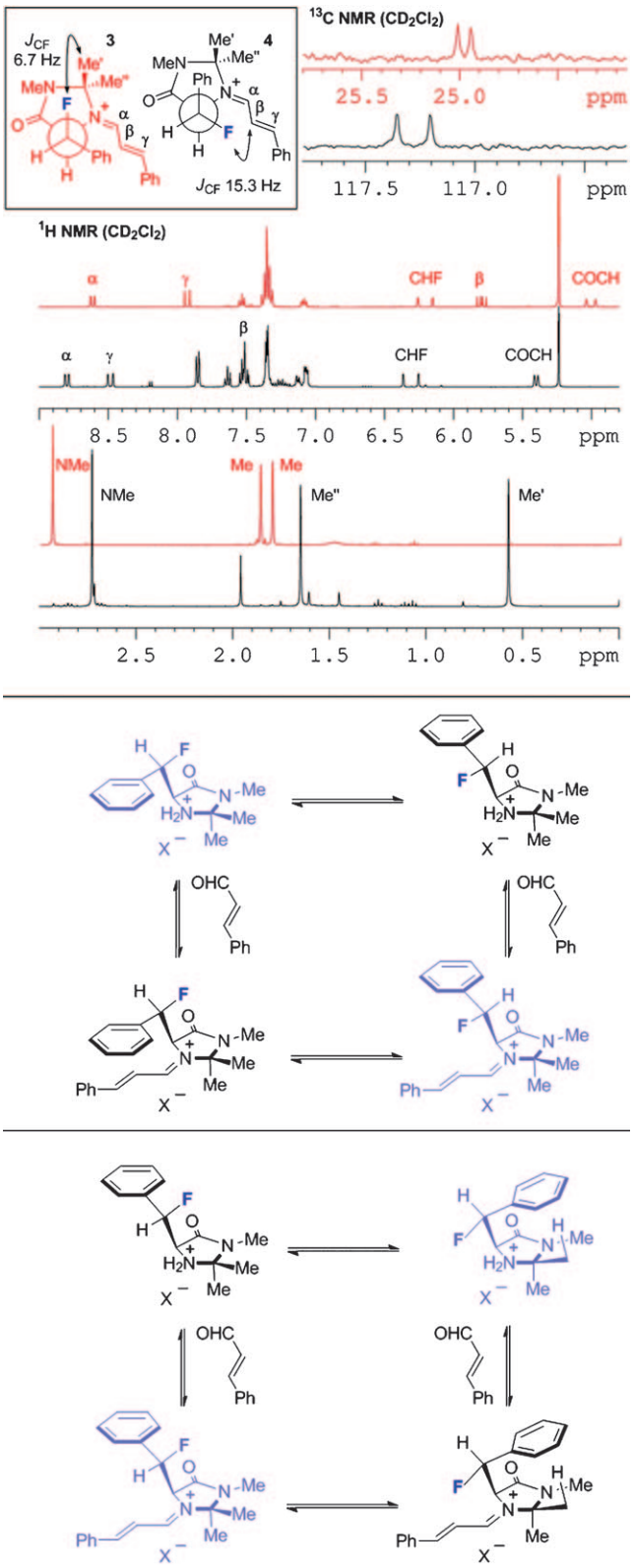
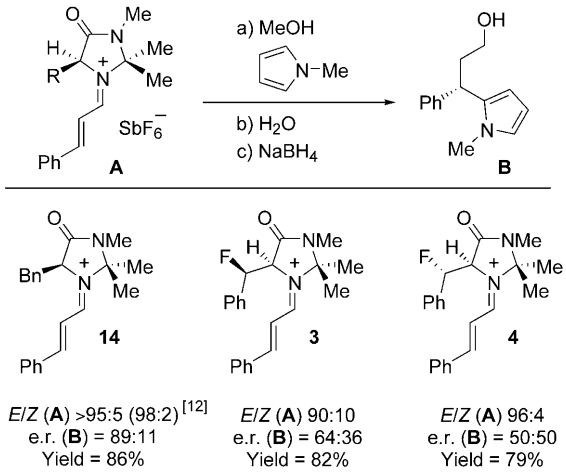


Figure 2. Selected regions of the ^{1}H and ^{13}C NMR spectra of iminium salts **3** (red) and **4** (black). Measurements were conducted in CD_2Cl_2. Conformations in black are observed by NMR and X-ray methods; conformations in blue are not observed.

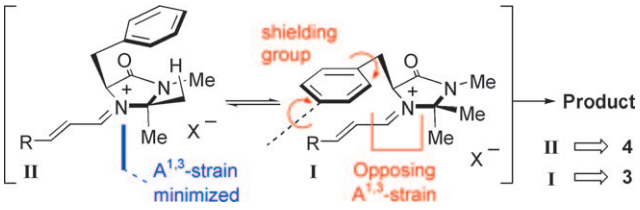
ratios for **3** and **4**, but a consistently lower *E*/*Z* ratio for **3**. This observation is consistent with conformer equivalent **I** (**3**) experiencing opposing steric stress from both the *gem*-dimethyl motif and the freely rotating C–C(Ph_{ipso}) bond which is placed in proximity as a result of the *gauche* effect. From these findings, we conclude that conformer **II** (Scheme 1) contributes to efficient catalysis by minimizing $A^{1,3}$ strain, thus allowing high levels of geometric control in reactions with preequilibrating conditions. It seems rational that while conformer **II** benefits from a stabilizing CH–π interaction it is also likely to be at least a partial manifestation of minimized nonbonding interactions.

Subsequently, we compared the selectivities of conjugate additions of *N*-methylpyrrole to iminium ions **3**, **4**, and **14** (Scheme 3). We observed enhanced levels of enantioinduc-



Scheme 3. Conjugate addition reactions of iminium ions **3**, **4**, and **14** to *N*-methylpyrrole: Addition reactions were performed at ambient temperature in methanol for a period of 1.5 hours. In situ reduction of the aldehyde to the corresponding primary alcohol facilitated HPLC analysis.

tion with iminium ion **3** (conformer equivalent of **I**) as compared to **4** (conformer equivalent of **II**; e.r. = 64:36 vs. racemic). Taking into consideration the lower *E*/*Z* ratio of **3** relative to **14** and **4**, this result is in agreement with MacMillan's original model for stereoinduction via conformation **I**. By exploiting the fluorine–iminium ion *gauche* effect in the design of mechanistic probes, it has been possible to "freeze out" the two iminium ion conformations that are widely accepted to be important for the remarkable catalytic activity of MacMillan's first-generation catalyst. From this preliminary study, we hope to have provided independent evidence that the topology of the benzyl shielding group is not only responsible for translation of chirality, but also in influencing the *E*/*Z* ratio of the transient iminium ions upon condensation. This conformational symbiosis suggests that conformation **II** (equivalent **4**) is likely responsible for assuring high levels of geometric control with conformation **I** (equivalent **3**) imparting high levels of enantioinduction (Scheme 4). Clearly bond rotation (**II**→**I**) prior to an addition reaction occurs faster than *E*/*Z* isomerization[5f] and is therefore inconsequential to the pre-set iminium ion ratio encoded by conformation **II**.



Scheme 4. An interpretation of the function of the phenyl group.

In summary, the concept of conformer equivalents as a tool to investigate noncovalent interactions in catalysis is disclosed. The diastereoselective syntheses of two, novel imidazolidinones are described together with the dynamic conformational behavior of these materials when condensed to form iminium ions. We have gained a preliminary insight into some of the noncovalent interactions that are important for further catalyst development. Namely, that the phenyl group functions both in controlling iminium ion geometry and conferring enantioinduction in the conjugate addition of *N*-methylpyrrole to **3**, **4**, and **14**. Efforts to expand upon the concept of conformer equivalents are currently on-going in our laboratory.

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[9] For full experimental details see the Supporting Information. CCDC 777914 (**3**), 777913 (**5**), and 777912 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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