Catalyst Design

DOI: 10.1002/anie.201102027

Fluorine Conformational Effects in Organocatalysis: An Emerging Strategy for Molecular Design

*Lucie E. Zimmer, Christof Sparr, and Ryan Gilmour**

asymmetric catalysis · conformation analysis · fluorine · organocatalysis · stereoelectronic effects

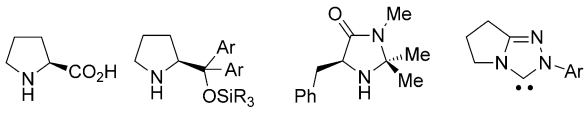
Dedicated to Professor David O'Hagan

Molecular design strategies that profit from the intrinsic stereoelectronic and electrostatic effects of fluorinated organic molecules have mainly been restricted to bio-organic chemistry. Indeed, many fluorine conformational effects remain academic curiosities with no immediate application. However, the renaissance of organocatalysis offers the possibility to exploit many of these well-described phenomena for molecular preorganization. In this minireview, we highlight examples of catalyst refinement by introduction of an aliphatic C–F bond which functions as a chemically inert steering group for conformational control.

> "*It is of great advantage to the student of any subject to read the original memoirs on that subject, for science is always most completely assimilated when it is in the nascent state.*"
>
> *James Clerk Maxwell (1831–1879)*

1. Introduction

Modern stereoelectronic theory appears to have nucleated upon unification of the visionary theories by Robinson[1] and Ingold[2] with the formalization of conformational analysis by Barton,[3] giving rise to a powerful tool for rationalizing the outcome of organic transformations.[4,5] The last 70 years have witnessed explosive developments in this discipline, transforming rudimentary considerations of electronic structure at the molecular level into logical thought processes to account for the perplexity of (bio)synthetic processes. As early as the 1950s, E. J. Corey coined the term "stereoelectronic control" to account for the importance of maximum overlap of perturbed molecular orbitals in transition state intermediates.[6] Contemporaneously, Eschenmoser and Arigoni formulated their "biogenetic isoprene rule" in which the Fürst–Plattner rule (*trans* diaxial effect)[7] was invoked to account for the stereochemical course of 1,5-diene cyclizations leading to triterpenoids.[8] Cumulative advances in conformational analysis, reaction design, and catalyst development have derived from this formative work.[9] Consequently, the notion that orbital symmetry and dynamics play a central role in governing conformation and reactivity is now regarded as a fundamental premise of organic chemistry. The conventional use of stereoelectronic considerations for post facto rationalization has now evolved into a well-developed strategy for the logical design of reactions and functional molecular systems. Stereoelectronic and electrostatic effects are particularly prominent in governing the behavior and conformation of fluorinated organic compounds; this observation is attributable to the electronegativity of fluorine ($\chi \approx 4$), the highly polarized nature of the C–F bond, and the vacant, low-lying $\sigma^*_{C\text{-}F}$ orbital that can interact with adjacent σ bonds or nonbonding electron pairs. Importantly, fluorine also has the capacity to interact with proximal electropositive centers through stabilizing electrostatic/charge-dipole processes. To date, strategic application of these effects to predictably control molecular topology remain elusive outside the boundaries of pharmaceutical and biological chemistry.[10] However, the renaissance of catalysis mediated by small organic molecules (organocatalysis) offers the possibility to tactically utilize these effects for molecular preorganization. This is principally due to the structural similarities that exist between many current secondary-amine-based organocatalysts (Scheme 1), and the fluorinated scaffolds that have conventionally been used for conformational analysis (Figure 1). Importantly, fluorine's low van der



proline | Hayashi/Jørgensen diarylprolinols | MacMillan imidazolidinones | N-heterocyclic carbenes

Scheme 1. Secondary-amine-derived organocatalysts.

[*] Dr. L. E. Zimmer, C. Sparr, Prof. Dr. R. Gilmour
ETH Zürich, Laboratorium für Organische Chemie
Departement Chemie und Angewandte Biowissenschaften
Wolfgang-Pauli-Str. 10, CH-8093 Zürich (Switzerland)
E-mail: ryan.gilmour@org.chem.ethz.ch
Homepage: http://www.gilmour.ethz.ch

WILEY ONLINE LIBRARY

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

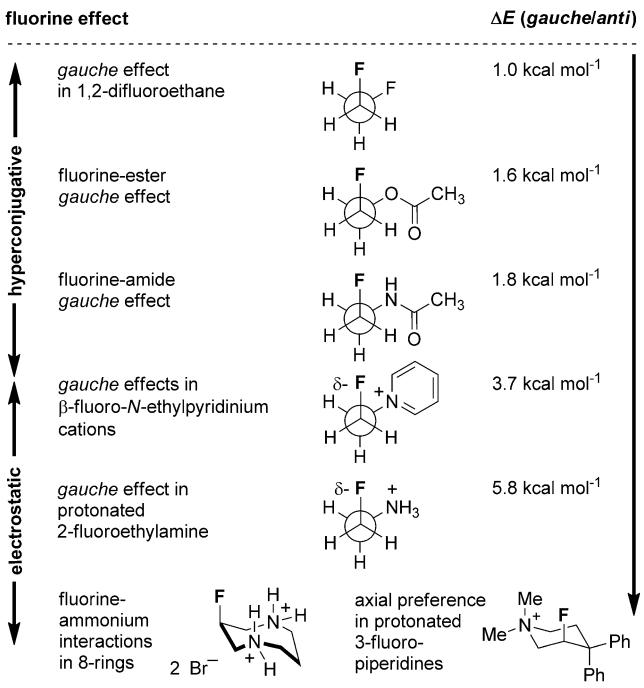


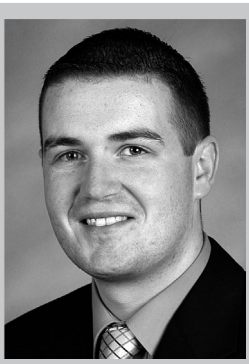
Figure 1. Selected fluorine stereoelectronic and electrostatic effects.

Waals radius and its high bond strength to carbon render it a small, chemically inert steering group for controlling molecular topology. This strategy of ensuring a high intermediate conformer population in a catalytic cycle is complementary to conventional steric governance and avoids many of the undesirable ramifications on reactivity. Herein we discuss examples of asymmetric catalysis, in which a single, aliphatic C–F bond plays a prominent role in establishing conformational rigidity, thus tipping the inevitable balance between multiple conformers to favor a single species and thus facilitate enantioinduction. This account is by no means a comprehensive survey,[11] rather it is intended to review selected examples, in which catalyst design and refinement has been directly influenced by subtle changes in charge distribution (electrostatics) or spatial orientation of filled or unfilled molecular orbitals (stereoelectronics) as a consequence of introducing a C–F bond.

1.1. An Overview of Fluorine Stereoelectronic and Electrostatic Effects

The term stereoelectronic effect refers to the relative spatial alignment and overlap of orbitals in which there is net stabilization.[4,12] The high electronegativity of fluorine and, by extension, the hybridization and the polarized nature of the $C^{\delta+}$–$F^{\delta-}$ bond, gives rise to a plenum of stereoelectronic and electrostatic effects.[13] The finest didactic example is the fluorine *gauche* effect (Scheme 2).[14]

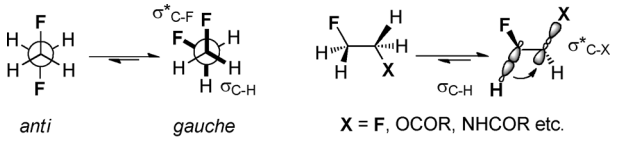
The preference by around 1 kcal mol^{-1} of 1,2-difluoroethane to reside in a *gauche* conformation rather than *anti*[15] may appear counterintuitive at first sight. Indeed, the *gauche* conformers of the corresponding dichloro- and dibromo-



Ryan Gilmour was born in Ayrshire, Scotland in 1980. He received a Masters degree (1st class) from the University of St Andrews in 2002 and completed a Ph.D. with Professor Andrew B. Holmes FRS at the University of Cambridge (marine natural product medium ring ether synthesis). Following a one year post-doctoral stay with Professor Alois Fürstner at the Max-Planck-Institut für Kohlenforschung, he joined Professor Peter H. Seeberger's group at the ETH Zurich. In August 2008 he was appointed Assistant Professor of Synthetic Organic Chemistry at the ETH Zurich.

Christof Sparr is from Appenzell (AI) Switzerland. After an apprenticeship at F. Hoffmann-La Roche AG (Basel) and a placement at the Zürcher Hochschule Winterthur, Christof moved to the ETH Zürich in 2005 to study chemistry where he earned a Masters degree. In August 2008, Christof joined the Gilmour group, where he is working on asymmetric catalysis. In September 2008 Christof was awarded a Roche Research Foundation Fellowship and in June 2009 he received a Novartis Doctoral Fellowship.

Lucie Zimmer completed her Masters degree in chemistry at the Ecole Nationale Supérieure de Montpellier, France. She carried out her doctoral studies at the Université de Montréal (Canada) under the supervision of Prof. A. B. Charette (enantio- and diastereo-selective syntheses of 1,2,3-substituted cyclopropanes using gem-dizinc carbenoids). Among others, Lucie has also completed research stays at the CNRS Strasbourg, France and the Ian Wark Institute (Adelaide, Australia). In 2010, Lucie moved to Zurich where she joined the Gilmour group and was awarded an ETH Fellowship.



Scheme 2. The fluorine *gauche* effect.[14]

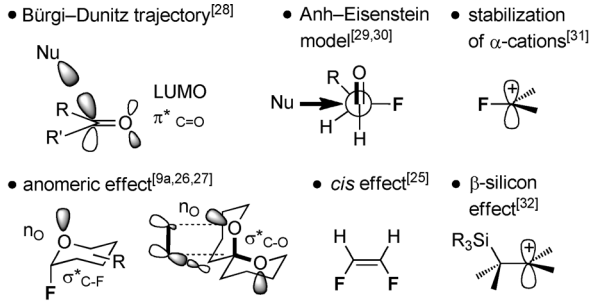
systems are destabilized, presumably because of electronic repulsion, thus favoring the *anti* arrangement.[16] One of the most cogent explanations to account for this phenomenon centers on hyperconjugative electron donation from the σ orbital of a vicinal C–H bond to the parallel, low-lying antibonding orbital of the C–F bond [$\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}F}$].[17] For maximum overlap, the *gauche* conformation places the best σ-donor bonds (e.g. C–H) *anti* to the best σ-acceptor bonds (e.g. C–F), thus overriding any electronic repulsion. By extension, the substitution of one fluorine atom for an electron-withdrawing group (X) leads to the same conformational preference [$\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}X}$]. Pertinent examples include the fluorine-

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

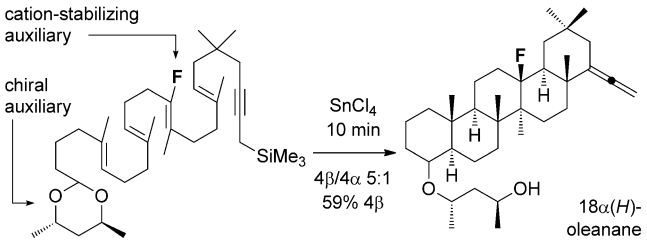
amide *gauche* effect (X = NHCOR), and the fluorine-ester *gauche* effect (X = OCOR; Figure 1).[18] Of the numerous *gauche* effects reported to date, the most significant involve an electrostatic component, in which the fluorine atom is proximal to an electropositive centre such that stabilizing charge-dipole type interactions are possible.[19] In a series of striking experiments by O'Hagan and Tozer, it was shown that both 2-fluoroethylamine and 2-fluoroethanol prefer a *gauche* conformation when protonated.[20] Pertinent to the latter sections of this review is the finding that the *gauche* conformer of protonated 2-fluoroethylamine is 5.8 kcal mol^{-1} more stable than the *anti* conformer. The stabilization energy (*gauche/anti*) is only approximately 1 kcal mol^{-1} in the unprotonated form (Figure 1). This conformational trend holds for a variety of related acyclic β-fluoroamine derivatives including β-fluoro-*N*-ethylpyridinium cations ($\Delta E_{(gauche\text{-}anti)} \approx 4$ kcal mol^{-1}).[21]

In addition to the aforementioned studies on acyclic β-fluoroamine derivatives, a number of cyclic variants have been reported including 3-fluoroazetidinium cations and 3-fluoro-1,5-diazacyclooctane systems, in which the conformation is dominated by stabilizing through space electrostatic interactions.[22] This result is consistent with the observations of Snyder, Lankin, and co-workers pertaining to the axial preference of protonated 3-fluoropiperidines (Figure 1, bottom).[23,24]

Moreover, the high electronegativity of fluorine, its low polarisability and low-lying $\sigma_{C\text{-}F}$* orbital 1) attenuate the related *cis* effect[25] and anomeric effect,[9a,26,27] 2) modulate the angle at which the HOMO of an incoming nucleophile interacts with the LUMO ($\pi^*_{C=O}$) of the carbonyl system (Bürgi–Dunitz trajectory)[28] during nucleophilic additions to α-fluorocarbonyl compounds (the Anh–Eisenstein 1,2-induction model),[29,30] and 3) demonstrate an aptitude for stabilizing α cations[31] in a manner complementary to the β-silicon effect (Scheme 3).[32] Interestingly, it is this attribute of fluorine that has found the widest use in stereoselective reaction development.[33] The seminal work of Johnson et al. on biomimetic polyene cyclizations demonstrates the ability of fluorine not only to promote but also to control these transformations by functioning as a cation-stabilizing auxiliary.[34] A classic example is the fluorine-assisted pentacyclization of the (*S*,*S*)-acetal to give 18α(*H*)-oleanane, which proceeded in 59% yield (4β; 86.5% *de*) in only 10 min (Scheme 4).[35,36] This observation is in sharp contrast to



Scheme 3. Selected fluorine effects; LUMO: lowest unoccupied molecular orbital.



Scheme 4. Fluorine-assisted asymmetric pentacyclisation.[35]

analogous reactions, in which the fluorine atom, or another cation-stabilizing auxiliary, is absent. Whilst the ability of fluorine to stabilize α cations is now broadly recognized, it is notable that the other (stereoelectronic) attributes of this functional group have not been better utilized. To the best of our knowledge, the first example of aliphatic C–F bonds being incorporated into a catalyst scaffold was not reported until the late 1990s (Section 2.1.1).

2. Molecular Preorganization in Asymmetric Catalysis using the C–F Bond: β-Fluoroamine Derivatives

2.1. Cyclic Conformational Control Using the C–F Bond

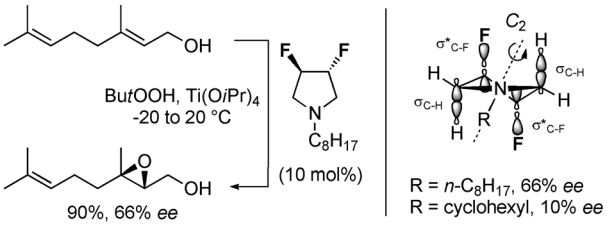
Historically, stereocontrol strategies often relied on intermediary cyclic species to ensure highly predictable reaction outcomes.[37] A beautiful example is the synthesis of erythronolide A by Woodward and co-workers, in which a *cis*-fused dithiadecalin provides conformational rigidity to facilitate the highly diastereoselective synthesis of the seco acid.[38] Consistent with these early induction strategies, the earliest compelling evidence of the ability of fluorine to bias the conformation of a catalyst has its origin in cyclic systems, namely pyrrolidine derivatives. To appreciate the role of the fluorine atom, let us first consider pseudo-rotation in five-membered rings and the implications of this rapid conformational flux on productive, enantioselective catalysis: cyclopentane is a pertinent example.[39] The competing torsional forces about the single bonds oppose the forces acting to retain the optimum tetrahedral geometry of the sp^3 centers giving rise to conformational isomerism with low interconversion barriers. The energy differences between the relevant interconverting species are small so that biasing conformational equilibria is of paramount importance in catalyst design. Five-membered heterocycles such as pyrrolidine may be considered a privileged class of organocatalyst scaffolds owing to their availability and ease of synthesis in enantiomerically enriched form from proline. Like cyclopentane, pyrrolidine has a relatively low barrier to pseudorotation of around 1.6 kcal mol^{-1},[40] hence it must be structurally modified in such a way as to "freeze out" conformational isomerism. Clearly, the modification of proline to create sterically demanding systems such as diarylprolinols (Scheme 1) is an effective strategy. Later we shall discuss examples of modified 3- and 4-F-pyrrolidine catalysts, in

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

which the strategic replacement of a C–H bond in a vicinal relationship to the nitrogen atom by C–F has a subtle, yet significant effect on catalyst performance.

2.1.1. Marson's C_2-Symmetric, Fluorinated Pyrrolidine for Epoxidation

The Sharpless asymmetric epoxidation of allylic alcohols remains the benchmark method for the preparation of optically active epoxides, largely because of the ease of reaction execution and its enzyme-like performance.[41] Unsurprisingly, the discovery of this transformation has resulted in the development of a multitude of variants. An important contribution, especially in the context of this Minireview, is the use of C_2-symmetric, enantiopure vicinal difluorides employed in combination with $[Ti(OiPr)_4]$ by Marson and Melling (Scheme 5).[42] Whilst the nitrogen substituent clearly influences the enantioselectivity of epoxidation (n-C_8H_{17} 66% *ee* versus cyclohexyl 10% *ee*), the only stereochemical information is relayed from the configurationally defined vicinal difluoro motif (β-fluoroamine) by virtue of its influence on the conformation of the pyrrolidine ring. Despite the energetic preference for a *gauche* relationship in acyclic vicinal polyfluorinated systems such as 1,2-difluoroethane,[43] this conformation is arduous in 3,4-pyrrolidines. Nonetheless, stabilizing hyperconjugative interactions $[\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}F}]$ are possible when the fluorine atoms occur in a quasi-axial arrangement, thus augmenting the ring pucker of the C_2-symmetric species:[44] an [F···N] *gauche* effect. Although no conclusive evidence has been offered to illuminate the precise role of the fluorine atoms, this remains a prominent example of enantioinduction conferred exclusively by the translation of chiral information through the pyrrolidine ring from configurationally defined fluorine centers.



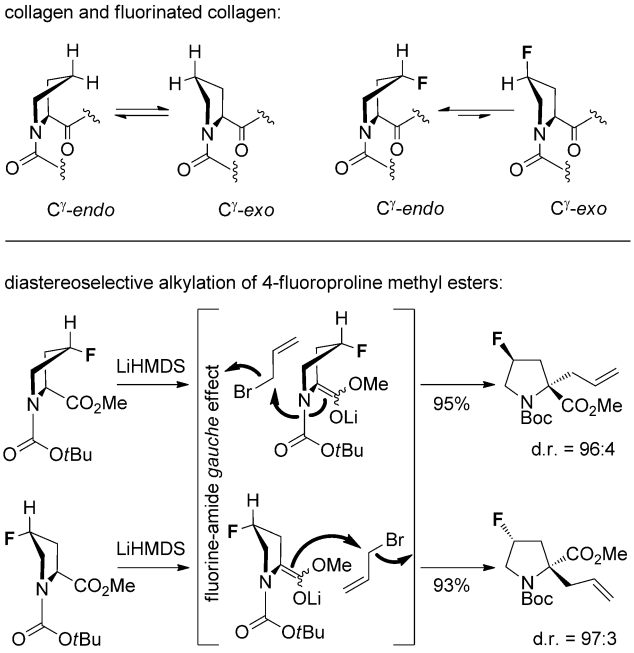
Scheme 5. Marson's C_2-symmetric difluoropyrrolidine catalyst.[42]

While this di-fluorinated pyrrolidine conforms to classic design principles of C_2-symmetry to promote asymmetric induction,[44] many more C_1-symmetric, fluoropyrrolidine catalysts have recently been reported for asymmetric organocatalysis. Without exception, these molecules have a β-fluoroamine functionality imbedded into the scaffold. In the following section, the development and application of some of these C_1-symmetric catalysts[45,46] will be discussed.

2.1.2. The Conformational Behavior of 4-Fluoroproline

4-Fluoroproline has emerged as a particularly valuable building block for molecular design. The early NMR studies of Gerig and McLeod on protonated *cis*- and *trans*-4-fluoroproline demonstrate the existence of a dominant conformer in solution, in which the C–F bond adopts a *quasi*-axial orientation placing it *gauche* to the C–N bond.[47] This conformational arrangement is also found in 4-fluoroproline derivatives, in which the nitrogen is electron deficient, such as in peptides. This is exemplified by the single crystal X-ray structure of *tert*-butoxycarbonyl-4(*S*)-fluoroproline.[48] However, one of the most spectacular examples of structural control imparted by fluorine atoms stems from the incorporation of 4-fluoroproline into collagen strands by Raines and co-workers, leading to hyperstability.[18c,f,49] The fluorine-amide *gauche* effect that results from maximum σ→σ* overlap constitutes the first example of a stereoelectronic effect modulating protein conformational stability (Scheme 6, top); a persuasive argument for the inclusion of fluorine effects in the design process.[49,50]

An additional manifestation of cyclic conformational control modulated by fluorine is the highly diastereoselective alkylation of 4-fluoroproline methyl esters reported by Filosa et al. (Scheme 6, bottom).[51] While the authors invoke formation of a transitory cyclic species, in which the fluorine chelates to lithium to account for the high *anti* selectivity of alkylation,[52] an alternative explanation is that the ring conformation is governed by a fluorine-amide *gauche* effect.[18] Consequently, alkylation occurs from the less sterically crowded convex face. It should be noted that the stereoselectivity of analogous reactions with substituted 4-hydroxy derivatives is dependent on the nitrogen atom substitution and the alkylating reagent.[53]

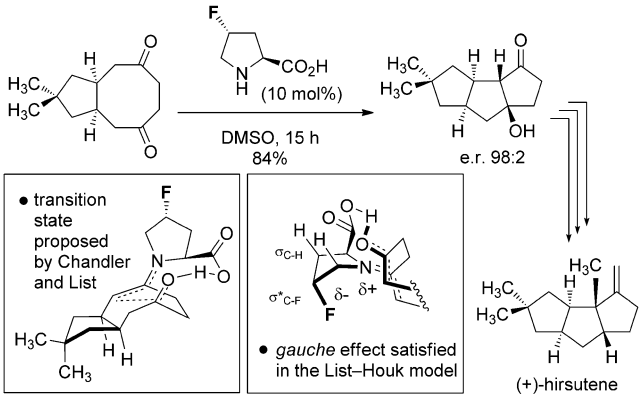


Scheme 6. Examples of fluorine biasing the ring conformation of proline derivatives. Top: the fluorinated collagen scaffold developed by Raines and co-workers.[49] Bottom: the highly diastereoselective alkylation of 4-fluoroproline methyl esters[51]; LiHMDS = lithium bis(trimethylsilyl)amide.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2.1.3. Catalytic Asymmetric Transaldolizations

Only a few years later, Chandler and List showcased *trans*-4-fluoroproline in organocatalytic transannular aldolizations of 1,4-cyclooctanediones under mild reaction conditions. Indeed, this transformation proved so powerful that it formed the key step in the shortest reported synthesis of (+)-hirsutene (Scheme 7).[54] The impressive levels of relative and absolute stereocontrol (98:2 e.r.) are rationalized by invoking a transition-state model that relies on a hydrogen-bond network and is consistent with earlier theoretical studies on proline-catalyzed aldolizations by Houk, List, and co-workers.[55]



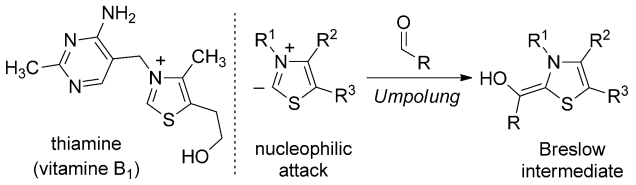
Scheme 7. Transannular aldolisation by Chandler and List.[54]

An interesting observation that emerged from this study was the lower yielding and less selective aldolization of 1,5-cyclononanedione using *cis*-4-F-Pro versus *trans*-4-F-Pro (50% conversion, e.r. 79:21 and 75% conversion, e.r. 90:10, respectively). It seems probable here that the conformational intricacies of the intermediate β-fluoroiminium ion/enamine manifold are largely responsible for the optimized transition state preorganization that manifests itself in high levels of asymmetric induction (Scheme 7, bottom, center). Stereoelectronic effects ($\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}F}$) may be implicated because of the dichotomy of the transient iminium/enamine intermediates involved, but the developing positive charge on the nitrogen atom during this process likely induces an electrostatic component to the fluorine-iminium ion *gauche* effect ($N^+ \cdots F^{\delta-}$),[18g] thus rigidifying the five-membered ring and possibly attenuating the requisite hydrogen-bond pattern. Generating this hydrogen-bond network would likely be challenging when using *cis*-4-F-proline and related 4-O substituted derivatives: this result complements the existing literature pertaining to the directing influence of fluoro substituents in diastereoselective alkylations of 4-fluoro-prolines.[51,53] The influence of the 4-fluoro substituent on the enantioselectivity of this reaction adds an additional degree of complexity to the current dialogue regarding the mechanism of proline-catalyzed aldol reactions.[56]

2.1.4. N-Heterocyclic Carbenes: Organocatalysts Par Excellence

N-heterocyclic carbenes (NHCs) are well known for their role as ligands for a number of highly active metathesis catalysts, in which their effectiveness depends on various stereoelectronic nuances, such as their dual σ-donor and π-acceptor ability.[57] However NHCs need not be ligated to a metal to be synthetically valuable. N-heterocyclic carbenes have become fashionable nucleophilic organocatalysts [58] that participate in a range of enantioselective transformations, in which their structural and reactivity similarities to the coenzyme thiamine (vitamin B_1, Scheme 8) are exploited.[59]

Early work on the structure and reactivity of natural thiazolium salts by Breslow[59] and Ukai et al.,[60] together with more recent advances by Enders and co-workers,[58a,c,61] have undoubtedly shaped the field of nucleophilic carbenes in asymmetric catalysis. As early as the 1950s, Breslow[59] described a catalytic benzoin condensation catalyzed by thiazolium salts and formulated a reaction mechanism that is still in common usage. Key to this mechanistic paradigm is the intermediacy of an acyl anion equivalent (Breslow intermediate, Scheme 8); an early example of "Umpolung" reactivity that was later formalized by Seebach.[62]

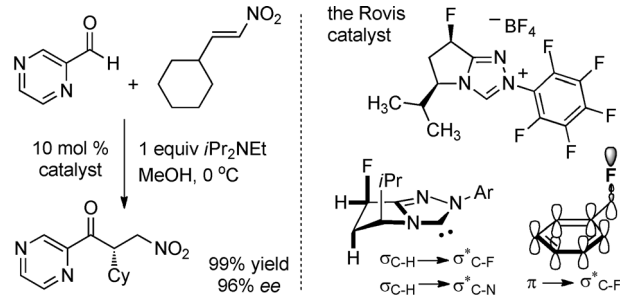


Scheme 8. The coenzyme thiamine and the Breslow intermediate.

2.1.5. Fluorine Interactions in NHC Design: the Rovis–Stetter Catalyst

The recent intermolecular Stetter reaction reported by Rovis and co-workers is a particularly striking example of NHC catalysis associated with a single, configurationally defined fluorine center on the ring annulated to the triazolium core (Scheme 9).[63,64]

Functionalized bicyclic triazolium salts are competent catalysts for the Stetter reaction of heterocyclic aldehydes with nitro-olefins. In this example, however, increasing steric bulk in the vicinity of the reactive center had a detrimental effect on performance, with an optimal balance between

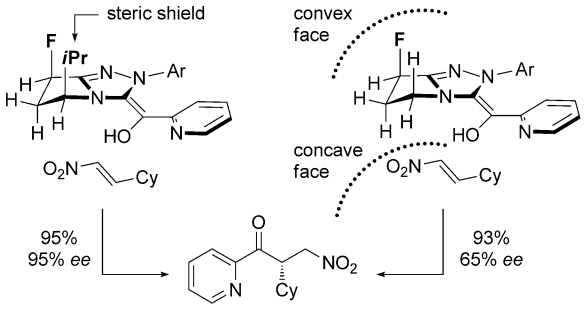


Scheme 9. The Rovis–Stetter catalyst;[63] Cy = cyclohexyl.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

shielding and turnover being observed with the isopropyl derivative. Further catalyst refinement turned to electronic avenues, with backbone fluorination giving remarkable results. The fluorinated catalyst proved to be highly efficient, furnishing the desired products with excellent yields and levels of enantioinduction (>90% *ee*). Intriguingly, X-ray analysis of the NHC precursor showed a counterintuitive *quasi*-axial orientation of the isopropyl and fluoro substituents, a result that the authors rationalize by stereoelectronic arguments ($\sigma_{C\text{-}H}\rightarrow\sigma^*_{C\text{-}F}$ and $\sigma_{C\text{-}H}\rightarrow\sigma^*_{C\text{-}N}$) supported by a wealth of literature data pertaining to the conformational preferences of β-fluoroamine derivatives. These are summarized in the introductory section of this review.[14–24] In a thoughtful discussion, the authors add a caveat regarding overanalysis of the precatalyst solid-state structures and discuss the possibility of $\pi\rightarrow\sigma^*_{C\text{-}F}$ hyperconjugation (Scheme 9, bottom),[65] although this is largely discounted as the dominant interaction. This example is particularly instructive because removal of the isopropyl group causes relatively little disruption to the enantiofacial preference. The fluorine atom presumably augments the pucker of the annulated five-membered ring, thus creating a rigidified core that, in the absence of any steric bias from the isopropyl substituent or the fluorine atom, confers asymmetric induction by the C^{γ}-exo ring conformation (Scheme 10; also see Scheme 6, top). It is noteworthy that the sense of enantioinduction does not change upon removal of the isopropyl unit. Intuitively, one might expect that the nitro-olefin would approach the Breslow intermediate from the less hindered "convex" face, and not from the concave face, as is observed. Intriguingly, all of the substrates described in this study feature aromatic aldehydes that bear heteroatom substituents. This remarkable example of asymmetric catalysis, in which a single, configurationally defined C–F bond is the only source of stereochemical information, beautifully captures the essence of this review.

Collectively, the striking examples of cyclic stereocontrol conferred by configurationally defined C–F bonds embedded in a β-fluoroamine scaffold by Marson, List, Rovis, and coworkers form a convincing argument for the strategic inclusion of an appropriately positioned C–F bond in the catalyst design process. In the following section, the field of acyclic conformational control using the C–F bond will be discussed; a field that has received even less attention to date.



Scheme 10. The Stetter reaction investigated by Rovis;[63] Cy = cyclohexyl.

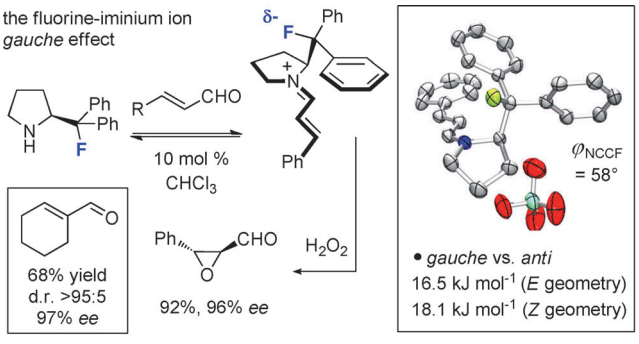
2.2. Acyclic Conformational Control Using the C–F Bond: Rotation about an Exocyclic Bond

2.2.1. A Dynamic Fluorine-Iminium Ion Gauche Effect

In early 2009, as part of our catalysis programme, our group reported a novel, fluorinated organocatalyst for the enantioselective epoxidation of α,β-unsaturated aldehydes.[18g] Central to our catalyst design process was the desire to create a conformationally dynamic ensemble that could be activated by a substrate-binding event, akin to the induced-fit process that is inherent to enzymatic processes (Scheme 11). To that end, we envisaged that a secondary β-fluoroamine, when condensed with an aldehyde, would form a charged iminium species, in which a dynamic electrostatic *gauche* effect would place the fluorine *syn*-clinal *endo* over the pyrrolidine ring system ($\phi_{NCCF} = 58°$ in the solid state) such that a stabilizing through-space interaction would cause pronounced energy differences between the conformers in the rotational profile of the key C–C bond. The consequence of this charge-dipole interaction is to direct a steric shield (Ph) over one face of the π system, thus directing an incoming nucleophile to the opposite Si face. This approach for amplifying asymmetric induction was validated both experimentally and computationally and provides a powerful method for the translation of chirality from the secondary amine vector to the reactive centre of the iminium ion. The synthetic potential of this concept was demonstrated in the operationally simple, stereoselective epoxidation of α,β-unsaturated aldehydes[66] using (S)-2-(fluorodiphenylmethyl)-pyrrolidine.[67] The levels of enantioinduction were higher than with the corresponding nonfluorinated catalyst (96% *ee* vs. 85% *ee* for *trans*-cinnamaldehyde), thus validating this strategy for the preorganization of the transient intermediates that are central to secondary-amine-catalyzed processes.[68]

2.2.2. Conformer Equivalents as a Tool for Mechanistic Studies: The Fluorine-Iminium Ion Gauche Effect in Action

Stabilizing hyperconjugative ($\sigma_{C\text{-}H}\rightarrow\sigma_{C\text{-}F}^*$) and/or electrostatic ($N^{+}\cdots F^{\delta-}$) interactions render the C–F bond an excellent steering group for controlling molecular topology. The realization that this inert, sterically nondemanding group could be used in a predictable manner to control the iminium ion topology has now been extended to the design of conformational probes to study the decisive interactions that



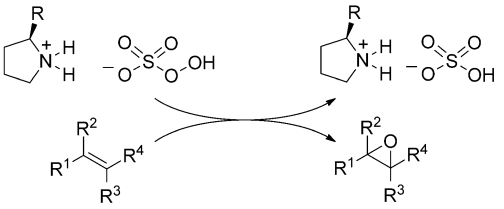
Scheme 11. A fluorinated organocatalyst for the stereoselective epoxidation of α,β-unsaturated aldehydes.[18g]

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

are involved in orchestrating chirality transfer in iminium-ion-mediated reactions. The remarkable performance of the MacMillan imidazolidinones has revolutionized carbonyl reactivity,[69] yet the precise manner by which the directing phenyl group confers enantioinduction was still to be firmly established.[70] Building on our earlier work on the fluorine-iminium-ion *gauche* effect, it seemed rational that the introduction of a fluorine atom at the benzylic position of the MacMillan imidazolidinone would provide a tool by which to probe the influence of the two contributing conformers believed to be responsible for the exquisite levels of stereocontrol. The predetermined configuration of the benzylic fluorine center would encode for a given topology, hence the two diastereoisomers function as "conformer equivalents" (Scheme 12).[71] Spectroscopic analysis of the two diastereomeric, fluorinated iminium salts revealed different *E*:*Z* selectivities: the *E*:*Z* ratio of the Ph-*exo* conformer equivalent was markedly lower than that of the Ph-*endo* one. Moreover, different levels of enantioselectivity were observed on treating the iminium salts with *N*-methylpyrrole. This unique empirical evidence supports the notion that the Ph-*endo* conformer is responsible for ensuring high levels of geometric control by minimizing $A_{1,3}$-strain whilst the Ph-*exo* conformer assures high levels of enantioinduction by shielding the π system in this particular reaction.

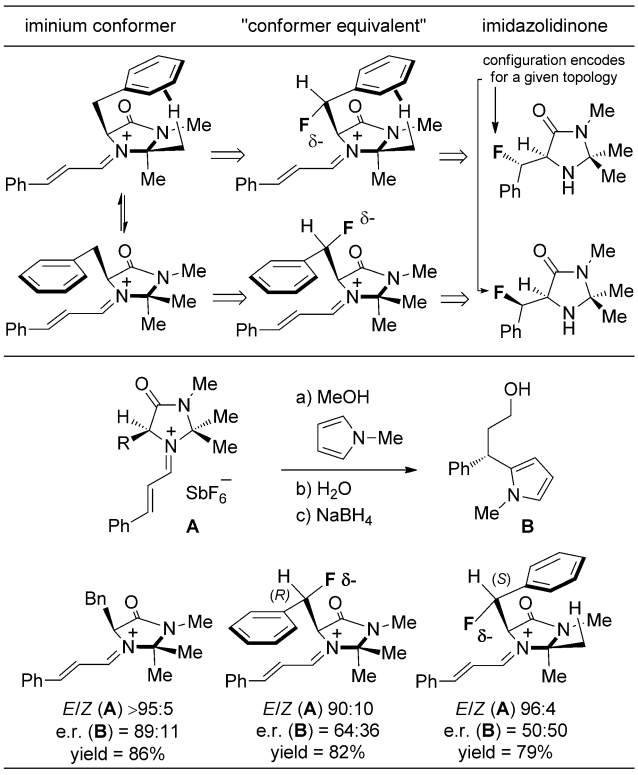
2.2.3. The Asymmetric Epoxidation of Stilbenes by 2-(Fluorodiphenyl methyl)pyrrolidine

In 2003, Aggarwal and co-workers described an elegant mechanistic study of amine-catalyzed epoxidations of alkenes using oxone.[72,73] The epoxidation of 1-phenylcyclohexene proceeded with good levels of enantiocontrol (46% *ee*) using only 10 mol% of (*S*)-2-(diphenylmethyl)pyrrolidine. In addition to its role as a phase-transfer catalyst, the chiral amine is thought to activate the oxone towards electrophilic attack through hydrogen bonding. Moreover, this study implicates the intermediacy of a charged pyrrolidinium peroxymonosulfate as the active oxidizing species (Scheme 13).

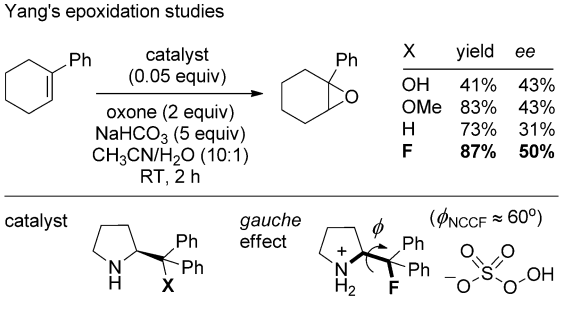


Scheme 13. Amine-catalyzed alkene oxidation.[72]

More recently, in 2005, Yang and co-workers showed that the introduction of a fluorine substituent in a vicinal relationship to the pyrolidine nitrogen atom increases the enantioselectivity of the epoxidation of 1-phenylcyclohexene from 31% *ee* to 50% *ee* (Scheme 14).[74] In addition, by functionalizing the 4-position of the aromatic rings, up to 61% *ee* (4-MeC_6H_4) could be obtained. Substitution of the benzylic hydrogen by a OH or OMe group also raised the enantioselectivities, albeit to a lesser extent (up to 43% *ee*). The reason for the enhanced performance of the fluorinated catalyst has a conformational origin. Yang and co-workers invoke a stabilizing charge-dipole interaction (*gauche* effect) in the intermediate pyrrolidinium peroxymonosulfate that is instrumental in controlling the molecular topology. The result of the fluorine-ammonium *gauche* effect[17] is to place one of the aromatic rings in proximity to the reactive peroxy group, thus enhancing facial discrimination.[75] However, in view of the multiple variants of the pyrrolidinium peroxymonosulfate species, a more detailed discussion could only be speculative. In addition to supporting the mechanistic findings of Aggarwal, this work constitutes a striking example of a fluorine effect that refines catalyst performance.



Scheme 12. Using the C–F bond to create conformer equivalents.[71]



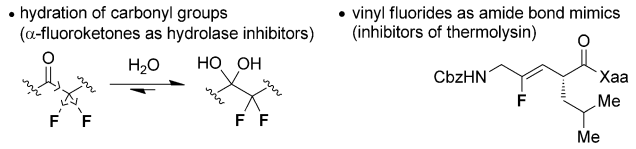
Scheme 14. Oxidation of 1-phenylcyclohexene by oxone and a fluoropyrrolidine-based chiral catalyst.[74]

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

3. Other Applications of the C–F Bond in Catalysis

It may be helpful here to briefly survey other properties of fluorinated organic molecules that have been shown to play a crucial role in influencing catalyst performance. Many of these effects are evocative of the role of fluorine substituents in drug discovery and development.

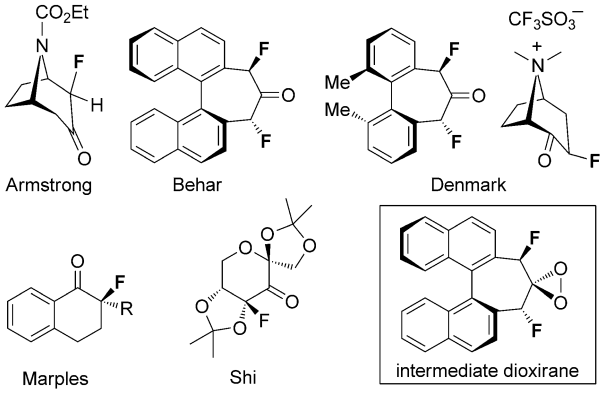
Examples include 1) the hydration of α-fluorocarbonyl groups as exemplified by many transition-state inhibitors[76] (Section 3.1), 2) the use of vinyl fluorides as amide bond mimics[77] (Section 3.2), and 3) modulating the acidity of neighboring functionalities (Section 3.3) by the introduction of fluorine substituents (Scheme 15).[78]



Scheme 15. The role of fluorine in hydrolase inhibitor design and vinyl fluorides as amide mimics;[76–78] Cbz = carbobenzyloxy.

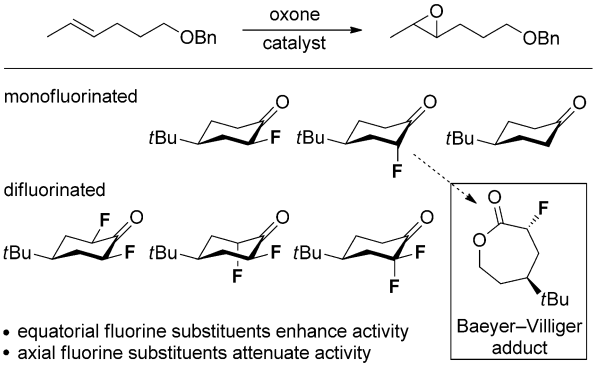
3.1. α-Fluoroketones for the Asymmetric Epoxidation of Olefins

Ketone-derived dioxiranes feature prominently in the development of catalytic methods for the enantioselective epoxidation of unfunctionalized alkenes.[79] Pertinent are the activating effects of α-fluoroketones, noted by Mello, Curci, and co-workers[80] that are a principal design feature of numerous epoxidation catalysts (Scheme 16).[81–87]



Scheme 16. Examples of fluorinated ketone catalysts for asymmetric epoxidation.[81–87]

The strongly electron-withdrawing properties of fluorine render the carbonyl carbon atom of α-fluoroketones highly electrophilic, hence these species readily form stable hydrates. Unsurprisingly, α-fluoroketones constitute some of the most efficient catalysts for the epoxidation of unactivated olefins when used in conjunction with oxone. In addition to increasing the electrophilicity of the carbonyl group, thus facilitating attack by the stoichiometric co-oxidant, fluorine substituents have been shown to modulate the reactivity of the intermediate dioxirane. This is exemplified by the systematic study of epoxidation by Denmark et al., using conformationally locked 4-*tert*-butyl-2-fluorocyclohexanones (Scheme 17).[82b]



Scheme 17. Fluorocyclohexanone catalysts by Denmark and Matsushashi;[82b] Bn = benzyl.

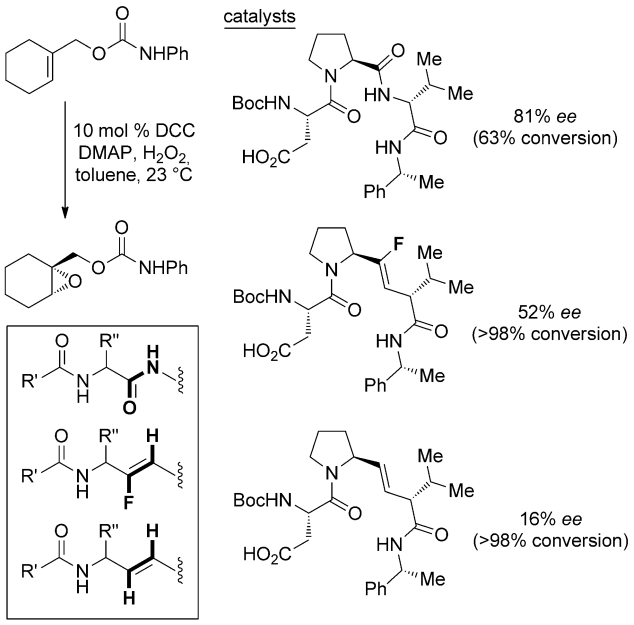
Intriguingly, the orientation of the fluorine substituent was shown to have a direct impact on the efficiency of catalysis. Whilst equatorial fluorine substituents improve the catalytic activity relative to 4-*tert*-butyl-2-fluorocyclohexanones, axial substituents reportedly attenuate it. Ketones that bear axial fluorine substituents were susceptible to Baeyer–Villiger oxidation, whereas the other ketones used in this study were stable under analogous reaction conditions. The authors conclude that efficient catalysis requires a suitably electrophilic carbonyl group to facilitate dioxirane formation, ease of oxygen transfer, and finally that the catalyst is not consumed by a competing Baeyer–Villiger process. This study demonstrates that the fluorine substituent imparts an important stereoelectronic control that depends on configuration. A theoretical analysis of the transition-state electronics by Armstrong, Houk, and co-workers concluded that the transition state is favored with the fluorine atom *anti* to the dioxirane oxygen atom that is retained in the ketone of the catalyst.[88] This requires the fluorine atom to be positioned *syn* to the alkene. In this remarkable example, the configuration of the fluorine substituent not only facilitates dioxirane formation and enhances its reactivity, but also influences enantioinduction.

3.2. Functional Analysis of an Aspartate-Based Epoxidation Catalyst with a Fluoroalkene Isosteric Catalyst

Miller and co-workers have skillfully exploited vinyl fluorines as bioisosteres of amides to create a powerful catalyst motif for the stereoselective epoxidation of trisubstituted olefinic carbamates (Scheme 18).[89] A direct comparison of epoxidation using the aspartate-derived parent peptide, the fluoro-olefin and the alkene-isostere showed a clear trend that is dependent on conformation.

The nonfluorinated catalyst was found to reside in a 3.5:1 mixture of conformers at room temperature and furnished the

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

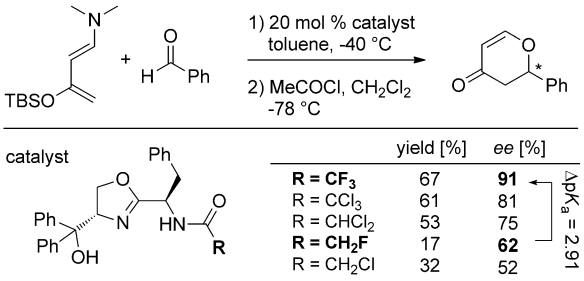


Scheme 18. Fluoro-alkene isostere for the mechanistic investigation of a peptide-catalyzed epoxidation by Miller and co-workers; Boc = *tert*-butoxycarbonyl; DCC = *N*,*N*-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine.

product epoxide with relatively low levels of enantioinduction (16% *ee*): this result is in contrast to the performance of the parent peptide (81% *ee*). The fluoro-olefin analogue proved to be conformationally more robust than the alkene-isostere (10:1 mixture of conformers at 23 °C) and furnished enantioselectivites between the other two systems (52% *ee*; Scheme 18). In this elegant study, Miller and co-workers probe the factors that regulate the conformation and performance of an aspartate-based epoxidation catalyst by simulating the amide-like character of the parent peptide by incorporating a fluoro-olefin moiety.

3.3. Modulating Acidity in H-Bonding Catalysts

The high electronegativity of fluorine leads to pronounced inductive effects that can have a direct influence on the nature of neighboring functional groups. Jensen and Sigman have exploited this fact in the design of a hydrogen-bonding catalyst for the asymmetric hetero-Diels–Alder reaction between Rawal's diene and benzaldehyde (Scheme 19).[90] Based on the assumption that a more acidic catalyst would improve substrate activation by functioning as a superior hydrogen-bond donor, a series of halogenated acetamide catalysts were prepared and screened. Consistent with this hypothesis, the more acidic trifluoromethyl catalyst promoted the reaction with excellent levels of enantioinduction and an amplified reaction rate. Moreover, a direct correlation of catalyst performance and acidity was established, thus beautifully demonstrating the ability of fluoro substituents to regulate the hydrogen-bond-donating character of catalysts.



Scheme 19. The asymmetric hetero-Diels–Alder reaction between Rawal's diene and benzaldehyde reported by Jensen and Sigman;[90] TBS = *tert*-butyldimethylsilyl.

4. Conclusion

Molecular design strategies that profit from the intrinsic stereoelectronic and electrostatic effects of fluorinated organic molecules have conventionally been restricted to bioorganic chemistry. However, the renaissance of organocatalysis offers a unique possibility to exploit many of these well-described phenomena for the preorganization of transient intermediates that are central to many organocatalytic processes. The examples highlighted in this review make a compelling argument for the incorporation of fluorine effects in molecular design either as the principal feature or as part of a synergistic approach.

We gratefully acknowledge generous financial support from the Alfred Werner Foundation (assistant professorship to R.G.), the Roche Research Foundation and Novartis AG (doctoral fellowships to C.S.), and the ETH Zurich (post-doctoral fellowship to L.Z.). We thank Prof. Dr. Jack D. Dunitz and Prof. Dr. Dieter Seebach for helpful comments and for their continued support of our research programme.

Received: March 22, 2011
Published online: September 26, 2011

[1] J. Allan, A. E. Oxford, R. Robinson, J. C. Smith, *J. Chem. Soc.* **1926**, *129*, 401–411; R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, Institute of Chemistry, London, **1932**; R. Robinson, *Memoirs of a Minor Prophet, 70 Years of Organic Chemistry*, Elsevier, Amsterdam, **1976**, pp. 184–228.

[2] C. Ingold, *Chem. Rev.* **1934**, *15*, 225–274; C. K. Ingold in *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, **1969**; K. T. Leffek in *Sir Christopher Ingold, A Major Prophet of Organic Chemistry*, Nova Lion Press, Victoria, BC, **1996**; J. H. Ridd, *Chem. World* **2008**, 50–53.

[3] D. H. R. Barton, *Experimentia* **1950**, *6*, 316–320; D. H. R. Barton, *Science* **1970**, *169*, 539–544; S. V. Ley, R. M. Myers, *Biogr. Mem. Fellows R. Soc.* **2002**, *48*, 1–23.

[4] K. Fukui, T. Yonezawa, C. Nagata, H. Shingu, *J. Chem. Phys.* **1954**, *22*, 1433–1442; K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57–64; I. Fleming in *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester, **1976**; P. Deslongchamps in *Stereoelectronic Effects in Organic Chemistry* (Ed.: J. E. Baldwin), Franklin Book Co. Inc., Pergamon, Oxford, **1983**; E. M. Burgess, C. L. Liotta, *J. Org. Chem.* **1981**, *46*, 1703–1708; A. J. Kirby in *Stereoelec-*

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tronic Effects (Ed.: S. G. Davies), Oxford University Press, Oxford, **1996**.
[5] For historical overviews, see: M. J. S. Dewar, *The Electronic Theory of Organic Chemistry*, Oxford University Press, London, **1949**; L. Pauling, *Modern Structural Chemistry*, Nobel Lecture, **1954**; J. W. Baker, *Electronic Theories of Organic Chemistry. An Introductory Treatment*, Oxford University Press, New York, **1958**; G. I. Brown, *An Introduction to Electronic Theories of Organic Chemistry*, Longmans, Green, London, **1958**; F. Serratosa, *J. Chem. Educ.* **1962**, *39*, 641 – 643.
[6] E. J. Corey, *J. Am. Chem. Soc.* **1954**, *76*, 175 – 179; E. J. Corey, *Experimentia* **1954**, *9*, 329; E. J. Corey, R. A. Sneen, *J. Am. Chem. Soc.* **1956**, *78*, 6269 – 6278; E. J. Corey, *J. Org. Chem.* **2004**, *69*, 2917 – 2919.
[7] A. Fürst, P. A. Plattner, *Helv. Chim. Acta* **1949**, *32*, 275 – 283.
[8] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890 – 1904; for an English translation, see A. Eschenmoser, D. Arigoni, *Helv. Chim. Acta* **2005**, *88*, 3011 – 3048; readers are also advised to see G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068 – 5077.
[9] For additional pertinent publications, see a) J. J. Irwin, T.-K. Ha, J. D. Dunitz, *Helv. Chim. Acta* **1990**, *73*, 1805 – 1817; b) A. Eschenmoser, D. Felix, G. Ohloff, *Helv. Chim. Acta* **1967**, *50*, 708 – 713; c) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalovoda, H. Kaufmann, P. Wieland, G. Anner, *Helv. Chim. Acta* **1967**, *50*, 2101 – 2108; d) A. Eschenmoser, C. E. Winter, *Science* **1977**, *196*, 1410 – 1420 (Footnote 11); e) P. Beak, *Acc. Chem. Res.* **1992**, *25*, 215 – 222; f) C. D. Johnson, *Acc. Chem. Res.* **1993**, *26*, 476 – 482.
[10] L. Hunter, *Beilstein J. Org. Chem.* **2010**, DOI: 10.3762/bjoc.6.38.
[11] We thank Professor Jack D. Dunitz for bringing the following quotation to our attention: "I very fully join in the regret … that scientific men do not know more perfectly what has been done, or what their companions are doing; but I am afraid the misfortune is inevitable. It is certainly impossible for any person who wishes to spend a portion of his time to chemical experiment, to read all the books and papers that are published in connection with his pursuit; their number is immense, and the labor of winnowing out the few experimental and theoretical truths which in many of them are embarrassed by a very large proportion of uninteresting matter, of imagination, and of error, is such, that most persons who try the experiment are quickly induced to make a selection in their reading, and thus, inadvertently, at times, pass by what is really good." M. Faraday, *Experimental Researches in Chemistry and Physics*, Taylor and Francis, London, **1853**, p. 212.
[12] P. Müller, *Pure Appl. Chem.* **1994**, *66*, 1077 – 1184; G. P. Moss, *Pure Appl. Chem.* **1996**, *68*, 2193 – 2222.
[13] For an excellent review, see D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319, and references therein.
[14] S. Wolfe, *Acc. Chem. Res.* **1972**, *5*, 102 – 111.
[15] J. R. Durig, J. Liu, T. S. Little, V. F. Kalaskinsky, *J. Phys. Chem.* **1992**, *96*, 8224 – 8233.
[16] K. Tanabe, *Spectrochim. Acta Part A* **1972**, *28*, 407 – 424.
[17] D. Y. Buissonneaud, T. Van Mourik, D. O'Hagan, *Tetrahedron* **2010**, *66*, 2169 – 2202; See Ref. [13]. Also see the bent bond analysis by Wiberg: K. B. Wiberg, M. A. Murcko, K. E. Laidig, P. J. MacDougall, *J. Phys. Chem.* **1990**, *94*, 6956 – 6969; K. B. Wiberg, *Acc. Chem. Res.* **1996**, *29*, 229 – 234.
[18] For selected examples, see a) D. O'Hagan, C. Bilton, J. A. K. Howard, L. Knight, D. J. Tozer, *J. Chem. Soc. Perkin Trans. 2* **2000**, 605 – 607; b) C. R. S. Briggs, D. O'Hagan, J. A. K. Howard, D. S. Yufit, *J. Fluorine Chem.* **2003**, *119*, 9 – 13; c) J. A. Hodges, R. T. Raines, *J. Am. Chem. Soc.* **2003**, *125*, 9263 – 9264; d) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta, J. A. K. Howard, *Org. Biomol. Chem.* **2004**, *2*, 732 – 740; e) D. Shoulders, J. A. Hodges, R. T. Raines, *J. Am. Chem. Soc.* **2006**, *128*, 8112 – 8113; f) J. A. Hodges, R. T. Raines, *J. Am. Chem. Soc.* **2005**, *127*, 15923 – 15932; g) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111 – 3114; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065 – 3068; h) C. Bucher, C. Sparr, W. B. Schweizer, R. Gilmour, *Chem. Eur. J.* **2009**, *15*, 7637 – 7647; i) S. Paul, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Organometallics* **2010**, *29*, 4424 – 4427.
[19] K. B. Wiberg, *J. Chem. Educ.* **1996**, *73*, 1089 – 1095.
[20] See Ref. [18d].
[21] N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer, R. J. Young, *Angew. Chem.* **2007**, *119*, 6008 – 6012; *Angew. Chem. Int. Ed.* **2007**, *46*, 5904 – 5908.
[22] N. E. J. Gooseman, D. O'Hagan, A. M. Z. Slawin, A. M. Teale, D. J. Tozer, R. J. Young, *Chem. Commun.* **2006**, 3190 – 3192.
[23] A. Sun, D. C. Lankin, K. Hardcastle, J. P. Snyder, *Chem. Eur. J.* **2005**, *11*, 1579 – 1591. Also see a) D. C. Lankin, N. S. Chandrakumar, S. N. Rao, D. P. Spangler, J. P. Snyder, *J. Am. Chem. Soc.* **1993**, *115*, 3356 – 3357; b) J. P. Snyder, N. S. Chandrakumar, H. Sato, D. C. Lankin, *J. Am. Chem. Soc.* **2000**, *122*, 544 – 545; c) D. C. Lankin, G. L. Grunewald, F. A. Romero, I. Y. Oren, J. P. Snyder, *Org. Lett.* **2002**, *4*, 3557 – 3560.
[24] For selected examples of stabilizing through-space electrostatic interactions, see a) M. Miljković, D. Yeagley, P. Deslongchamps, Y. L. Dory, *J. Org. Chem.* **1997**, *62*, 7597 – 7604; b) D. M. Smith, K. A. Woerpel, *Org. Biomol. Chem.* **2006**, *4*, 1195 – 1201; c) L. Svansson, B. D. Johnston, J.-H. Gu, B. Patrick, B. M. Pinto, *J. Am. Chem. Soc.* **2000**, *122*, 10769 – 10775; d) M. G. Szczepina, B. D. Johnston, Y. Yuan, B. Svensson, B. M. Pinto, *J. Am. Chem. Soc.* **2004**, *126*, 12458 – 12469; e) J. Antoinette, C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2000**, *122*, 168 – 169; f) L. Ayala, C. G. Lucero, J. Antoinette, C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 15521 – 15528; g) C. H. Larsen, B. H. Ridgeway, J. T. Shaw, D. M. Smith, K. A. Woerpel, *J. Am. Chem. Soc.* **2005**, *127*, 10879 – 10884; h) G. Baghdasarian, K. A. Woerpel, *J. Org. Chem.* **2006**, *71*, 6851 – 6858; i) M. T. Yang, K. A. Woerpel, *J. Org. Chem.* **2009**, *74*, 545 – 553; j) J. R. Krumper, W. A. Salamant, K. A. Woerpel, *J. Org. Chem.* **2009**, *74*, 8039 – 8050.
[25] N. C. Craig, E. A. Entemann, *J. Am. Chem. Soc.* **1961**, *83*, 3047 – 3050.
[26] A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, New York, **1982**.
[27] F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827 – 856.
[28] H. B. Bürgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973**, *95*, 5065 – 5067; H. B. Bürgi, J. D. Dunitz, J.-M. Lehn, G. Wipff, *Tetrahedron* **1974**, *30*, 1563 – 1572.
[29] N. T. Anh, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61 – 70.
[30] a) S. S. Wong, M. N. Paddon-Row, *J. Chem. Soc. Chem. Commun.* **1990**, 456 – 458; b) S. S. Wong, M. N. Paddown-Row, *J. Chem. Soc. Chem. Commun.* **1991**, 327 – 330; c) D. O'Hagan, H. Rzepa, *J. Chem. Soc. Perkin Trans. 2* **1994**, 3 – 4; d) C. F. Bridge, D. O'Hagan, K. A. Reynolds, K. K. Wallace, *J. Chem. Soc. Chem. Commun.* **1995**, 2329 – 2330; e) D. O'Hagan, H. Rzepa, *Chem. Commun.* **1997**, 645 – 652; f) A. Deleuze, C. Menozzi, M. Sollogoub, P. Sinaÿ, *Angew. Chem.* **2004**, *116*, 6848 – 6851; *Angew. Chem. Int. Ed.* **2004**, *43*, 6680 – 6683; g) C. Bucher, R. Gilmour, *Angew. Chem.* **2010**, *122*, 8906 – 8910; *Angew. Chem. Int. Ed.* **2010**, *49*, 8724 – 8728.
[31] R. E. Banks, J. C. Tatlow, *J. Fluorine Chem.* **1986**, *33*, 227 – 346.
[32] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063 – 2192.
[33] "Current Fluoroorganic Chemistry": J. Ichikawa, *ACS Symp. Ser.* **2007**, *949*, 155 – 168.
[34] W. S. Johnson, B. Chenera, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 493 – 497; W. S. Johnson, V. R. Fletcher, B.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chenera, W. R. Bartlett, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 497 – 504; W. S. Johnson, R. A. Buchanan, W. R. Bartlett, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 504 – 515; W. S. Johnson, M. S. Plummer, S. P. Reddy, W. R. Bartlett, *J. Am. Chem. Soc.* **1993**, *115*, 515.

[35] P. V. Fish, W. S. Johnson, G. S. Jones, F. S. Tham, R. K. Kullnig, *J. Org. Chem.* **1994**, *59*, 6150 – 6152.

[36] Also see M. C. de la Torre, M. A. Sierra, *Angew. Chem.* **2004**, *116*, 162 – 184; *Angew. Chem. Int. Ed.* **2004**, *43*, 160 – 181; R. A. Yoder, J. N. Johnson, *Chem. Rev.* **2005**, *105*, 4730 – 4756; E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**, pp. 187 – 188.

[37] F. Johnson, *Chem. Rev.* **1968**, *68*, 375 – 413; for an excellent review of acyclic conformational control see R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134 – 2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054 – 2070.

[38] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B.-W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, R. B. Chênevert, A. Fliri, K. Frobel, H.-J. Gais, D. G. Garratt, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim, Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Ong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. Williams, H. N.-C. Wong, *J. Am. Chem. Soc.* **1981**, *103*, 3210 – 3213.

[39] J. E. Kilpatrick, K. S. Pitzer, R. Spitzer, *J. Am. Chem. Soc.* **1947**, *69*, 2483 – 2488; J. P. McCullough, *J. Chem. Phys.* **1958**, *28*, 966 – 967; B. Fuchs, *Top. Stereochem.* **1978**, *10*, 1 – 94.

[40] C. Pfafferott, H. Oberhammer, J. E. Boggs, W. Caminati, *J. Am. Chem. Soc.* **1985**, *107*, 2305 – 2309.

[41] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976.

[42] a) C. M. Marson, R. C. Melling, *Chem. Commun.* **1998**, 1223 – 1224; b) C. M. Marson, R. C. Melling, *J. Org. Chem.* **2005**, *70*, 9771 – 9779.

[43] a) L. Hunter, P. Kirsch, A. M. Z. Slawin, D. O'Hagan, *Angew. Chem.* **2009**, *121*, 5565 – 5568; *Angew. Chem. Int. Ed.* **2009**, *48*, 5457 – 5460; b) D. Farran, A. M. Z. Slawin, P. Kirsch, D. O'Hagan, *J. Org. Chem.* **2009**, *74*, 7168 – 7171; c) L. Hunter, P. Kirsch, J. T. G. Hamilton, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 3105 – 3108; d) L. Hunter, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 2843 – 2848.

[44] For selected discussions, see a) H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429 – 6433; b) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) Y. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691 – 1693; d) A. Pfaltz, W. J. Drury III, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5723 – 5726.

[45] For a review of C_1-symmetric phosphinoxazoles, see G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336 – 345.

[46] a) J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769 – 1772; b) P. von Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614 – 615; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566 – 568; c) G. J. Dawson, C. G. Frost, J. M. J. Williams, *Tetrahedron Lett.* **1993**, *34*, 3149 – 3150; d) A. Pfaltz, *Acta Chim. Scand.* **1996**, *50*, 189 – 194; e) M. J. M. Williams, *Synlett* **1996**, 705 – 710.

[47] J. T. Gerig, R. S. McLeod, *J. Am. Chem. Soc.* **1973**, *95*, 5725 – 5729. Also see reference [20].

[48] M. Doi, Y. Nishi, N. Kiritoshi, T. Iwata, M. Nago, H. Nakano, S. Uchiyama, T. Nakazawa, T. Wakamiyad, Y. Kobayashi, *Tetrahedron* **2002**, *58*, 8453 – 8459.

[49] S. K. Holmgren, K. M. Taylor, L. E. Bretscher, R. T. Raines, *Nature* **1998**, *392*, 666 – 667. Also see a) L. E. Bretscher, C. L. Jenkins, K. M. Taylor, M. L. DeRider, R. T. Raines, *J. Am. Chem. Soc.* **2001**, *123*, 777 – 778; b) M. Doi, Y. Nishi, S. Uchiyama, Y. Nishiuchi, T. Nakazawa, T. Ohkubo, Y. Kobayashi, *J. Am. Chem. Soc.* **2003**, *125*, 9922 – 9923; c) W. Kim, K. I. Hardcastle, V. P. Conticello, *Angew. Chem.* **2006**, *118*, 8321 – 8325; *Angew. Chem. Int. Ed.* **2006**, *45*, 8141 – 8145.

[50] M. C. Yoder, K. Kumar, *Chem. Soc. Rev.* **2002**, *31*, 335 – 341.

[51] R. Filosa, C. Holder, Y. P. Auberson, *Tetrahedron Lett.* **2006**, *47*, 8929 – 8932.

[52] T. Yamazaki, M. Ando, T. Kitazume, T. Kubota, M. Omura, *Org. Lett.* **1999**, *1*, 905 – 908.

[53] S. Nagumo, M. Mizukami, N. Akutsu, A. Nishida, N. Kawahara, *Tetrahedron Lett.* **1999**, *40*, 3209 – 3212.

[54] C. L. Chandler, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6737 – 6739.

[55] S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475 – 2479.

[56] The mechanism of proline-catalyzed reactions is the subject of much conjecture. Please see a) H. Iwamura, D. H. Wells, Jr., S. P. Mathew, M. Klussmann, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312 – 16313; b) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425 – 471; c) A. Armstrong, Y. Bhonoah, A. J. P. White, *J. Org. Chem.* **2009**, *74*, 5041 – 5048; d) T. Kanzian, S. Lakhdar, H. Mayr, *Angew. Chem.* **2010**, *122*, 9717 – 9720; *Angew. Chem. Int. Ed.* **2010**, *49*, 9526 – 9529.

[57] S. Díez-González, S. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874 – 883; J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 2370 – 2375; X. Cattoën, H. Gornitzka, D. Bourissou, G. Bertrand, *J. Am. Chem. Soc.* **2004**, *126*, 1342 – 1343; M. Poyatos, J. A. Mata, E. Peris, *Chem. Rev.* **2009**, *109*, 3677 – 3707.

[58] a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534 – 541; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046 – 3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; c) D. Enders, O. Niemeier, A. Henseller, *Chem. Rev.* **2007**, *107*, 5606 – 5655.

[59] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726.

[60] T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296 – 300.

[61] D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119 – 1122; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021 – 1023; J. H. Teles, J. P. Melder, K. Ebel, R. Schneider, E. Geher, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61 – 83; D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899 – 1902.

[62] D. Seebach, *Angew. Chem.* **1979**, *91*, 259 – 278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239 – 258.

[63] D. A. DiRocco, K. M. Oberg, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10872 – 10874.

[64] For related studies, see a) D. Enders, J. Han, A. Henseler, *Chem. Commun.* **2008**, 3989 – 3991; b) D. Enders, J. Han, *Synthesis* **2008**, 3864 – 3868; c) Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14066 – 14067; d) Q. Liu, T. Rovis, *Org. Lett.* **2009**, *11*, 2856 – 2859; e) T. Jousseaume, N. E. Wurz, F. Glorius, *Angew. Chem.* **2011**, *123*, 1446 – 1450; *Angew. Chem. Int. Ed.* **2011**, *50*, 1410 – 1414.

[65] T. Schaefer, R. W. Schurko, R. Sebastian, F. E. Hruska, *Can. J. Chem.* **1995**, *73*, 816 – 825.

[66] M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964 – 6965.

[67] C. Sparr, E.-M. Tanzer, J. Bachmann, R. Gilmour, *Synthesis* **2010**, 1394 – 1397.

[68] This work constitutes the first example of an enantioselective, organocatalytic epoxidation of an α-branched enal. Also see a) O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227 – 10229; b) B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 5434 – 5437.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[69] For seminal examples, see a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243 – 4244; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874 – 9875; c) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370 – 4371; d) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172 – 1173.
[70] a) R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175 – 1185; b) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543 – 3553; c) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999 – 2034; d) U. Grošelj, W. B. Schweizer, M.-O. Ebert, D. Seebach, *Helv. Chim. Acta* **2009**, *92*, 1 – 13; e) J. B. Brazier, G. Evans, T. J. K. Gibbs, S. J. Coles, M. B. Hursthouse, J. A. Platts, N. C. O. Tomkinson, *Org. Lett.* **2009**, *11*, 133 – 136; f) D. Seebach, U. Grošelj, W. B. Schweizer, S. Grimme, C. Mück-Lichtenfeld, *Helv. Chim. Acta* **2010**, *93*, 1 – 16.
[71] C. Sparr, R. Gilmour, *Angew. Chem.* **2010**, *122*, 6670 – 6673; *Angew. Chem. Int. Ed.* **2010**, *49*, 6520 – 6523.
[72] V. K. Aggarwal, C. Lopin, F. Sandrinelli, *J. Am. Chem. Soc.* **2003**, *125*, 7596 – 7601.
[73] Also see M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *J. Am. Chem. Soc.* **2000**, *122*, 8317 – 8318.
[74] C.-Y. Ho, Y.-C. Chen, M.-K. Wong, D. Yang, *J. Org. Chem.* **2005**, *70*, 898 – 906.
[75] For the crystal structure of (*S*)-2-(fluorodiphenylmethyl)-pyrrolidinium chloride see A. S. Batsanov, J. A. K. Howard, *Acta Crystallogr. Sect. C* **2000**, *56*, e467 – e468. Also see reference [18g].
[76] a) D. B. Berkowitz, K. R. Karukurichi, R. de La Salud-Bea, D. L. Nelson, C. D. McCune, *J. Fluorine Chem.* **2008**, *129*, 731 – 742; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369.
[77] P. A. Bartlett, A. Otake, *J. Org. Chem.* **1995**, *60*, 3107 – 3111.
[78] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3 – 11.
[79] a) W. Adam, R. Curci, J. O. Edwards, *Acc. Chem. Res.* **1989**, *22*, 205 – 211; b) R. W. Murray, *Chem. Rev.* **1989**, *89*, 1187 – 1201.
[80] a) R. Mello, M. Fiorentino, O. Sciacovelli, R. Curci, *J. Org. Chem.* **1988**, *53*, 3890 – 3891; b) R. Mello, M. Fiorentino, C. Fusco, R. Curci, *J. Am. Chem. Soc.* **1989**, *111*, 6749 – 6757.
[81] a) A. Armstrong, B. R. Hayter, *Chem. Commun.* **1998**, 621 – 622; b) A. Armstrong, G. Ahmed, B. Dominguez-Fernandez, B. R. Hayter, J. S. Wailes, *J. Org. Chem.* **2002**, *67*, 8610 – 8617; c) G. Sartori, A. Armstrong, R. Maggi, A. Mazzacani, R. Sartorio, F. Bigi, B. Dominguez-Fernandez, *J. Org. Chem.* **2003**, *68*, 3232 – 3237.
[82] a) S. E. Denmark, Z. Wu, C. M. Crudden, H. Matsuhashi, *J. Org. Chem.* **1997**, *62*, 8288 – 8289; b) S. E. Denmark, H. Matsuhashi, *J. Org. Chem.* **2002**, *67*, 3479 – 3486; c) The following review discusses the development of fluoroketones for epoxidation: S. E. Denmark, Z. Wu, *Synlett* **1999**, 847 – 859.
[83] a) D. Yang, M. K. Wong, Y. C. Yip, *J. Org. Chem.* **1995**, *60*, 3887 – 3889; b) D. Yang, *Acc. Chem. Res.* **2004**, *37*, 497 – 505.
[84] D. S. Brown, B. A. Marples, P. Smith, L. Walton, *Tetrahedron* **1995**, *51*, 3587 – 3606.
[85] a) Y. Tu, Z.-X. Wang, M. Frohn, M. He, H. Yu, Y. Tang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 8475; b) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488 – 496.
[86] A. Solladié-Cavallo, L. Bouérat, L. Jierry, *Eur. J. Org. Chem.* **2001**, 4557 – 4560.
[87] C. J. Stearman, V. Behar, *Tetrahedron Lett.* **2002**, *43*, 1943 – 1946.
[88] A. Armstrong, I. Washington, K. N. Houk, *J. Am. Chem. Soc.* **2000**, *122*, 6297 – 6298.
[89] C. E. Jakobsche, G. Peris, S. J. Miller, *Angew. Chem.* **2008**, *120*, 6809 – 6813; *Angew. Chem. Int. Ed.* **2008**, *47*, 6707 – 6711.
[90] K. H. Jensen, M. S. Sigman, *Angew. Chem.* **2007**, *119*, 4832 – 4834; *Angew. Chem. Int. Ed.* **2007**, *46*, 4748 – 4750.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim