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Perspective

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Looking for Treasure in Stereochemistry-Land. A Path Marked by Curiosity, Obstinacy, and Serendipity[1]

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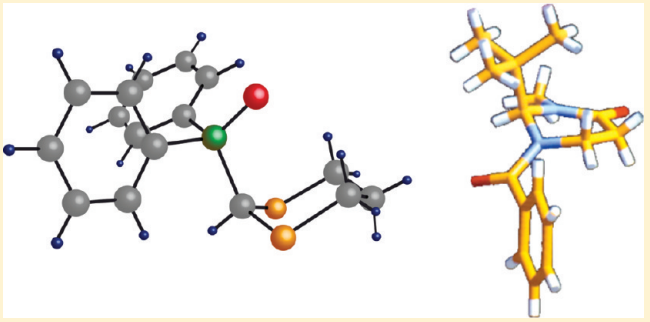
ABSTRACT: Over the past 40 years, much of my research has evolved around various topics of conformational analysis and asymmetric synthesis. This Perspective describes some of my salient contributions in eight different areas of organic stereochemistry: (1) conformational analysis of six-membered rings, (2) evaluation of stereoelectronic interactions in $^{1}J_{C-H}$ one-bond coupling constants in six-membered rings, (3) eclipsed conformation in *cis*-2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1,3-dioxane, (4) determination of enthalpic and entropic contributions to $\Delta G^{\circ}(CH_2Ph)$ and $\Delta G^{\circ}(t\text{-Bu})$, (5) study of the "attractive *gauche* effect" in O−C−C−O segments, (6) examination of salt effects on conformational equilibria, (7) asymmetric synthesis of *β*-amino acids, and (8) asymmetric organocatalysis and "Green" chemistry. It will be appreciated that a basic understanding of the principles of physical organic chemistry has been essential in all projects. Furthermore, curiosity, enthusiasm, obstinacy, and paying attention to unexpected observations will lead to many new (stereo)chemical discoveries.



1. MY (STEREO)CHEMICAL JOURNEY

I was probably ten years old when the main character in a Walt Disney movie[2]—a young man who carried out experiments in his basement laboratory—woke up in me the interest in exploring and inventing things. When I finished high school, thanks to a scholarship granted by the local Rotary Club on the recommendation of one of its members, my grandfather Gregorio Juaristi, I was able to study chemistry at Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM). Most of my classmates and new friends at the "Tec" were registered in the Chemical Engineering program so I was seriously considering a move to that undergraduate program, but Professor Xorge A. Domínguez, Chair of the Chemistry Department (Figure 1), showed me through his teaching in the basic organic chemistry course the beauty, intelectual appeal, and enormous potential of organic chemistry. In additional conversations he revived my vocation for scientific research. Thus, I stayed in the Bachellor in Science (in Chemistry) program.

Two events were most relevant for me in 1970, when I was a third-year undergraduate student: first, with the recommendation of Professor Domínguez I was accepted for "summer training" at the Syntex Company laboratories in Mexico City. This experience gave me the opportunity to be in contact with brilliant chemists such as Pierre Crabbé, Paul Ortiz de Montellano, and Esperanza Velarde, who introduced me to the exciting world of the synthesis of valuable, biologically active compounds. Furthermore, Miguel Ángel Vera, a classmate at the "Tec" in Monterrey, who also spent that summer at Syntex, introduced me to the recently advanced proposals of Woodward and Hoffmann regarding the relevance of orbital symmetry in dictating the viability and stereochemical consequences of

Figure 1. Dr. Xorge A. Domínguez (photograph taken in May 1980).

concerted reactions.[3] Second, in December 1970 I attended a short course of stereochemistry and conformational analysis tought by Professors Ernest Eliel, Pedro Lehmann, and Xorge Domínguez at Universidad Autónoma de Guadalajara. I was fascinated by the subject, and indeed, stereochemistry would become the central theme in my subsequent work (undergraduate and graduate theses and independent research work in Mexico City's Centro de Investigación y de Estudios Avanzados (CINVESTAV, see below). In particular, following the closing ceremony of the stereochemistry course, and again with the recommendation of Professor Domínguez, I "got the nod" from

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Figure 2. Exact moment (December 1970) when Dr. Xorge A. Domínguez (left) was recommending me to Dr. Ernest L. Eliel (center) to accept me in his research group for graduate work.

Figure 3. My father (Eusebio Juaristi-Milanesio, 1926−1983) traveled to San Francisco to be with me during my first presentation at a meeting of the American Chemical Society (August 1976).

Professor Eliel to undertake graduate work in his laboratories at the University of Notre Dame once I finished my undergraduate studies (Figure 2).[4]

In the meantime, Professor Eliel moved to the University of North Carolina at Chapel Hill (UNC−CH) in August 1972, so I followed him and joined his group during that summer. My doctoral thesis consisted of four projects: two related with the development of stereoselective reactions of organometallic compounds[5] and two dealing with the conformational analysis of sulfur-containing heterocycles.[6] On two memorable occasions I had the chance to present my thesis results before a formal audience: during the 1976 Fall meeting of the American Chemical Society that took place in San Francisco, CA (Figure 3), and then in my final Ph.D. examination at UNC in March 1977.

During the development of my doctoral thesis I repeatedly consulted articles published by Professors Andrew Streitwieser and Dieter Seebach, whose work has always marveled me. Thus it may not be surprising that in 1977−1978 I had a posdoctoral stay with Andy Streitwieser at the University of California—Berkeley. Years later, I spent two sabbatical recesses (1985−1986 and 1992−1993) at the E.T.H. in Zurich, Switzerland, with Seebach and one more (1999−2000) with Streitwieser while also teaching the advanced physical organic chemistry course that he used to impart. (The notes and references that I borrowed from Carolyn Bertozzi were most helpful).

In 1979, during a second postdoc carrying out research in a pharmaceutical company, the Diagnostics Division of Syntex, Palo Alto, CA, I received an invitation to visit and interview at the Chemistry Department of Centro de Investigación y de Estudios Avanzados (CINVESTAV) of the National Polytechnic Institute in Mexico City. By then I was convinced that I wanted to create my own research group and carry out

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independent research. I had also concluded that my potential contributions as teacher and as researcher would have a much greater impact in Mexico relative to the United States, so I was more than ready to seek an academic position in my home country.

From the moment I started my independent research work, I have been fortunate to count on the assistance of capable and enthusiastic students, by now nearly 200, among undergraduate, graduate, and postdoctoral. Furthermore, although we had to be rather careful with the available resources and essential financial support, I can say that there is practically no research project that we had to abandon owing to lack of means. We have a saying in Mexico: "God tightens the grip but does not strangle".

Furthermore, when I joined CINVESTAV in September of 1979, I had the great fortune of having Dr. Fernando Walls as my boss (Figure 4). Fernando was the Head of the Chemistry

Figure 4. Dr. Fernando Walls (photograph taken in 1994).

Department and provided me with generous advice and administrative support in order for me to put together a "lab" and to be able to incorporate the first students. Fernando Walls also distinguished me with a close friendship that would grow stronger as time passed, and that I will always cherish.[7]

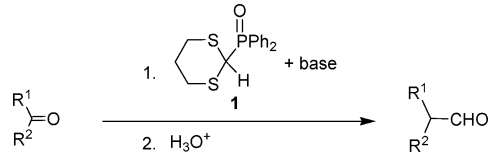
In May of 1980, with the support of Fernando Walls and Saúl Villa, a CINVESTAV colleague in charge of the Institute's outreach program, I obtained financial resources from the Mexican Ministry of Education to organize a short stereochemistry course in the city of Guanajuato. In this course I became an instructor together with my "old" teachers of 1970, Domínguez, Eliel, and Lehmann. Furthermore, with the material prepared for the course, the book *Tópicos Modernos de Estereoquímica* was written.[8] With time, this book became the first in a series of stereochemistry textbooks, both in Spanish and in English[9] (Figure 5). I believe that these books, as well as a significant number of stereochemistry courses that I thought elsewhere,[10] have had a positive impact in the promotion of the study and application of stereochemistry at various levels.

2. A PATH MARKED BY CURIOSITY, OBSTINACY, AND SERENDIPITY

2.1. Conformational Analysis of Six-Membered Rings.

Before I describe some of the salient research projects that we have carried out, I want to say that several unexpected observations led to what may be some of our most relevant contributions. One example is an accidental discovery that was made in the course of the very first project that was undertaken. The idea was to develop a novel Wittig-type reagent combining the 1,3-dithianyl ring and the diphenylphosphinoyl substituent, so that compound **1** could be used in the homologation of carbonylic substrates (Scheme 1).

Scheme 1. Homologation of Carbonylic Compounds by Means of Heterocycle 1.[11]



Regardless of the fact that this idea proved successful,[11] the assignment of the proton NMR spectrum of compound **1** offered evidence of a very large (ca. 1.2 ppm) chemical shift difference between axial and equatorial protons at C(4,6). (By comparison, $\Delta\delta_{ax/eq}$ for H(4,6) in 2-*tert*-butyl-1,3-dithiane is less than 0.1 ppm). These spectroscopic observations suggested a manifestation of a deshielding effect on the *syn*-axial H(4,6) protons by the phosphoryl group in a *predominantly axial* orientation of the diphenylphosphinoyl group (Scheme 2).[12]

Figure 5. (Left) "Tópicos Modernos de Estereoquímica" (reprinted with permission from LIMUSA, Mexico, 1983). (Middle) "Introducción a la Estereoquímica y al Análisis Conformacional" (reprinted with permission from Minal, Mexico, 1989). (Right) "Introduction to Stereochemistry and Conformational Analysis" (reprinted with permission from Wiley, New York, 1991; reprinted in 2000).

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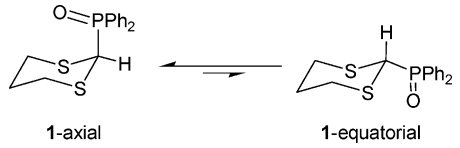
Scheme 2. Predominance of the Axial Conformation in the Conformational Equilibrium of 1[12]



We had, therefore, evidence for an unprecedented, strong anomeric interaction between the second-row elements sulfur and phosphorus. In view of the considerable steric size of the diphenylphosphinoyl substituent, its axial orientation appeared incredible (and I was told so by several skeptical colleagues). Nevertheless, definite evidence for the stereostructure of **1** was obtained by single-crystal X-ray diffraction (Figure 6).

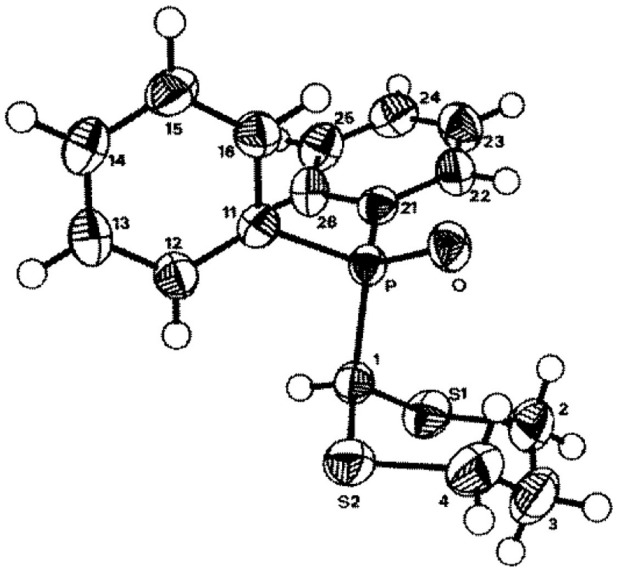
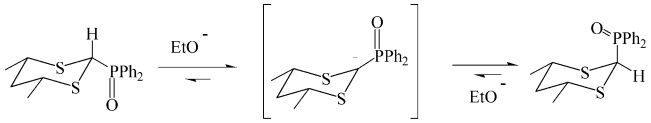


Figure 6. Perspective view of the molecular structure of **1**, where the axial orientation of the diphenylphosphinoyl group was confirmed.[12]

Interestingly, comparison of precise structural data on axial-**1** and conformationally fixed equatorial analogue **2** (Scheme 3)

Scheme 3. Chemical Equilibration of Anancomeric (Conformationally Fixed) 2 and 3, Models for Axial and Equatorial 1



was not in line with the anticipated (in terms of a $n_S \rightarrow \sigma^*_{C-P}$ stereoelectronic interaction) shortening of the S–C(2) bond and lengthening of the C(2)–P bond in axial-**1**. That is, structural data were not in agreement with expectation in terms of $n_S \rightarrow \sigma^*$ hyperconjugation as the interaction stabilizing axial-**1**.[12]

In order to quantitate this conformational effect, the anancomeric derivatives **2** and **3** (Scheme 3) were prepared, and their proton NMR spectra were compared with that for **1**. Most interestingly, the coupling constant of H(2) to phosphorus in **1**–**3** varies considerably: 6, 15, and 4.2 Hz, respectively. On the assumption that $^2J_{H(2)/P}$ in the mobile dithiane (**1**) corresponds to the weighed average of those for the model diastereomers **2** and **3**, then $K = (J_{ax} - J_{mobile})/(J_{mobile} - J_{eq}) = 5.0$, which from Gibbs equation affords $\Delta G^\circ = +1.0$ kcal/mol, for the free energy difference favoring **1**-ax over **1**-eq.

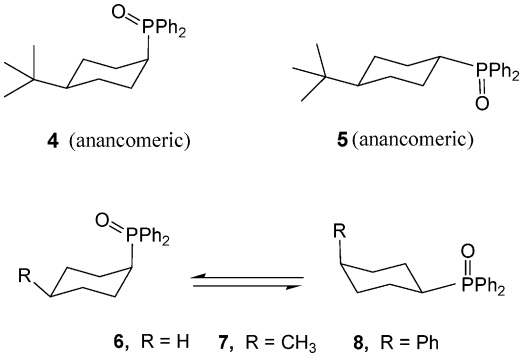
The estimated conformational free energy difference for the axial–equatorial equilibrium of heterocycle **1**, $\Delta G^\circ = +1.0$ kcal/mol, was confirmed by chemical equilibration of anancomeric **2** (equatorial model) and **3** (axial model) under basic catalysis (Scheme 3).

Generally,[13] the magnitude of the anomeric effect is defined as the difference of the free energy differences ($\Delta\Delta G^\circ$) for the equilibrium under study (Scheme 1) and the conformational energy of the same substituent in cyclohexane (*A* value) (eq 1).

$$\text{AE} = \Delta\Delta G^\circ + A \text{ value} \quad (1)$$

Accordingly, in order to quantitate the magnitude of the anomeric effect operative in the conformational equilibrium depicted in Scheme 1 (**1**-ax ⇌ **1**-eq), the conformational preference of the diphenylphosphinoyl group in cyclohexane (*A* value) was determined. To this end, the anancomeric models **4** and **5** were synthesized, and their spectroscopic behavior was compared with that presented by conformationally mobile **6** (Scheme 4). As it turned out, spectroscopic comparison of **6**

Scheme 4. Anancomeric (Conformationally Fixed) Models 4 and 5 and Mobile Diphenylphosphinoylcyclohexanes 6–8



with anancomeric **4** and **5** by means of Eliel's equation[14] (eq 2) indicated the equilibrium **6**-ax ⇌ **6**-eq to be too highly biased, with a large predominance of the equatorial conformer.

$$K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax}) \quad (2)$$

Nevertheless, equilibrium constants closer to unity were observed for **7** and **8**, which incorporate "counterpoise" substituents and permitted a more precise calculation of the *A* value of the diphenylphosphinoyl group, $\Delta G^\circ[P(O)Ph_2] = 2.74$ kcal/mol.[15] Comparison of this value with the corresponding conformational free energy difference in 2-diphenylphosphinoyl-1,3-dithiane (**1**, Scheme 1) affords an anomeric effect for the S–C–P segment in the heterocyle worth well over 3.0 kcal/mol, AE = ΔG° + *A* value = +1.0 + 2.74 = 3.74 kcal/mol.

Significant effort was dedicated for more than one decade by us[16–19] and others,[20] to explain the nature and scope of the "anomeric effect in the S–C–P molecular segment". For example, in 1986 we observed that the axial preference of the diphenylphosphinoyl group in **1** (Scheme 1) decreases substantially in trifluoroacetic acid as solvent. This observation was explained in terms of protonation of the phosphoryl oxygen, that apparently neutralizes electrostatic, attractive

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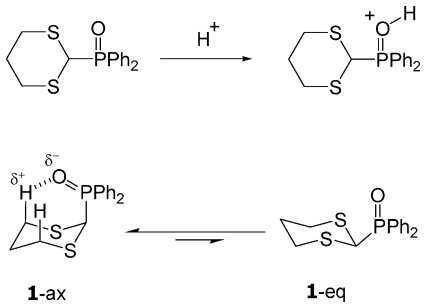
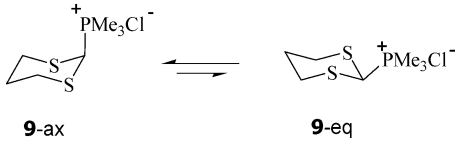
interaction between the phosphoryl oxygen and the axial hydrogens H(4,6ax) in **1**-ax (Scheme 5).[12c]

Scheme 5. Protonation of the Phosphoryl Oxygen under Strongly Acidic Conditions (Top) Is Likely To Turn off Some Electrostatic, Attractive Interaction in 1-ax (Bottom)[12c]



Indeed, more recently, Cuevas has reported a theoretical analysis of the anomeric effect in S−C−P units. Thus, using computational resources and 2-dimethylphosphinoyl-1,3-dithiane as a model system it is argued that the polar nature of the P−O bond promotes a high charge concentration at the oxygen atom, which is then able to interact with the 1,3-*syn*-diaxial hydrogen atoms, resulting in a stabilizing contribution.[21] Nevertheless, an interpretation based solely on hydrogen-bonding terms cannot be correct since for example, a significant anomeric effect worth at least 2.2 kcal/mol has been found in trimethylphosphonium analogue **9**,[19] which by the nature of the phosphorus moiety is unable to participate in a hydrogen-bonding interaction with the *syn*-diaxial hydrogens at H(4,6) (Scheme 6).

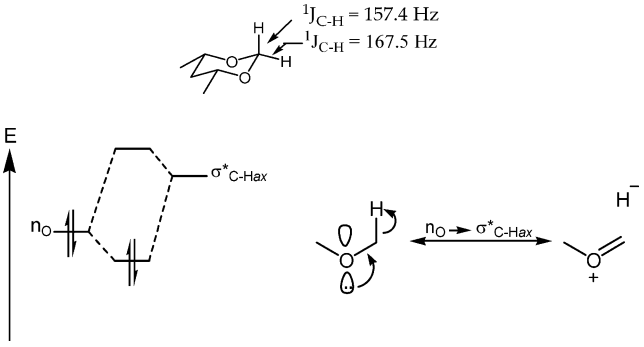
Scheme 6. A Definite Preference for the Axial Conformation 9-ax, $\Delta G°$ = +0.36 kcal/mol, Reflects a Substantial S−C−$^{+}$PMe$_3$ Anomeric Effect in This System, Worth at Least 2.2 kcal/mol[19]



2.2. Manifestation of Stereoelectronic Interactions in $^{1}J_{C-H}$ One-Bond Coupling Constants in Six-Membered Rings. One of the reasons stereoelectronic effects are not yet fully accepted as a "proven" concept is the indirect nature of the evidence that is usually advanced to support its relevance. Nevertheless, various studies during the last 20 years have provided *strong evidence that combined empirical and theoretical analysis of one-bond C−H coupling constants is a powerful tool for the identification of stereoelectronic interactions*. In particular, coupling trends can be rationalized in terms of stereospecific interactions involving $\sigma \rightarrow \sigma^*$, $\sigma \rightarrow \pi^*$, and $n \rightarrow \sigma^*$ electron delocalization. Furthermore, the relative magnitude of the coupling constants usually correlates as well with structural parameters such as bond length and reactivity.[22]

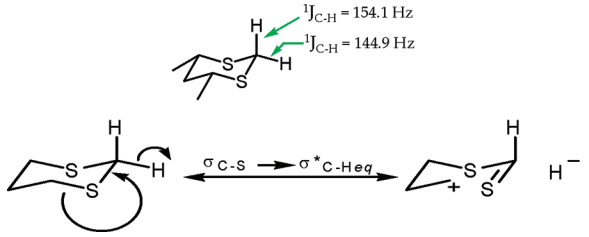
In this regard, four decades ago, Perlin and Casu[23] observed that the magnitude of the one-bond coupling constant for an axial C−H bond adjacent to oxygen or nitrogen in a six-membered ring is smaller by 8−10 Hz than $^{1}J_{C-H}$ for an equatorial C−H bond; that is, $^{1}J_{C\text{-}Heq} > {}^{1}J_{C\text{-}Hax}$. This finding has been interpreted in terms of an $n_X \rightarrow \sigma^*_{C\text{-}Happ}$ interaction between a pair of nonbonded electrons on oxygen or nitrogen and the axial (antiperiplanar) adjacent C−H bond; that is, double bond-no bond resonance weakens the C−H$_{ax}$ bond and attenuates the one-bond ^{13}C−^{1}H coupling constant (Scheme 7).

Scheme 7. Stereoelectronic Interpretation of the Smaller $^{1}J_{C-H}$ in the Axial C−H Bond Adjacent to Oxygen



In contrast with the situation in *cis*-4,6-dimethyl-1,3-dioxane where $^{1}J_{C(2)\text{-}Hax} < {}^{1}J_{C(2)\text{-}Heq}$, Bailey et al.[24] reported in 1988 that the dithiane analogue exhibits an opposite behavior: $^{1}J_{C(2)\text{-}Hax}$ = 154.1 Hz > $^{1}J_{C(2)\text{-}Heq}$ = 144.9 Hz. This reversal of the relative magnitudes of the coupling constants at C(2) in dioxanes and dithianes was explained by Wolfe et al.[25] as a result of dominant $\sigma_{C-S} \rightarrow \sigma^*_{C\text{-}Heq}$ or $\sigma_{C\text{-}Heq} \rightarrow \sigma^*_{C-S}$ (rather than $n_S \rightarrow \sigma^*_{C\text{-}Hax}$) interactions in the dithiane (Scheme 8).

Scheme 8. Stereoelectronic Interpretation of the Smaller $^{1}J_{C-H}$ in the Equatorial C−H Bond Adjacent to Sulfur



All equatorial C−H bonds in 1,3-dithiane (**10**) are antiperiplanar (app) to C−S bonds in the ring. Thus, should $\sigma_{C-S} \rightarrow \sigma^*_{C\text{-}Heq}$ or $\sigma_{C\text{-}Heq} \rightarrow \sigma^*_{C-S}$ stereoelectronic interactions dominate over $n_S \rightarrow \sigma^*_{C\text{-}Hax}$ interactions, then one would expect $^{1}J_{C(2)\text{-}Hax} > {}^{1}J_{C(2)\text{-}Heq}$ for *all* C−H one-bond couplings in 1,3-dithiane. Indeed, the values of the $^{1}J_{C-H}$ coupling constants, determined from the proton-coupled ^{13}C NMR spectra, show this to be the case; all axial H(2) protons in **10** present the larger $^{1}J_{C-H}$ coupling constant (Scheme 9).[26] This finding is in line with a dominant $\sigma_{C-S} \rightarrow \sigma^*_{C\text{-}Heq}$ and/or $\sigma_{C\text{-}Heq} \rightarrow \sigma^*_{C-S}$ hyperconjugative interactions that weakens the equatorial C−H bond.[26] That is, in 1,3-dithiane **10** the donor capacity of the sigma C−S orbital toward the σ^* C−H$_{eq}$ antibonding orbital evidently surpasses the "anomeric type" $n_S \rightarrow \sigma^*_{C\text{-}Hax}$ interaction that weakens the axial C(2)−H$_{ax}$ bond.

One-bond C−H coupling constants, $^{1}J_{C-H}$, are amenable to accurate computation, and in particular ab initio calculations that take into account electron correlation are convenient in the study of stereoelectronic effects. Cyclohexane (**11**) and oxygen-, sulfur-, and/or nitrogen-containing six-membered heterocycles **12**−**15** (Scheme 10) were studied theoretically.[27]

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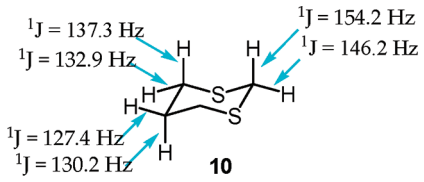
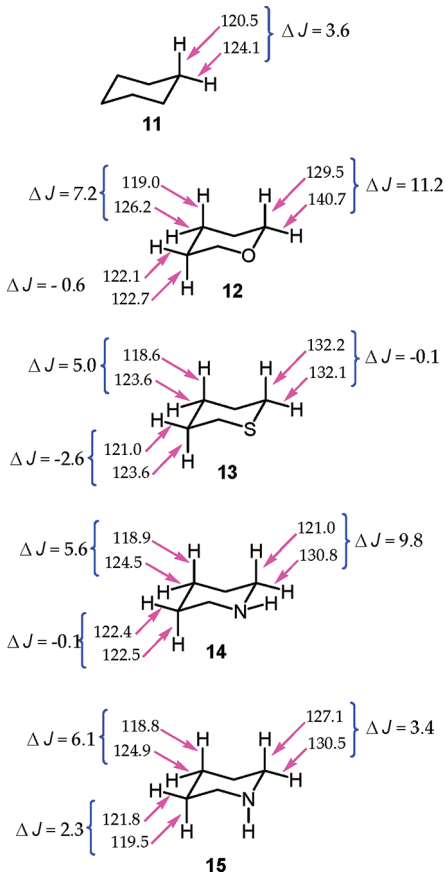
Scheme 9. All Equatorial C−H Bonds in 1,3-Dithiane Are Associated to Smaller $^1J_{C-H}$ Coupling Constants as a Consequence of Dominant $\sigma_{C-S} \rightarrow \sigma^*_{C\text{-}Heq}$ or $\sigma_{C\text{-}Heq} \rightarrow \sigma^*_{C-S}$ Stereoelectronic Interactions[26]



^1J values in Hz. At -90°C, in methylene chloride-d_2.

Scheme 10. Calculated One-Bond $^{13}C-^1H$ Coupling Constants (Hz) for Cyclohexane (11) and Monoheterocyclohexanes 12−15[27]



Density functional theory [B3LYP/6-31G(*d*,*p*)] was able to reproduce the structural (in particular C−H bond distances). The results confirmed the importance of $n_X \rightarrow \sigma^*_{C-Happ}$ (where X = O, N), $\sigma_{S-C} \rightarrow \sigma^*_{C-Happ}$, $\sigma_{C-S} \rightarrow \sigma^*_{C-Happ}$, $\beta\text{-}n_O \rightarrow \sigma^*_{C-H}$, and $\sigma_{C-H} \rightarrow \sigma^*_{C-Happ}$ hyperconjugation.

Cyclohexane **11** served as the parent, reference compound, whereas heterocycles **12**−**15** provided the fundamental information on the consequences of replacing a methylene group in cyclohexane for oxygen (**11** → **12**), sulfur (**11** → **13**), equatorial N−H (**11** → **14**), and axial N−H (**11** → **15**). Specifically, all C−H bond lengths in **12**−**15** are compared with the reference $C-H_{ax}$ and $C-H_{eq}$ bond lengths in cyclohexane: any C−H bond lengthening observed in **12**-**15** might reflect stereoelectronic interactions, where σ^*_{C-H} is the acceptor orbital. (Nevertheless, interactions where σ_{C-H} is a donor orbital, as in $\sigma_{C-Hax} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation, should also result in C−H bond lengthening since electron density is removed from a bonding orbital). Furthermore, weaker C−H bonds are expected to be associated with smaller $^1J_{C-H}$ coupling constants.

With respect to the reference cyclohexane (**11**) molecule, calculations reproduce the relative magnitude of both the $C-H_{ax}$ and $C-H_{eq}$ coupling constants, that is, the normal "Perlin effect" observed in cyclohexane, as well as the absolute values, within reasonable limits (±2−3 Hz). Indeed, the calculated values $^1J_{C-Hax}$= 120.5 Hz and $^1J_{C-Heq}$ = 124.1 Hz are to be compared with the corresponding experimental values, 122.4 and 126.4 Hz, respectively.[28]

There exist three distinct methylenic pairs of C−H bonds in oxane **12**. As anticipated, $n_O \rightarrow \sigma^*_{C-Happ}$ hyperconjugation weakens the axial C−H bonds at C(2,6), so that $^1J_{C(2,6)\text{-}Hax}$ = 129.5 Hz is significantly smaller than $^1J_{C(2,6)\text{-}Heq}$ = 140.7 Hz; thus, the calculated $\Delta^1J_{ax/eq}$ is 11.2 Hz. In strong contrast, $^1J_{C(3,5)\text{-}Hax}$ = 122.7 Hz > $^1J_{C(3,5)\text{-}Heq}$ = 122.1 Hz, and $\Delta^1J_{ax/eq}$ = −0.6 Hz. This *reverse* correlation of ^1J values relative to cyclohexane is in agreement with the $\beta\text{-}n_O \rightarrow \sigma^*_{C(5)\text{-}Heq}$ stereoelectronic interaction advanced by Alabugin[29] (Figure 7).

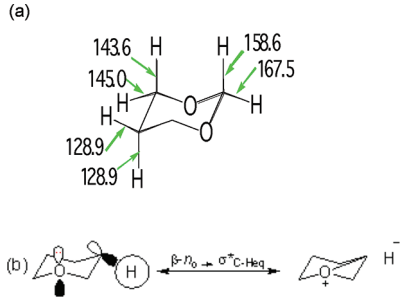


Figure 7. (a) Experimentally obtained one-bond coupling constants in 1,3-dioxane.[26] (b) Through-space hyperconjugative interaction between a *p*-type lone pair at the *β*-oxygen and the back lobe of the antibonding $C(5)-H_{eq}$ orbital.[29]

Finally, the calculated coupling constants for the methylenic C−H bonds at C(4) [$^1J_{C(4)\text{-}Hax}$ = 119.0 Hz < $^1J_{C(4)\text{-}Heq}$ = 126.2 Hz; $\Delta^1J_{ax/eq}$ = 7.2 Hz] are those expected for a "cyclohexane-like" methylenic segment.

The one bond C−H coupling constants calculated for thiane **13** reveal two effects: (1) at C(2), where $n_S \rightarrow \sigma^*_{C(2)\text{-}Hax}$ hyperconjugation is not relevant, $\sigma_{C(3)\text{-}H} \rightarrow \sigma^*_{C(2)\text{-}Hax}$ interaction is offset by a dominant $\sigma_{C(6)\text{-}S} \rightarrow \sigma^*_{C(2)\text{-}Heq}$ stereoelectronic effect, and (2) at C(3) $^1J_{C-Heq}$ < $^1J_{C-Hax}$ (121.0 and 123.6 Hz, respectively). This observation is best interpreted in terms $\sigma_{S-C(2)} \rightarrow \sigma^*_{C(3)\text{-}Heq}$ electron transfer that is apparently more important than two $\sigma_{C-H} \rightarrow \sigma^*_{C(3)\text{-}Hax}$ and *two* $\sigma_{C(3)\text{-}Hax} \rightarrow \sigma^*_{C-H}$ hyperconjugative interactions. Other interactions that weaken the equatorial C(3)-H bond are $\sigma_{C(3)\text{-}Heq} \rightarrow \sigma^*_{S-C(2)}$, $\sigma_{C(3)\text{-}Heq} \rightarrow \sigma^*_{C(4)-C(5)}$, and $\sigma_{C(4)-C(5)} \rightarrow \sigma^*_{C(3)\text{-}Heq}$, although these contributions are anticipated to be less important in view of the lower acceptor ability of the σ^*_{S-C} and σ^*_{C-C} orbitals, as well as the poor donor ability of the σ_{C-C} orbital.[30]

Analysis of the $^1J_{C-H}$ coupling constants in azanes **14** and **15** is particularly interesting because of the possible consequences of the pseudoaxial and pseudoequatorial orientation of the nitrogen lone pair in these models. Indeed, in azane **14** (equatorial N−H), a substantial Perlin effect is appreciated at C(2): $^1J_{C-Hax}$ = 121.0 Hz < $^1J_{C-Heq}$ = 130.8 Hz; $\Delta^1J_{ax/eq}$ = 9.8 Hz. By contrast, in azane **15**, where the nitrogen lone pair is

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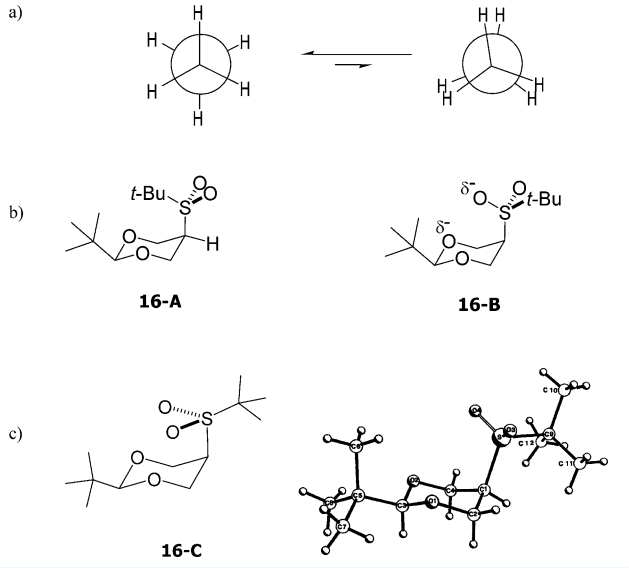
gauche to both C(2)−H bonds, a much diminished normal Perlin effect is found: $\Delta J_{ax/eq}$ = 3.4 Hz. Importantly, in azane **14** $^1J_{C(3)\text{-}Hax} \approx {}^1J_{C(3)\text{-}Heq}$ = 122.5 Hz, whereas in epimeric azane **15** the normal trend is observed: $^1J_{C(3)\text{-}Hax}$ = 119.5 Hz < $^1J_{C(3)\text{-}Heq}$ = 121.8 Hz. This result does fit expectation in terms $\beta\text{-}n_{Nax} \rightarrow \sigma^*_{C(3)\text{-}Heq}$ hyperconjugation (cf. Figure 7b). Finally, normal Perlin effects ($^1J_{C-Hax} < {}^1J_{C-Heq}$) are seen at C(4), both in **14** and **15**.

It can be appreciated that spectroscopic manifestations of stereoelectronic interactions are particularly useful experimental signatures of these effects which can be utilized for testing molecular models. Empirical observations together with theoretical interpretations in cyclohexane and six-membered heterocycles confirm the relevance of $\sigma_{C-Hax} \rightarrow \sigma^*_{C-Hax}$, $n_X \rightarrow \sigma^*_{C-Hax}$ (X = O or N), $\sigma_{C-S} \rightarrow \sigma^*_{C-Heq}$, $\beta\text{-}n_O \rightarrow \sigma^*_{C-Heq}$, $\sigma_{C2-Hax} \rightarrow \pi^*_{C=Y}$ (Y = O, S, CH_2) and $\sigma_{C2-Hax} \rightarrow \sigma^*_{S-Oax}$ two-electron/two-orbital stereoelectronic interactions that weaken the acceptor (or donor) C−H bonds and attenuate the Fermi contribution to the one-bond $^{13}C-{}^1H$ coupling constants.[31,32]

2.3. Finding an Eclipsed Conformation in *cis*-2-*tert*-Butyl-5-(*tert*-butylsulfonyl)-1,3-dioxane. It was also by serendipity that we found a rare example of an eclipsed conformation in the title compound. It is of course anticipated that staggered rather than eclipsed conformations are present in organic molecules (Scheme 11a); nevertheless, while measuring

Scheme 11. (a) Preferred Staggered Conformation in Ethane. (b) Anticipated Staggered Rotamers in *cis*-16. (c) Solid-State Structure and Conformation of Heterocycle *cis*-16[33]



(in collaboration with Richard Glass, University of Arizona) the electrochemical oxidation potentials of several 5-substituted 1,3-dioxanes[33] we came to synthesize the *cis*-2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1,3-dioxane derivative *cis*-**16**, which was expected to adopt either one of the rotameric conformations **A** or **B** (Scheme 11b). Rotamer **A**, presenting an axial sulfonyl group with the alkyl (*tert*-butyl) substituent inside the ring, should lead to significant steric congestion, whereas a rotamer with the *tert*-butyl group turned outward (structure **B** in Scheme 11b) places the negative ring oxygens close to the (negatively charged) sulfonyl oxygen, leading to an unfavorable electrostatic interaction.

Definite evidence for the structure of *cis*-**16** in the solid state was obtained by single-crystal X-ray diffraction; a perspective view is shown in Scheme 11c. To our surprise, the crystallographic data (Scheme 11c) do not correspond to structure **A** or **B**: the sulfonyl *tert*-butyl group is outside the ring in a *nearly eclipsed conformation* (average torsional angles O−S−C−C and C−S−C−H are 8.25° and 7.6°, respectively). Thus, this constituted an unprecedented observation of a molecule presenting three pairs of eclipsed vicinal bonds, two S−O/C−C and one S−C/C−H eclipsed vicinal bond pairs.[33]

In order to pinpoint the effect(s) responsible for the unusual stability of the eclipsed conformation in *cis*-**16**, the X-ray crystallographic analysis of cyclohexyl analogue *cis*-**17** was undertaken.[34] As can be appreciated in Figure 8, the sulfonyl

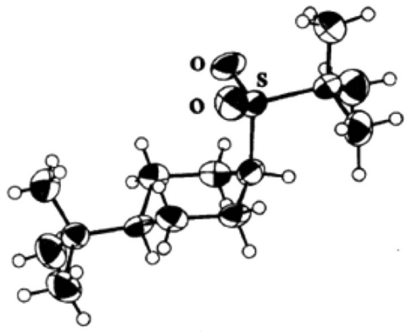


Figure 8. Solid-state structure and conformation of *cis*-4-*tert*-butyl-1-(*tert*-butylsulfonyl)cyclohexane (*cis*-**17**).[34].

group turned out to be nearly eclipsed, indicating that the ring oxygens present in *cis*-**16** are not essential for the observed eclipsing.

In order to determine whether the steric crowding between the *t*-Bu and the *gauche* endocyclic methylenes is serious enough to account for the observed eclipsing, MMP2 force-field calculations were performed for *cis*-**16** and *cis*-**17**.[34] In the case of the dioxane *cis*-**16**, the force-field calculations predict energy minima at C−S−C−H torsion angle = 20−30° (midway between staggered and eclipsed) indicating that *tert*-butyl steric repulsion is responsible, at least in part, for the eclipsing phenomenon.[35] The difference between the calculated stable rotamer and the experimentally observed one (τ = 8.25°) may suggest the involvement of an additional quantum mechanical effect responsible for the stabilization of the observed nearly eclipsed conformation.[36]

2.4. Enthalpic and Entropic Contributions to $\Delta G°(CH_2Ph)$ and $\Delta G°(t\text{-Bu})$. The energy differences between the equatorial and axial conformations of monosubstituted cyclohexanes (*A* values) are of great interest to organic chemists since they serve as models for more complicated molecules. Alkyl groups prefer equatorial over axial positions in order to avoid the repulsive steric interactions with the axial hydrogens at C(3,5), and it is usually observed that the bulkier the alkyl group the larger the preference for the equatorial form.[37] In this regard, the accepted *A* values for methyl, ethyl, and isopropyl are 1.74, 1.8, and 2.15 kcal/mol, respectively, in line with their increasing size. However, early force-field calculations indicated that the *enthalpic* contributions to the equatorial preference actually *decrease* along this series.[38] Experimental NMR data agreed with the theoretical results, affording, in kcal/mol, $-\Delta H°$(Me) = 1.75, $-\Delta H°$(Et) = 1.6, and $-\Delta H°$(*i*-Pr) = 1.52.[39]

The conformational study of benzylcyclohexane was deemed important in this context because the analysis of the *gauche*

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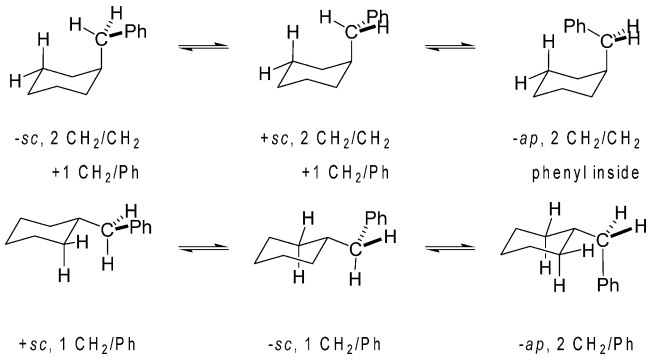
interactions present in the axial and equatorial conformers (Scheme 12) suggests that the overall enthalpy difference must

Scheme 12. Repulsive *Gauche* Interactions Present in the Axial and Equatorial Conformers of Benzylcyclohexane[a]



[a]The phenyl inside rotamer of axial phenylcyclohexane is nearly 3 kcal/mol higher in energy and can be disregarded.

be *less* than the two *gauche* butane interactions present in axial methylcyclohexane; i.e., $-\Delta H^{\circ}(CH_2Ph)$ must be smaller than $-\Delta H^{\circ}(Me)$ = 1.75 kcal/mol. On the other hand, three populated rotamers in equatorial benzylcyclohexane versus two in the axial form imply that the entropy of mixing be positive, and should make a substantial contribution to the free energy difference, $\Delta G^{\circ}(CH_2Ph)$.

The conformational equilibrium of benzylcyclohexane is highly biased toward the equatorial isomer; thus, *cis*- and *trans*-1-benzyl-4-methylcyclohexane were used for the required NMR studies. Below coalescence temperature, the conformational equilibrium of *cis*-**18** (eq 3) is displaced to the left, with

(3)

ΔG°_{202K} = +0.08 kcal/mol; that is, the conformer with equatorial methyl and axial benzyl groups is favored in spite of the larger size of the latter.

Most interestingly, application of Eliel's equation[14] [$K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax})$] to the ^{13}C NMR data afforded ΔG°_{298K} = −0.04 kcal/mol. That is, at ambient temperature the equilibrium in eq 3 is displaced to the right, so that now the bigger benzyl substituent predominates over the methyl group in the equatorial position. The contrasting temperature dependent behavior (positive ΔG° at 202 K, but negative ΔG° at 298 K) clearly reflects a substantial entropy effect. Indeed, from the conformational free energy diferences at ambient temperature (298 K) and at 202 K, ΔS° = +1.17 cal/K.mol and ΔH° = +0.31 kcal/mol are obtained. Therefore, at low temperature, i.e., 170−200 K, the ΔG° for eq 3 is dominated by the *enthalpy term* and the preference for the equatorial orientation follows the order $CH_3 > CH_2Ph$. On the other hand, at ambient and higher temperatures, the ΔG° values are dominated by the *entropy term* $T\Delta S^{\circ}$, ensuring that the preference for an equatorial orientation follows the "expected" order $CH_2Ph > CH_3$.

These thermodynamic data were confirmed by means of plots of ln K versus $1/T$, which were linear and allowed for the derivation of ΔH° and ΔS°.[40] The resulting average values of six experiments for the equilibrium depicted in eq 3 are ΔH° = +0.23 kcal/mol and ΔS° +0.90 cal/K.mol. Consideration of $\Delta H^{\circ}(Me)$ = −1.75 kcal/mol and $\Delta S^{\circ}(Me)$ = −0.03 cal/K.mol,[39] gives $\Delta H^{\circ}(CH_2Ph)$ = −1.52 kcal/mol and $\Delta S^{\circ}(CH_2Ph)$ = +0.81 cal/K·mol.[41]

The experimental results were well reproduced by molecular mechanics calculations. Furthermore, determination of the entropy of mixing using the corresponding fractional populations in axial and equatorial benzylcyclohexane (Figures 9 and 10)

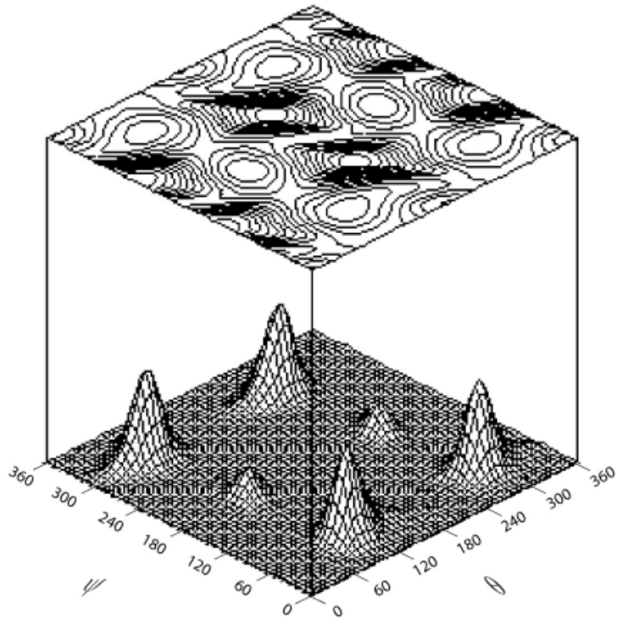


Figure 9. Conformational energy map (+ signs correspond to energy maxima and − signs correspond to energy minima) and Boltzmann populations in equatorial benzylcyclohexane.[41]

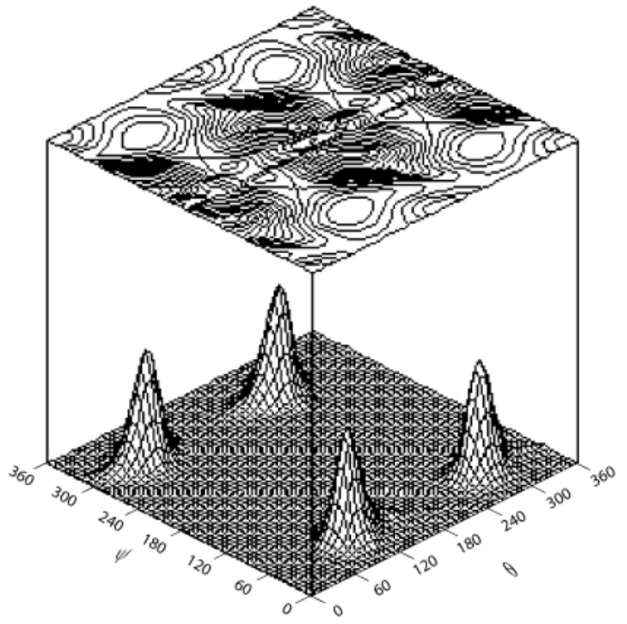


Figure 10. Conformational energy map (+ signs correspond to energy maxima and − signs correspond to energy minima) and Boltzmann populations in axial benzylcyclohexane.[41]

provided ΔS° = +0.63 cal/K·mol, in agreement with the experimental estimate.[41]

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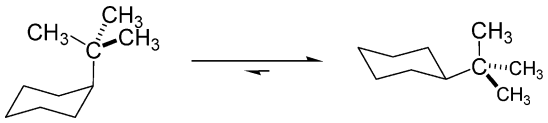
In contrast with methyl-, ethyl-, and isopropylcyclohexane, the axial isomer of *tert*-butylcyclohexane necessarily orients a methyl group inside the ring. Indeed, the conformational preference of *tert*-butyl for the equatorial position in cyclohexane is so large (ΔG° = 4.9 kcal/mol[42]) that this group is effectively used as an anchoring substituent in many reference compounds. The initially estimated[38] $\Delta S^\circ = 0$ for the **19**-axial ⇌ **19**-equatorial depicted in eq 4 seems intuitively plausible by



(4)

consideration of three isoenergetic staggered conformers both in **19**-axial and in **19**-equatorial.

Consideration of the fundamental importance of the *tert*-butyl group in chemistry motivated us to carry out a theoretical reexamination of the enthalpic and entropic contributions to the conformational preference of the *tert*-butyl group in cyclohexane.[43] The MM2[44a] and MM3(92)[44b] force fields were used to evaluate the intramolecular energetics. Figure 11 presents the MM2 energy profiles for rotation around the C−C$(CH_3)_3$ bond in axial and equatorial *tert*-butylcyclohexane (**19**, eq 4), as well as the corresponding population distribution of rotamers. An interesting feature of these plots is the presence of two minima for each staggered arrangement in axial **19** relative to only one for each staggered rotamer in **19**-equatorial. The conformers of minimum energy in axial *tert*-butyl cyclohexane were found at dihedral angles τ that deviate 19.8° from the perfectly staggered rotamer, which lies 0.50 kcal/mol higher in energy.

The higher energy associated with the perfectly staggered rotamers in **19**-axial originates essentially from nonbonded steric interactions, which are minimized at τ = 19.8°. Thus, as clearly shown in Figure 12, a *libration* phenomenon results in twice as many conformational states available to axial *tert*-butylcyclohexane relative to the equatorial isomer. This is reflected in increased entropy content for **19**-axial, as confirmed in the calculated $S^\circ_{axial} - S^\circ_{equatorial} = \Delta S^\circ_{ax/eq} = -0.44$ cal/K·mol.[43,45]

2.5. Study of the "Attractive *Gauche* Effect" in O−C−C−O Segments. Conformational equilibria in 1,2-disubstituted ethanes involve, as shown in eqs 5 and 6, *gauche* ⇌ *anti* interconversion of the 1,4-heterobutane segments present in the molecules.

Repulsive steric and polar interactions usually make the *gauche* conformation significantly *less* stable relative to the *anti* one. There are, however, cases in which the *gauche* conformation is favored more than calculated by consideration of steric and polar interactions. These cases have been treated in terms of a special "attractive *gauche* effect".[46]

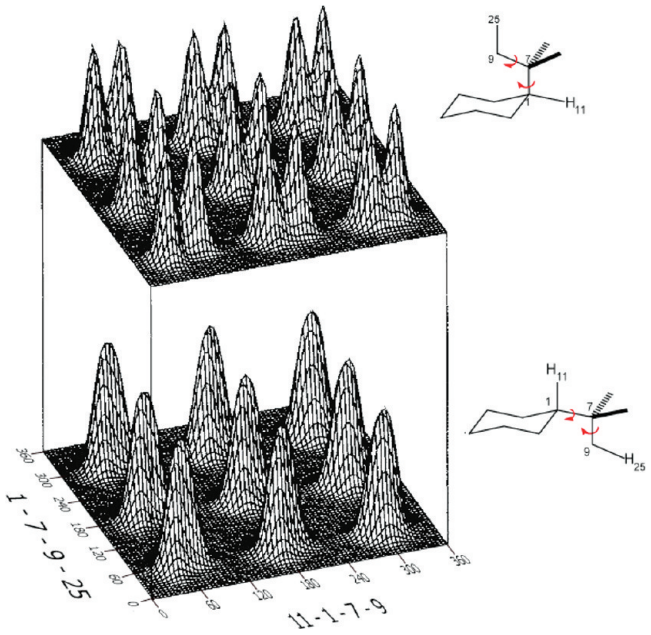
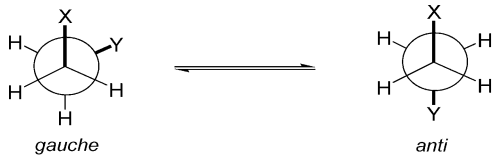


Figure 12. Population surfaces for axial (top) and equatorial (bottom) *tert*-butyl rotation in *tert*-butylcyclohexane.



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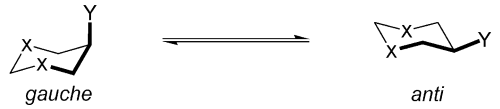
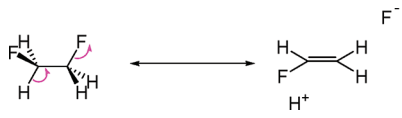


(6)

The "attractive *gauche* effect" can be interpreted as a hyperconjugative effect, in particular, bond−antibond orbital interactions.[47] Thus, for example, in the *gauche* conformation of 1,2-difluoroethane the C−H bonds serve as donors to the antiperiplanar C−F bonds (acceptors) (eq 7).



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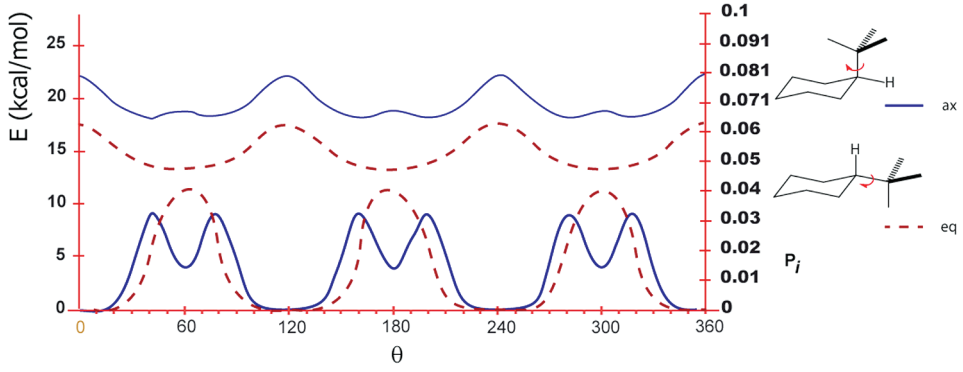

Figure 11. Energy plots (top, left scale) and population plots (bottom, right scale) for *tert*-butyl group rotation in cyclohexane.

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Equilibration (*cis* ⇌ *trans*) of diastereomeric 2,5-disubstituted 1,3-dioxanes **20**−**23** was readily performed by means of BF_3.[48] The corresponding free energy differences are summarized in Table 1, which includes, for comparison purposes, the

Table 1. Conformational Equilibria (kcal/mol) and Magnitude of the Attractive *Gauche* Effect in 2,5-Disubstituted 1,3-Dioxanes 20−23[48]

X	ΔG°_{exptl}	$\Delta G^\circ_{cyclohexane}$ [a]	ΔG°_{steric}	$\Delta\Delta G^\circ$ (*gauche* effect)[b]
20, OMe	−0.24	−0.55	−0.29	0.05
21, OTs	−0.01	−0.52	−0.26	0.25
22, ONs	+0.34	*c*	−0.26	0.60
23, OMs	+0.48	0.56	−0.26	0.74

[a]Reference 37. [b]$\Delta\Delta G^\circ = \Delta G^\circ_{exptl} - \Delta G^\circ_{steric}$. [c]Not known.

conformational preference of the methoxy, mesylate, tosylate, and nosylate substituents in cyclohexane.

Quantitation of the attractive *gauche* effect in **20**−**23** is not straightforward owing to the different steric requirements of a substituent at C(5) in 1,3-dioxane and in cyclohexane. For example, the usual equatorial preference of substituents in cyclohexane is largely due to the repulsive steric interactions with the axial hydrogens of the 3- and 5-positions; such repulsive interaction is absent in the analogous 5-substituted 1,3-dioxane, and therefore, the magnitude of the attractive *gauche* effect tends to be overestimated. Application of a correction factor α that is based in the relative steric environments of the six-membered rings (eq 8)[48] provided values of the *gauche* effect operative in **20**−**23** (eq 9 and fifth column in Table 1).

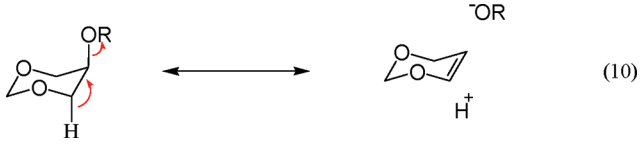
$$\Delta G^\circ_{steric} = \alpha\Delta G^\circ_{cyclohexane} \quad (8)$$

$$\textit{gauche}\ \text{effect} = \Delta\Delta G^\circ = \Delta G^\circ_{heterocycle} - \Delta G^\circ_{steric} \quad (9)$$

In the case of **20**, subtracting the observed equatorial preference of −0.24 kcal/mol from the ΔG°_{steric} for a 5-methoxy group [(0.55 × 0.52) − 0.24] indicates a rather small attractive *gauche* effect of 0.05 kcal/mol. By contrast, substantial "attractive *gauche* effects" are derived for the tosylate, nosylate, and mesylate substituents (Table 1).[48]

Regarding a plausible interpretation of the observed *gauche* effects in **20**-**23**, a good correlation was found between $\Delta\Delta G^\circ$ and the proton NMR chemical shifts for $H(4,6_{ax})$ in **20**-**23** (Figure 13).

The excellent correlation between the magnitude of the attractive *gauche* effect and the chemical shifts for the antiperiplanar hydrogens in *cis*-**20**-**23**, provides support for a hyperconjugative $\sigma_{C-H} \rightarrow \sigma^*_{C\text{-}OR}$ mechanism as responsible for the stabilization of the axial isomer, i.e., the "attractive *gauche* effect" (eq 10).



(10)

2.6. Salt Effects on Conformational Equilibria. It is well-known that the course of a chemical reaction may be

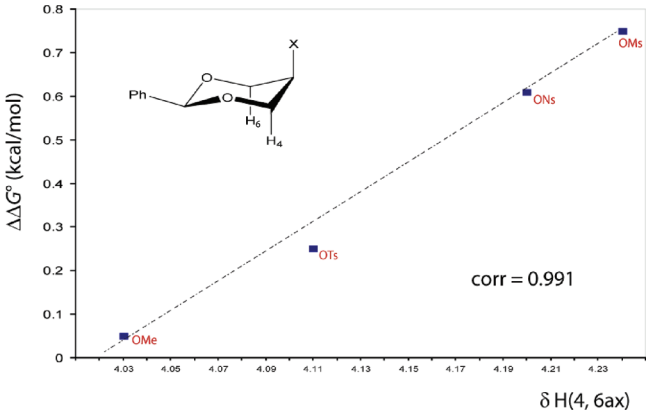
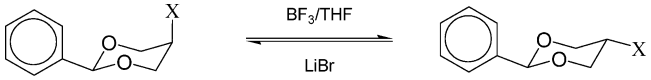


Figure 13. $\Delta\Delta G^\circ$ in dioxanes **20**−**23** versus ^1H NMR chemical shifts for $H(4,6_{ax})$ in the *cis* isomers of **20**−**23**.[48]

influenced by the surrounding medium. For example, the solvent can alter reaction rates and yields, product stereochemistry, and the position of chemical equilibria.[49] Furthermore, such changes can also be produced by addition of "chemically inert" salts to the reaction medium.[50] Although solvent effects on conformational equilibria have received much attention, there are few thermodynamic data dealing with salt effects.[51] With this consideration, we carried out the chemical equilibration of a series of anancomeric 5-substituted 1,3-dioxanes **24**−**32**, both in the presence and absence of lithium bromide (Scheme 13).[52]

Scheme 13. Chemical Equilibration of 2-Phenyl 5-Substituted 1,3-Dioxanes 24−32[52]



24, X = CO_2H
25, X = CO_2CH_3
26, X = $CONHCH_3$
27, X = CH_2OH
28, X = OH
29, X = $OCOCH_3$
30, X = $OCOCH_2OC_6H_4$-*o*-OCH_3
31, X = NO_2
32, X = $NHCOCH_3$

Equilibration of diastereomeric 1,3-dioxanes *cis*- and *trans*-**24**−**32** was readily performed by means of BF_3. The corresponding free energy differences are summarized in Table 2, which includes the ΔG° values of interest in the presence of 0.0, 1.0, and 10 equiv of LiBr. The observed salt effects revealed three tendencies upon salt addition: (1) increased axial preference when salt is present in the equilibria of dioxanes **24**−**27**, (2) increased equatorial preference upon salt addition, most notably for **32**, and (3) no significant salt effect in the conformational equilibria of **28**−**31** (Table 2).

A plausible explanation for the increased axial preference in the presence of lithium salt in dioxanes **24**−**27** is that addition of LiBr causes a general salt effect; that is, it mimicks a change to higher dielectric in the solvent. The increased polarity of the solvent is reflected in increased stability of the more polar axial isomers.

An alternative interpretation for the increased axial population of 5-X-1,3-dioxanes with X = CO_2H, CO_2CH_3, and $CONHCH_3$ in the presence of LiBr may be that lithium cation interacts both with the endocyclic oxygen atoms and the carbonyl oxygen, leading to a stabilization of the *cis* (axial) form.[53]

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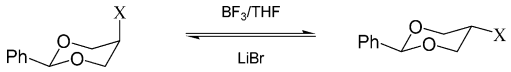
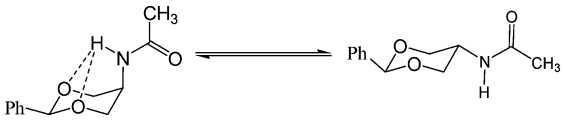
Table 2. Conformational Equilibria in 5-Substituted 2-Phenyl-1,3-dioxanes 24−32 in the Absence or Presence of LiBr, at 25 °C



		ΔG° (kcal/mol)		
compd	X	0.0 equiv	1.0 equiv[b]	10.0 equiv[c]
24	CO_2H	−0.77	−0.41	−0.17
25	CO_2CH_3	−0.50	−0.15	−0.43
26	$CONHCH_3$	−0.76	−0.67	−0.60
27	CH_2OH	−0.20	−0.04	+0.22
28	OH	−0.38	−0.35	−0.43
29	$OCOCH_3$	+0.47	+0.45	+0.43
30	$OCOCH_2OAr$[a]	+0.56	+0.89	+0.43
31	NO_2	+0.73	+0.52	+0.57
32	$NHCOCH_3$	+0.94	+0.44	−0.13

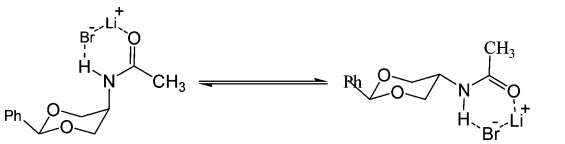
[a]Ar = 2-$CH_3OC_6H_4$. [b]Concentration, 8 × 10^{-2} M. [c]Concentration, 0.8 M.

The most clear-cut case is with the NHAc substituent (dioxane **32**) where Li salt addition results in a complete reversal of conformational preference, from a robust axial predominance in absence of salt (ΔG° = +0.94 kcal/mol) to a clear preference for the equatorial orientation in the presence of 10 equiv of LiBr (ΔG° = −0.13 kcal/mol). That the *cis* isomer presents an intramolecular hydrogen bond between the amide hydrogen and ring oxygens (eq 11) could be established by means of infrared



(11)

spectroscopy. Upon salt addition, the lithium ion binds to the carbonyl oxygen while simultaneously the bromide anion binds to the amide hydrogen, so the hydrogen bond is disrupted and the equilibrium shifts toward the equatorial isomer (eq 12).[52,54]



(12)

As a consequence of the fundamental importance of peptides and proteins in physiological events, interest in the structural characterization of peptides has increased exponentially in recent years. In particular, it is very important to gain knowledge on the nature of the interactions that allow supramolecular recognition between the peptide's secondary structure and potential substrates, since such understanding paves the way to potential developments of pharmacologically promising peptidomimetics.[55]

The binding of metal ions to certain functional groups in a peptide chain can induce the formation of stable helix or turn conformations.[56] Furthermore, peptides are able to transport metals through cellular walls;[57] hence, evaluation of peptidic affinity toward metal ions is fundamental for the understanding of catalytic processes by proteins.

Binding properties of alkali/alkaline earth and transition metal ions to 34 α,β-tetrapeptides (α/β-tP) were evaluated by electrospray ionization−mass spectrometry (ESI−MS) methods. These α,β-tetrapeptides were selected as representative of peptides presenting the β-amino acid residue in different positions of the α/β-tP. Chloride salts of the following metals were used: Li^+, Na^+, K^+ (alkali metals), Mg^{2+}, Ca^{2+} (alkaline earth metals), and Cu^{2+}, Zn^{2+} (transition metals).[58]

In the case of α/β-tP β^3-hPhg-α-Ile-α-Phe-α-Phe (**33**, a representative tetrapeptide exhibiting particularly ready to interpret mass spectra) where the β-amino acid is located at the *N*-terminus, it is observed that the relative affinity among the alkali metal mixture is $Na^+ > K^+ > Li^+$, whereas the relative abundances of adducts produced in the presence of divalent alkaline earth metals were $Mg^{2+} > Ca^{2+}$. On the other hand, for transition metals Cu^{2+} and Zn^{2+} α,β-tetrapeptide **33** showed similar affinity.[58]

Computational data were deemed relevant to interpret the experimental observations, and α,β-tetrapeptide **33** was selected as a representative system. To this effect, the structure of nearly 40 conformers of low energy obtained by MMFF molecular mechanics Montecarlo methods were optimized by ab initio Hartree−Fock methods at the 3-21G level, and then the three lowest energy structures obtained at this level were reoptimized at the DFT B3LYP 6-31G level of theory before a single-point calculation at B3LYP 6-311++G level was realized by means of the Gaussian 03 software package. Figure 14 depicts the lowest energy conformation.

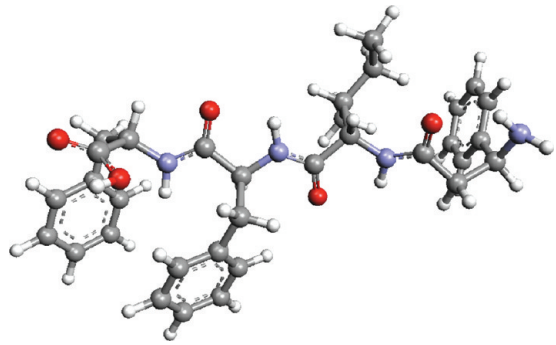


Figure 14. Conformation of lowest energy for α/β-tetrapeptide **33** (B3LYP 6-311++G//DFT B3LYP 6-31G level). The hydrogen atoms on the α-Ile residue were removed for clarity.

It can be appreciated in Figure 14 that the lowest energy conformation for α/β-tP **33** is a "linear" conformation, where steric repulsion among substituents is minimum. On the other hand, the arrangement adopted by the β-amino acid residue β^3-hPhg (far right in Figure 14) allows for hydrogen-bond formation between the terminal amino group and the carboxy carbonyl group in the same amino acid. Finally, the lowest energy conformation of α/β-tP **33** depicted in Figure 14 allows for π−π interaction between the aromatic groups of the phenylalanine segments.

Significant conformational differences are appreciated among the complexes of α/β-tP **33** and the metals studied. For example, with Li^+ (small and hard) a tricoordinated species is predicted, where the metal ion induces a folded conformation via association with the α-Phe-α-Ile-β^3-hPhg segment (Figure 15). It is apparent then that the ionic radius of the metal is determinant, where the larger Na^+ y K^+ ions (102 y 138 pm, respectively) bind more easily to the terminal β-amino acid residue inducing only small changes in the peptidic conformation, whereas the electrostatic stabilization afforded by the smaller and harder Li^+ ion (76 pm radius) upon

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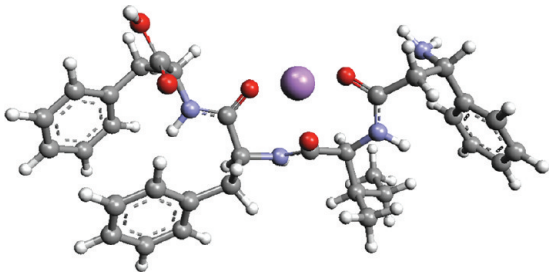

Figure 15. Optimized conformation and molecular structure for α/β-tP **33**·Li^+ complex (B3LYP 6-311++G//B3LYP 6-31G level).

coordination to the three carbonyls of the α-Phe-α-Ile-β^3-hPhg segment compensates for the otherwise increased energy of the folded peptide.

Interestingly, complexation to Li^+ does provoke significant folding of the original, "linear" conformation of the free peptide (compare Figures 14 and 15). Nevertheless, the experimental ESI–MS metal affinity studies reported above indicate that complexation to lithium cation is energetically not so favorable. That is, coordination to sodium cation causes few conformational changes in the original peptide, and the resulting complex seems to be most stable by comparison with those where metal coordination affects the receptor peptide's native conformation. This observation might be relevant in examination of related substrate–receptor phenomena such as in enzymatic activity where conformational changes of the native protein structure probably lead to modified structures in the active adducts.[59]

By the same token, tight Mg^{2+} ion (ionic radius for Mg^{2+} = 72 pm) affords a pentacoordinated adduct with tetrapeptide **33**. In particular, Mg^{2+} binds to the four available carbonyl groups as well as the amino group on the β-amino acid residue, β^3-hPhg. This coordination gives rise to a drastically folded conformation (Figure 16).[58]

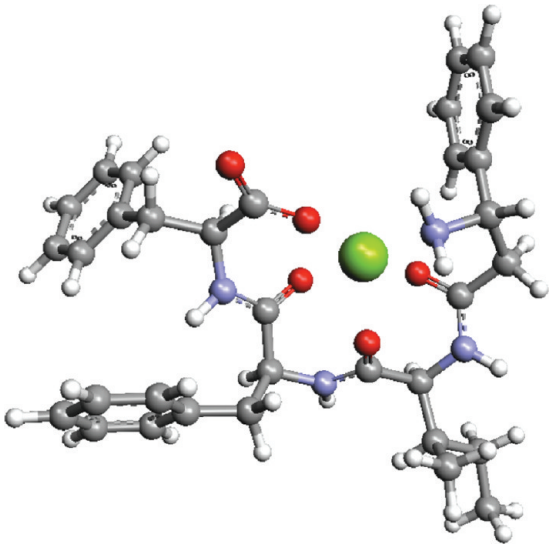

Figure 16. Optimized conformation and molecular structure for α/β-tP **33**·Mg^{2+} complex (B3LYP 6-311++G//B3LYP 6-31G level).

2.7. Asymmetric Synthesis of β-Amino Acids. In scientific research it is most important to keep well informed of research advances reported in the literature by others. Thus, besides reading the chemistry journals and attending lectures and conferences, collaborative residences in other research groups can be most useful.[60] In my case, the sabbatical year (August 1985–July 1986) that I spent in the research group of Professor Dieter Seebach at the E.T.H. in Zurich (Figure 17) turned out to be decisive for the direction that some of my scientific projects would take in the future. Indeed, during that sabbatical year I had the opportunity to work in the area of enantioselective synthesis of α-amino acids, a frontier topic at that time, and even now. In the particular Seebach strategy that I was involved with, glycine—an inexpensive, achiral α-amino acid—was converted into chiral and enantiomerically pure α-amino acids via the sequence of reactions that is presented in Scheme 14.[61]

Upon my return to Mexico, I had a relatively simple idea that would allow me to benefit from the acquired experience in the asymmetric synthyesis of α-amino acids but yet sufficiently different and novel: could it be possible to carry out an enantioselective synthesis of β-amino acids starting from the achiral β-amino acid β-alanine (β-aminopropionic acid) via chiral pyrimidinone **34** (Scheme 15)?

The idea advanced in Scheme 15 was not necessarily good since the inducing center of chirality in the six-membered heterocycle **34** is significantly removed from the molecular segment where the new center of chirality (marked with an asterisk in the final product) would be generated. Nevertheless, the project was attractive because at the end of the 1980s one could count with one hand's fingers the number of reports in the literature dealing with the enantioselective synthesis of β-amino acids, and none was efficient in spite of the fact that β-amino acids are relevant compounds as they are an essential starting material for the preparation of pharmacologically important β-lactams, which are present in antibiotics such as penicillin and cephalosporin. Furthermore, a significant number of natural products incorporate β-amino acids in their structure—one prominent example being paclitaxel, a useful antitumoral agent. Finally, one can ask a more fundamental question, why did Nature choose α- and not β-amino acids as components of biomolecules?

Thus, we embarked on the synthesis of pyrimidinone **34**, whose X-ray crystallographic structure (Figure 18) showed an unexpected conformation, presenting the bulky *tert*-butyl group in the axial rather than equatorial orientation. This unexpected finding turned out very fortunate since the sterically bulky axial substituent would allow for the required highly stereoselective reactions.

Indeed, addition of electrophiles to the enolate derived from **34** takes place with high selectivity from the face opposite to the *tert*-butyl group to generate predominantly the products of *trans* configuration (Scheme 16).[62] Once more, while the preferred axial orientation of the *tert*-butyl group was later understood as a consequence of allylic $A^{1,3}$ strain,[63] the initially unexpected finding shows how serendipity can play a determinant role in the final outcome of a research project.

While the results described in the previous paragraphs paved the road for the development of a novel asymmetric methodology for the enantioselective synthesis of β-amino acids, a procedure was required for the efficient preparation of enantiomerically pure starting pyrimidinone **34**. Accordingly, (*S*)-asparagine was condensed with pivalaldehyde following the procedure described by Konopelski and co-workers[64] to give heterocycle *cis*-**35**, which was decarboxylated, *N*-methylated, and hydrogenated to afford enantiopure (*S*)-**34** (Scheme 17).[65,66]

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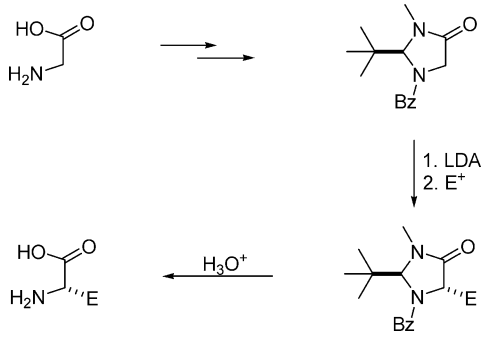
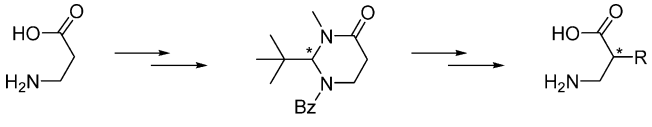
Figure 17. Albert Beck (left), Dieter Seebach (middle), and me in Zurich. Photograph taken in 1992 (copyright Rolf Haefliger).

Scheme 14. Enantioselective Synthesis of Chiral α-Amino Acids Starting from Glycine, an Achiral, Inexpensive α-Amino Acid[61]



Scheme 15. Proposed Strategy for the Preparation of α-Substituted β-Amino Acids Starting from Achiral β-Aminopropionic Acid[62]



34

Enantiopure pyrimidinone (*S*)-**34** was then successfully used as a convenient substrate for the enantioselective synthesis of α-substituted β-amino acids. To this end, enolate (*S*)-**34**-Li was treated with several electrophiles to produce the *trans*-alkylated products (2*S*,5*R*)-**36** with high diastereoselectivities and good yields (Table 3).[67]

The last step in the overall conversion of β-alanine to enantiopure α-substituted β-amino acids (β^2-amino acids), namely the hydrolysis of the alkylated pyrimidinones, was achieved by acid hydrolysis (6 N HCl, 90−100 °C) followed by purification on an ion-exchange column (Table 4).[67]

As it can be appreciated from Tables 3 and 4, starting from heterocycle (*S*)-**34** one obtains α-substituted β-amino acids of (*R*) configuration. Enantiomeric products were obtained by

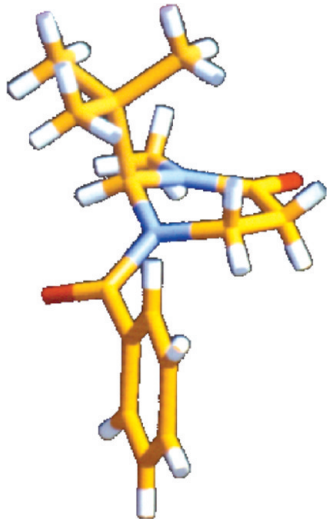
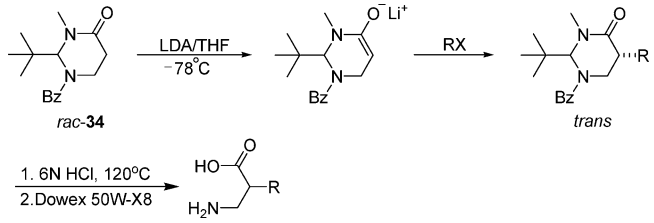


Figure 18. Solid-state structure and conformation of heterocycle **34**, showing an axial orientation of the *tert*-butyl substituent.[62]

Scheme 16. Stereoselectivity in the Reaction of Electrophiles with the Li-Enolate of Heterocycle 34, Followed by Acid Hydrolysis of the Corresponding Products To Generate the α-Substituted β-Amino Acids of Interest[62]



epimerization of the *trans* into the *cis* alkylated derivatives, so that final hydrolysis afforded the β-amino acids of (*S*) configuration (Scheme 18).

The preparation of enantiopure α,α-dialkylated β-amino acids is of great importance in view of the useful chemical and

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Scheme 17. Synthesis of Enantiopure (*S*)-34 from (*S*)-Asparagine[65,66]

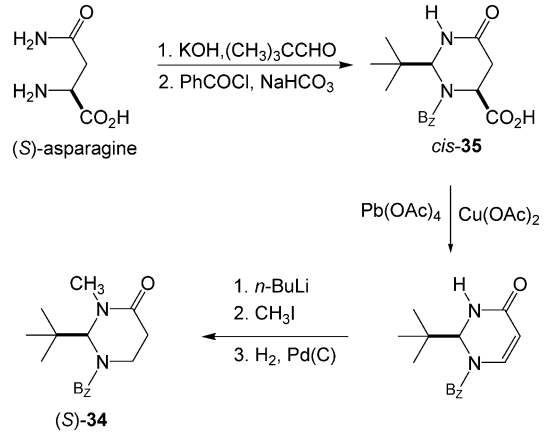
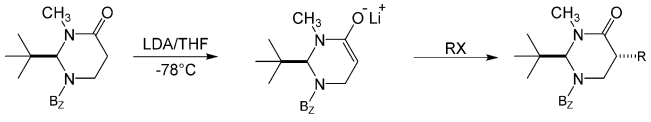
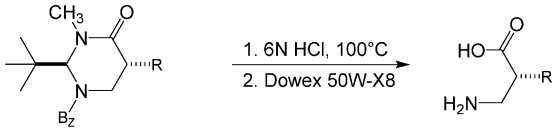


Table 3. Diastereoselectivity of Enolate (*S*)-34–Li Alkylations[67]



RX	$[\alpha]^{28}_D$	mp (°C)	ds (%)	yield (%)
CH_3I	+39.5	121–122	>95	77
n-C_4H_9I	+26.7	80–81	95	75
n-$C_6H_{13}I$	+31.2	70–71	95	80
$PhCH_2Br$	−64.0	173–174	>95	80

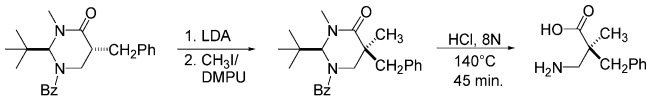
Table 4. Hydrolysis and Isolation of (*R*)-α-Substituted β-Amino Acids (β²-Amino Acids)[67]



R	$[\alpha]^{28}_D$	mp (°C)	yield (%)
a, CH_3	−11.8	185–186	80
b, n-C_4H_9	+5.3	170–171	80
c, n-C_6H_{13}	+6.6	219–220	80
d, $PhCH_2$	+11.3	225–226	85

biological properties exhibited by these compounds. Furthermore, β-peptides containing α,α-dialkylated β-amino acids are resistant to enzymatic hydrolysis, which makes them attractive for the preparation of medicinal drugs with longer lasting effect in the patient's body. As shown in Scheme 19, alkylation of *trans*-**36d**, takes place with very high diastereoselectivity to give

Scheme 19. Enantioselective Preparation of α,α-Dialkylated β-Amino Acids[68,69]



the dialkylated derivatives **37**. Subsequent hydrolysis afforded the desired β-amino acids **38** in enantiopure form.[68,69]

As indicated above, paclitaxel is a valuable natural product in the fight against certain types of cancer. The molecule of paclitaxel incorporates in its structure a side chain consisting of an α-hydroxy-β-amino acid that is essential for the useful biological activity. Scheme 20 presents the route followed in our laboratory to synthesize the methyl ester of the *like* diastereomer of the amino acid of interest.[70]

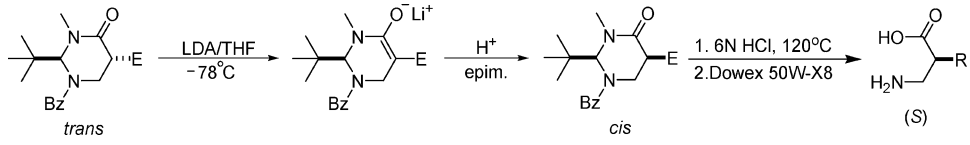
More recently, a convenient, one-pot procedure for the synthesis of 1-benzoyl-2(*S*)-substituted-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones (**39**) by tandem decarboxylation-β-iodination of the corresponding 6-carboxyperhydropyrimidin-4-ones was developed. Subsequently, Sonogashira coupling of the halogenated heterocyclic enones with various terminal alkynes produced 1-benzoyl-2(*S*)-isopropyl-5-alkynyl-2,3-dihydro-4(*H*)-pyrimidin-4-ones in good yields. Hydrogenation of the unsaturated C–C moieties in the Sonogashira products followed by acid hydrolysis afforded highly enantioenriched α-substituted β-amino acids (Scheme 21).[71,72]

The work described above (sketched in Figure 19[73,74]) attracted the attention of a significant number of chemists and biologists, who contributed to the development of numerous novel protocols for the asymmetric synthesis of β-amino acids, as well as applications in biological projects.

In 1993, I received an invitation to contribute a review article on the subject for *Aldrichimica Acta*[75] and in 1996 an invitation from Wiley to write or edit a more extensive monograph.[76] These reviews have had an extraordinary impact as can be seen by the number of citations from other researchers, which exceeds 1500. Furthermore, before 1990 there were no efficient strategies for the asymmetric synthesis of β-amino acids, whereas by the year 2011 more than 700 reports had appeared in the literature. This extraordinary activity has justified the preparation of a new, second edition of *Enantioselective Synthesis of β-Amino Acids*.[77,78]

The enormous growth in the field is due to a large extent to the importance of β-amino acids in medicine[79] and also because they have been used as precursors in the synthesis of non-natural peptides and proteins exhibiting interesting and useful properties. In particular, many such β-analogues of α-peptides exhibit increased resistance to enzymatic hydrolysis,[55,80] which allows for the development of longer-lasting pharmaceuticals, or potentially, the control of insect plagues transmitted by insects such as mosquitoes or ticks.[81]

Scheme 18. Preparation of (*S*)-Configured α-Substituted β-Amino Acids (β²-Amino Acids) via *trans* → *cis* Epimerization Followed by Hydrolysis[67]



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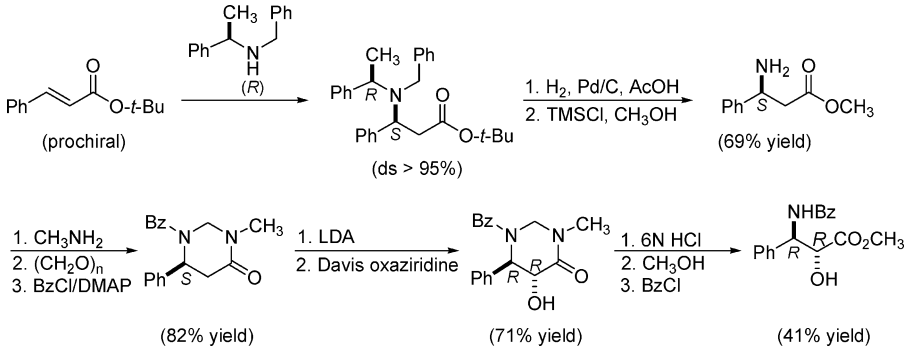
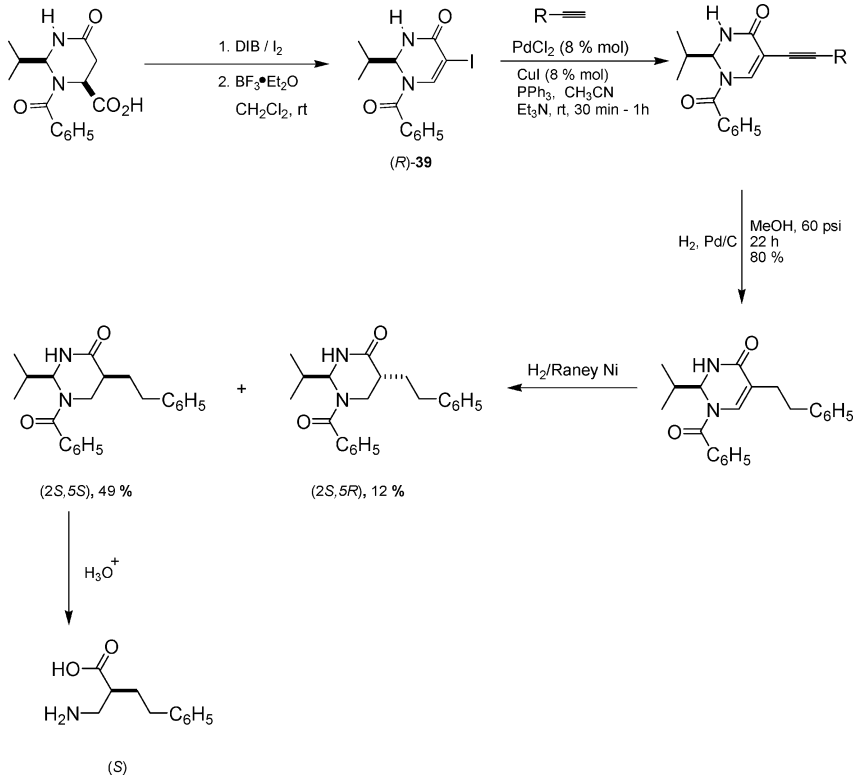
Scheme 20. Enantioselective Synthesis of the *like* Diastereomer of the α-Hydroxy-β-amino Acid Present in Paclitaxel[70]



Scheme 21. Sonogashira Coupling of 1-Benzoyl-2(*S*)-substituted 5-Iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones (*R*)-39 in the Preparation of Highly Enantioenriched α-Substituted β-Amino Acids[71,72]



2.8. Recent Incursions in Asymmetric Organocatalysis and "Green" Chemistry. The ongoing studies in our group on the enantioselective synthesis of amino acids described in the previous section brought our attention to the recently reported organocatalytic enantioselective electrophilic amination reactions of α-substituted α-cyanoacetates and α-substituted β-ketoesters with azodicarboxylates.[82] Indeed, the α-aminated products thus formed have the potential to be converted to either α- or β-amino acids.

The application of natural products (chiral pool) as organocatalysts constitutes a relevant concept in the field of enantioselective organocatalysis;[83] nevertheless, organocatalysis with natural products can suffer from their structural complexity, large molecular weight, and in some cases high cost of their isolation. Since one of the challenges in asymmetric catalysis is to develop a highly enantioselective reaction under convenient conditions using a simple catalyst system which is as cheap as possible, development of synthetic structurally simpler organic molecules for organocatalysis is highly desirable. In addition, the main advantages of synthetic over natural molecules are that both enantiomers are readily available and that their structure can be easily modified.

With the aim finding practical and simple organocatalysts to promote the enantioselective amination of racemic ethyl α-phenyl-α-cyanoacetate with di-*tert*-butyl azodicarboxylate, we proceeded to explore the use of several derivatives of inexpensive α-phenylethylamine[84] as chiral organocatalysts for the reaction.[85] In the event, several chiral derivatives were found to catalyze the desired enantioselective amination process, the product (**40**) thus formed being a precursor of amino acids, with enantioselectivities as high as 84% ee in excellent yields. In this study, amination could be performed without significant loss of enantioselectivity with catalyst loadings as low as 1 mol % (Table 5).

On the other hand, the asymmetric reduction of ketones having enantiotopic faces is an extremely important methodology for the synthesis of chiral secondary alcohols, and in the

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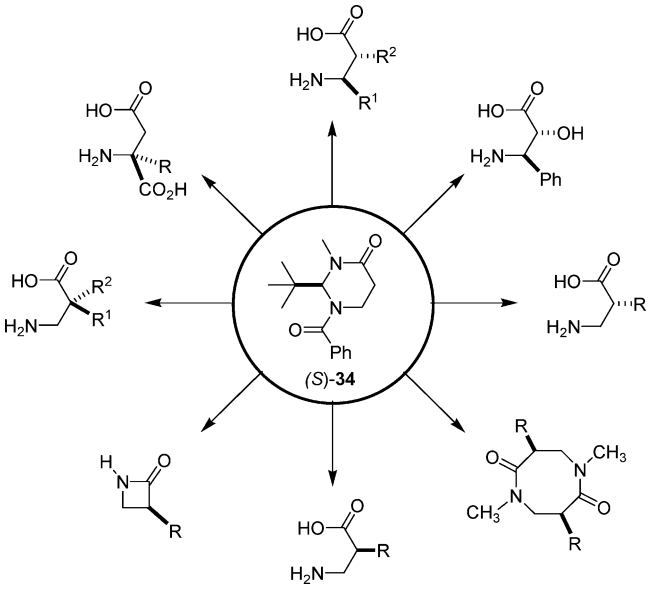


Figure 19. Pyrimidinone (*S*)-**34** as convenient substrate for the enantioselective synthesis of *β*-amino acids, *β*-lactams, and cyclo-*β*-dipeptides.[73,74]

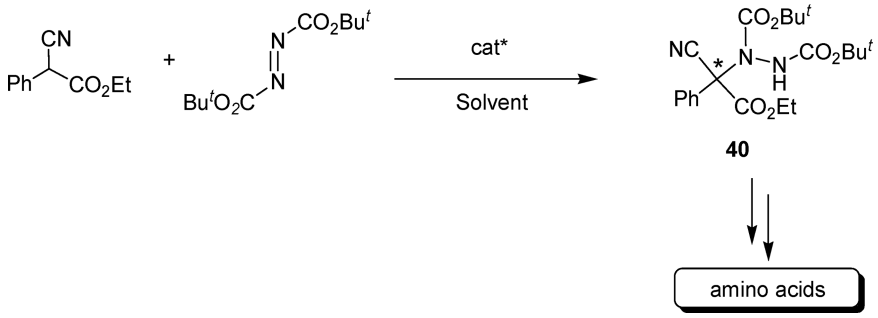
last years there has been a deluge of papers describing research on the enantioselective reduction of ketones. In particular, the application of various borane-based chiral reducing agents in this reaction is well documented.[86]

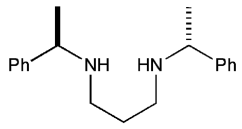
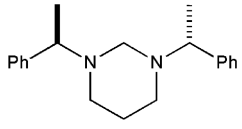
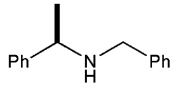
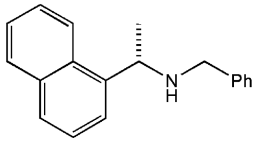
Attracted by pioneering reports on the application of (*S*)-2-(*N*-substituted aminomethyl)pyrrolidines **41**−**45** in asymmetric synthesis,[87] we were intrigued by the potential of previously unreported, highly hindered diamines (*S*)-1,1-diphenyl-*N*-(pyrrolidin-2-ylmethyl)methanamine ((*S*)-**46**), (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methyl amine ((*S*)-**47**), and (*S*)-(pyrrolidin-2-yl)diphenyl methyl amine ((*S*)-**48**) (Figure 20) in borane-mediated enantioselective reduction of ketones having heterotopic faces.[88]

Novel diamines (*S*)-**47** and (*S*)-**48** were prepared according to Scheme 22, and the desired diazaborolidine derivatives were obtained under microwave irradiation,[89] as evidenced by the difference in ^{11}B NMR chemicals shifts in the starting borane−dimethyl sulfide reagent, −20.1 ppm, and the corresponding signal in the diazaborolidine, +28.3 ppm. Furthermore, the infrared spectrum in toluene showed a characteristic B−H stretching band at 2404 cm^{-1} as well as N−H stretching at 3584 cm^{-1}, in line with Corey's observations in oxazaborolidine analogues.[90]

Table 6 collects the results of the asymmetric reduction of acetophenone with diazaborolidines derived from diamines (*S*,*R*)-**41**, (*S*,*S*)-**42**, and (*S*)-**43**−**48** in the presence of one additional equivalent of borane-dimethyl sulfide. It is appreciated that best results were obtained with catalysts derived from chiral diamines (*S*,*R*)-**41**

Table 5. Chiral Amines Containing the *α*-Phenylethylamino Group That Are Efficient Organocatalysts in the Enantioselective Amination of Ethyl (±)-*α*-Phenyl-*α*-cyanoacetate[84]



Toluene/Hexane (1:1), –78 °C		
	30 min	91% yield 84% ee (*R*)
	60 min	92% yield 56% ee (*R*)
	60 min	95% yield 74% ee (*S*)
	120 min	96% yield 76% ee (*R*)

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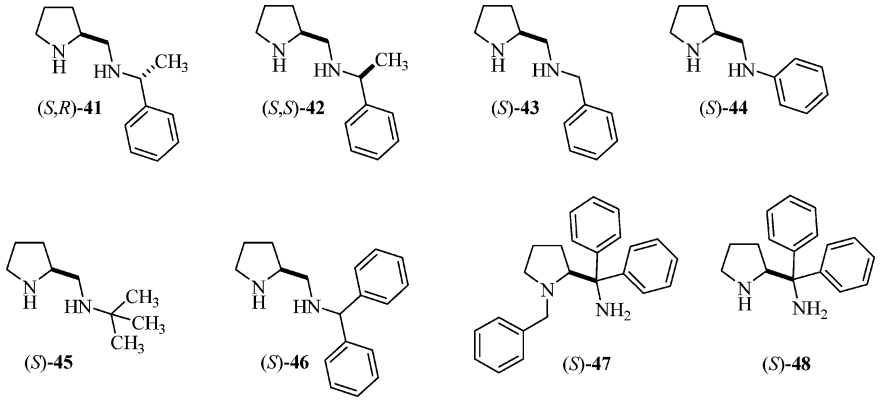
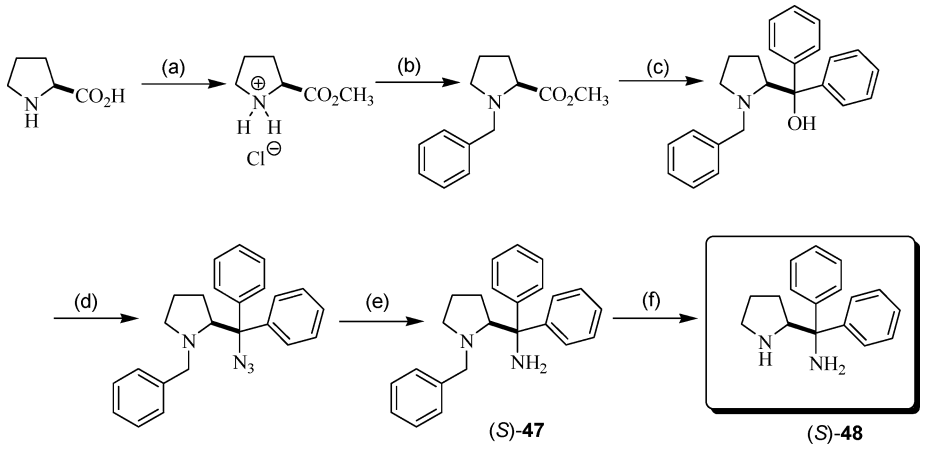


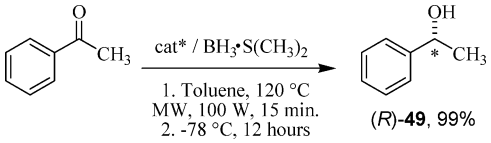
Figure 20. Chiral diamines (*S*,*R*)-**41**, (*S*,*S*)-**42**, and (*S*)-**43**−**48** derived from (*S*)-proline.

Scheme 22[a]



[a]Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C, 1 h, 100%; (b) BnBr, Et_3N, CH_2Cl_2, 25° C, 8 h, 95%; (c) bromobenzene, Mg, THF, 25 °C, 12 h, 97%; (d) 57% H_2SO_4−$CHCl_3$, NaN_3, 0 °C, 12 h, 96%; (e) $LiAlH_4$, THF, reflux, 8 h, 95%; (f) H_2/Pd−C, MeOH, 60 psi, 25 °C, 99%.

Table 6. Enantioselective Reduction of Acetophenone Using Chiral Diamines 41−48 in the Preparation of the Diazaborolidine Catalyst[88]



entry	organocatalyst	ee (%)	entry	organocatalyst	ee (%)
1	(*S*,*R*)-**41**	70	9	(*S*)-**45**	40
2	(*S*,*R*)-**41**	96	10	(*S*)-**45**	55
3	(*S*,*S*)-**42**	52	11	(*S*)-**46**	48
4	(*S*,*S*)-**42**	71	12	(*S*)-**46**	63
5	(*S*)-**43**	40	13	(*S*)-**47**	22
6	(*S*)-**43**	46	14	(*S*)-**47**	30
7	(*S*)-**44**	66	15	(*S*)-**48**	64
8	(*S*)-**44**	72	16	(*S*)-**48**	84

and novel chiral diamine (*S*)-**48**; indeed, the reduction afforded (*R*)-1-phenylethanol, (*R*)-**49**, in 99% yield and 96% ee and 84% ee, respectively (see entries 2 and 16 in Table 6).[88]

Scheme 23 presents a plausible mechanism for the catalytic process, based on the proposal advanced by Corey and co-workers for the corresponding oxazaborolidine catalysts.[90] According to this proposal, the first step consists of the coordination of a second molecule of borane to the pyrrolidine endocyclic nitrogen in catalyst **D** to give reactive species **E**. The basic oxygen in the substrate ketone associates then to the Lewis acidic boron in **E** to give complex **F**, where the bulkier phenyl substituent is oriented away from the heterocycle, so that the *Si* face of the carbonyl substrate is exposed to the N-BH_3 reducing group providing carbinol (*R*)-**49** via intermediate **G** and boronate **H** (Scheme 23).

In the past decade, interest in Green chemistry has expanded, and it now encompasses wide areas of the chemical enterprise. Of particular interest are developments with potential impact in industry and laboratory research as a means to continue chemical development in a more sustainable manner.[91] Indeed, Noyori has stated that the future of chemists and actually the survival of humankind depends on our ability to manufacture useful compounds in an economical, energy-efficient, resource-preserving, and environmentally benign way.[92]

In this context, high-speed ball-milling (HSBM) is a sustainable mechanochemical technique that has commonly been used for milling minerals into fine particles as well as in the synthesis and modification of inorganic solids and organometallic materials. Furthermore, in the area of synthetic organic chemistry, this technique has been successfully used to promote several solvent-free reactions.[93]

Recently, Lamaty and co-workers reported a novel strategy for the synthesis of α-peptides under solvent-free conditions by means of ball-milling activation.[94] The methodology of Lamaty and co-workers requires no solvent, and it is based on

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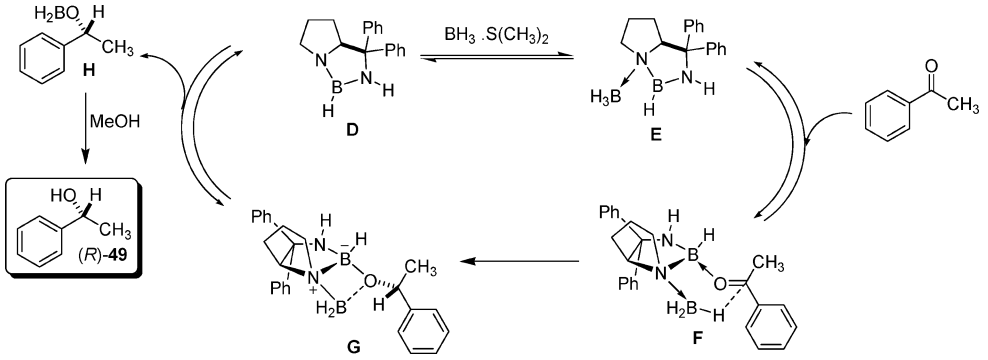
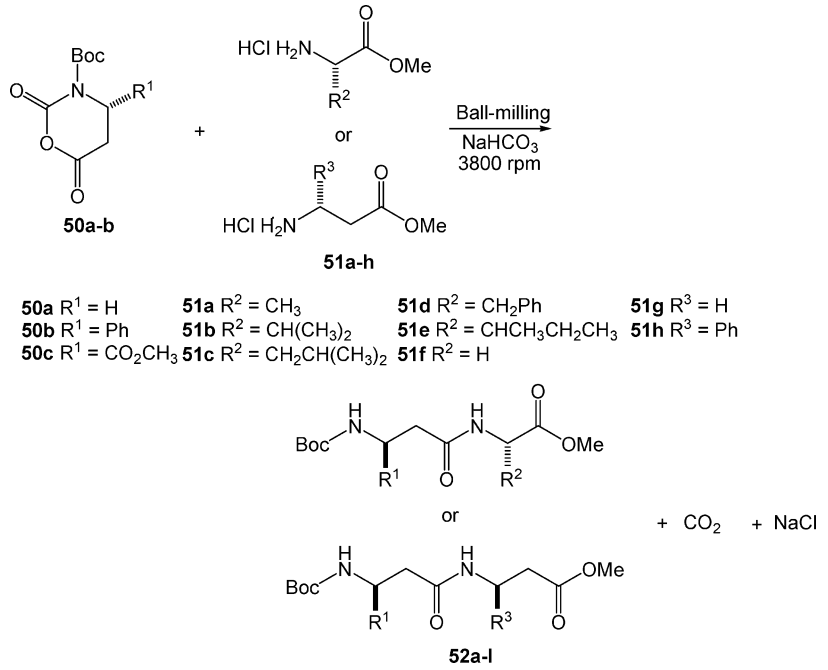
Scheme 23. Plausible Mechanism in the Enantioselective Reduction of Acetophenone with Diazaborolidine D from Diamine (*S*)-48 and Borane Dimethyl Sulfide



Scheme 24. Synthesis of *α,β*- and *β,β*-Dipeptides under Solvent-Free Conditions[95]



mechanochemical mixing of the starting amino acids, thus fulfilling the aforementioned principles for a green synthesis. As part of our current interest in the chemistry of *β*-amino acids and *β*-peptides (see Section 2.7), we deemed it of interest to apply Lamaty's strategy to the synthesis of *α,β*- and *β,β*-dipeptides. This required the coupling of urethane-protected *β*-amino acid *N*-carboxyanhydride (UNCA) derivatives with hydrochloride salts derived from *α*- and *β*-amino acid esters (Scheme 24).[95]

Following the preparation of the required *β*-UNCAs, we carried out the coupling reaction between **50a** and *α*-amino ester hydrochlorides **51a−f** in the presence of $NaHCO_3$ (1.5 equiv) and using the high energy ball-milling process. The capsule containing the mixture of solid substrates was shaken at a frequency of 3800 rpm. The change in mass of the capsule was quantified during the shaking process until the recorded difference in mass was constant. This indicated that the reaction had ended; i.e., no more CO_2 was being liberated. In general, the required reaction time was 2 h. The reaction mixture was removed from the capsule, dissolved in EtOAc, washed with brine and dried to afford the desired *α,β*-dipeptides as colorless solids, except for **52f** (oil) in good yields (Table 7).

Although not many examples of *α,β*-dipeptides exist in nature, L-carnosine, a mammalian dipeptide composed of the amino acids *β*-alanine and L-histidine and found in muscle and brain tissues, is one salient example (Figure 21).

Given the importance of L-carnosine as an antiglycating agent and its antioxidant and hydroxyl-radical scavenger properties[96] and in order to demonstrate the general applicability of the present synthetic procedure for the preparation of *α,β*-dipeptides under solvent-free conditions, we deemed it of interest to synthesize dipeptide Boc-*β*-Ala-L-His-OMe **53** as an approach to the architecture of L-carnosine (Scheme 25).

The aminoester hydrochloride **51i** was prepared from commercial L-histidine. Ball-milling of **50a**, **51i**, and $NaHCO_3$ for 2 h yielded the protected dipeptide **53** in excellent yield.

The aldol reaction is one of the most powerful strategies in synthetic organic chemistry since it allows for the formation of new C−C bonds, that is, facilitates the construction of larger molecules from smaller ones. The development of *enantioselective* versions of the aldol reaction was based for a long time on the use of preformed enolates, which added to carbonyl substrates having enantiotopic faces with activation by metal-based chiral catalysts.[97] Nevertheless, the ability of (*S*)-proline

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Table 7. α,β- and β,β-Dipeptides Prepared under Solvent-Free Conditions in This Work[95]

entry	*N*-Boc-β-NCA	amino methyl ester hydrochloride	dipeptide *N*-Boc-aa-aa-OMe	yield (%)
1	β-ala	Ala	β-ala-Ala (**52a**)	88
2	β-ala	Val	β-ala-Val (**52b**)	82
3	β-ala	Leu	β-ala-Leu (**52c**)	87
4	β-ala	Phe	β-ala-Phe (**52d**)	83
5	β-ala	Ile	β-ala-Ile (**52e**)	80
6	β-ala	Gly	β-ala-Gly (**52f**)	88
7	β-ala	β-ala	β-ala-β-ala (**52g**)	96
8	β-ala	(*S*)-β^3-hPhg	β-ala-(*S*)-β^3-hPhg (**52h**)	91
9	(*S*)-β^3-hPhg	β-ala	(*S*)-β^3-hPhg-β-ala (**52i**)	93
10	(*S*)-β^3-hPhg	(*S*)-β^3-hPhg	(*S*)-β^3-hPhg-(*S*)-β^3-hPhg (**52j**)	94
11	(*S*)-β^3-chg-(CO_2CH_3)	Ala	(*S*)-β^3-chg(CO_2CH_3)-Ala (**52k**)	79
12	(*S*)-β^3-chg-(CO_2CH_3)	β-ala	(*S*)-β^3-chg(CO_2CH_3)- β-ala (**52l**)	91

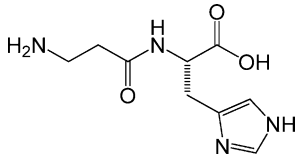
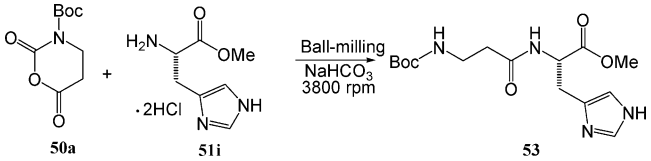
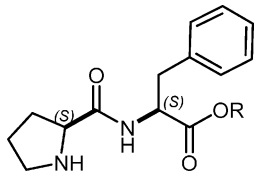


Figure 21. Natural product L-carnosine.

Scheme 25. Synthesis of Dipeptide Boc-β-Ala-L-His-OMe (53) under Solvent-Free Conditions[95]



to act as an organic catalyst in intramolecular asymmetric aldol reactions,[98] has recently motivated the search of other chiral organic catalysts that might act as efficient organocatalysts.[99] Remarkable examples are (*S*)-proline-containing α,α-dipeptides,[100] In particular, dipeptide (*S*)-proline-(*S*)-phenylalanine [(*S,S*)-**54**, Figure 22] has been shown to retain the catalytic



54, R = H **55**, R = Me

Figure 22. Structure of dipeptides (*S,S*)-**54** and (*S,S*)-**55**.

properties of (*S*)-proline. With the exception of the work reported by Lei et al.,[100d] the above work was carried out using an organic solvent as a reaction medium.

As part of our current interest in high-speed ball-milling (HSBM, see above), we decided to prepare the methyl ester of (*S*)-proline-(*S*)-phenylalanine [(*S,S*)-**55**, Figure 22] and evaluate its organocatalytic activity under solvent-free, "green" reactions conditions. There exists the precedent that (*S*)-proline (10 mol %) catalyzes the aldol reaction between acetone and 4-nitrobenzaldehyde under solvent-free conditions in a ball mill.[101] Although high-speed ball-milling has been applied in the area of synthetic organic chemistry to promote several solvent-free reactions,[102] only a few organocatalyzed asymmetric reactions have been explored under HSBM conditions. Thus, the study of enantioselective organocatalyzed reactions under solvent-free conditions was attractive in the search of alternatives to the traditional organocatalytic methodologies in the solution phase.

Therefore, we proceeded to carry out the aldol reaction of acetone with 4-nitrobenzaldehyde under HSBM conditions in order to compare dipeptide (*S,S*)-**55** with (*S*)-proline as chiral organocatalysts, both under HSBM conditions. We also compared the efficiency of dipeptide (*S,S*)-**55** as organocatalyst in solvent-free conditions relative to traditional conditions in solution. The aldol reaction was carried out at −20 °C for 4 h in a ball mill at 2760 rpm, using 7 mol % of (*S,S*)-**55**. The expected product (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one **56** was obtained in 82% yield and with 69% ee (entry 3 in Table 8).

Table 8. Enantiomeric Excesses and Yields of Aldol Product 56 Observed in the Aldol Reaction of Acetone with 4-Nitrobenzaldehyde

entry	catalyst (mol %)	ref	ArCHO (equiv)	time (h)	yield (%)	ee (*R*) (%)
1	(*S*)-Proline(10)[a]	101a	2.0	19	73	56
2	(*S,S*)-**55** (20)[b]	101b	>27	24−48	88	28
3	(*S,S*)-**55** (7)[a]	103	2.0	4	82	69[c]

[a]Under ball-milling conditions. [b]The reaction was carried out in neat acetone with a concentration of 0.5 M of aldehyde. [c]Determined by chiral-phase HPLC.

It can be appreciated that under solvent-free methodology dipeptide (*S,S*)-**55** showed superior catalytic activity, both in terms of required reaction time and enantioselectivity, relative to (*S*)-proline as organocatalyst (cf, entries 1 and 3 in Table 8). Furthermore, dipeptide (*S,S*)-**55** was more efficient organocatalyst under HSBM solvent-free conditions relative to traditional solution conditions (cf. entries 2 and 3 in Table 8).[103]

An examination of the effect the amount of catalyst, the reaction temperature, and the time and frequency of milling in the reaction of cyclohexanone with 4-nitrobenzaldehyde (1.1:1 ratio of ketone and aldehyde) in the presence of catalyst (*S,S*)-**55** was undertaken. Initially, the amount of catalyst employed was 22 mol %, and the reactants were ball milled at 2760 rpm. After 4 h at 30 °C, the aldol product was obtained in high yield, in a diastereomeric ratio of 2:1 in favor of the *anti*-diastereomeric product; however, the observed ee_{anti} was low, 33% (entry 1 in Table 9). In order to increase the enantioselectivity of the reaction, it was decided to carry out the reaction at lower temperature. After 4 h at −20 °C, the

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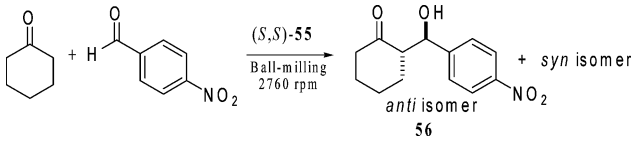
Table 9. Enantioselective Aldol Addition between Cyclohexanone and 4-Nitrobenzaldehyde Catalyzed by Dipeptide (*S*,*S*)-55 under Ball-milling, Solvent-Free Conditions[103]



entry[a]	cat. mol %	time (h)	temp (°C)	yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	22	4	30	96	67:33	33
2	22	4	−20	99	80:20	72
3	22	2	−20	86	83:17	84
4	22	1	−20	66	80:20	92
5	15	4	−20	90	78:22	93
6	**7**	**4**	**−20**	**92**	**90:10**	**95**
7	4	4	−20	56	91:9	90
8	1	4	−20	46	80:20	88

[a]Reaction conditions: ketone (0.22 mmol), aldehyde (0.20 mmol), dipeptide (*S*,*S*)-**55** (1−22 mol %). [b]Combined yield of the isolated diastereomers. [c]Determined by ^{1}H NMR spectroscopic analysis. [d]Determined by chiral-phase HPLC analysis of the *anti* isomer.

anti diastereomeric product was obtained with excellent yield (99%) and high diastereo- (80% ds) and enantioselectivity (72% ee, entry 2 in Table 9). We then examined the reaction at shorter reaction times; this greatly favored the enantioselectivity, 84% ee and 92% ee after 2 and 1 h, respectively, although the yields were lower (cf. entries 2−4 in Table 9).

As proposed for other cases where catalysis by dipeptides[99b,104] and prolinamides[105] is operative, it is likely that dipeptide (*S*,*S*)-**55** catalyzes the aldol reaction via the transition state depicted in Figure 23. It is suggested that a hydrogen

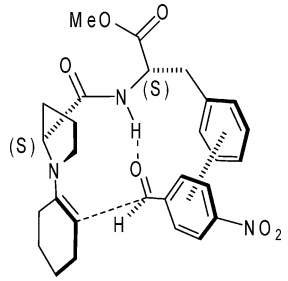


Figure 23. Proposed transition-state model of the aldol reaction catalyzed by (*S*,*S*)-**55**.

bond between amide group and the aldehyde is the essential controlling interaction. In solution, this interaction is apparently weakened by solvation and therefore enantioinduction is less effective. Additional recent studies support this transition state.[106]

In summary, we were able to demostrate that dipeptide (*S*,*S*)-**55** is a more efficient organocatalyst in the asymmetric aldol reaction under solvent-free conditions, relative to reaction in solution. In particular, it was shown that ball milling activates the aldol reaction between cyclohexanone and various aromatic aldehydes. The reaction proceeds efficiently affording the *anti* aldol products with good diastereo- and enantioselectivities. In addition, aldol products were usually obtained in short reaction times and with higher steroselectivity using 7 mol % of dipeptide (*S*,*S*)-**55**.

3. CLOSING REMARKS

For more than three decades of research work at Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional in Mexico City, I have had the opportunity to develop several relevant projects in the area of stereochemistry—from the conformational analysis of heterocyclic compounds to asymmetric synthesis using natural products as starting materials (the "chiral pool") to prepare chiral auxiliaries, chiral ligands, and chiral organocatalysts. Among the chiral products that have been synthesized, several unnatural β-amino acids and peptides are relevant because of their potential in medicine and in pest control.

In the summary presented here, as well as in other studies that were carried out in my laboratories, nearly two hundred students and postdoctoral collaborators have been involved (Figure 24). Many of them are now independent academic researchers and contribute to the advancement of chemistry in Mexico. Working with them has been most gratifying and enriching.

Stereochemistry-land continues to be a wonderful and challenging place to be. Indeed, in the 21st century we are witnessing a renewed and focused interest in conformational analysis. For example, the nature of the "anomeric effect" continues to be a matter of controversy,[107] and it is interesting to note that this challenging situation has attracted the attention of chemists and physicists for over half a century. It has been shown that steric, electrostatic, and stereoelectronic factors are *all* important forces which influence the anomeric effect and therefore the conformational arrangement and reactivity of heterocycles. It is evident that further investigation of this important effect, with the use of new model compounds and application of novel and insightful experimental and computational strategies will lead to progress in the understanding of the fundamental nature of the anomeric effect.

By the same token, recently the *gauche* effect has been found to dictate the preferred conformation of large, biologically relevant molecules such as 4-fluoroproline, 4-azidoproline, and 9,10-difluorostearic acid.[108] The *gauche* effect has also been used recently to control conformations of reactants without introducing strain in the first examples of a 5-*endo*-dig cyclizations of carbon-centered radicals.[109,110]

Of course, asymmetric catalysis (biocatalysis, heterogeneous and homogeneous catalysis, chiral organocatalysis, chiral catalytic materials, supported chiral catalysts, etc.) will be one of the most active fields in chemistry in the 21st century, having an immediate impact in the development of new energy

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Figure 24. Recent photograph (2012) of my research group. First row, left to right: Omar Sánchez-Antonio, Yamir Bandala, Carlos A. Cruz-Hernández, Alberto Vega-Peñaloza, and Carlos González-Barragán. Second row: Eusebio Juaristi, Gloria Reyes-Rangel, Margarita Escudero-Casao, Elizabeth Machuca-Delapaz, Erika Jiménez-González, and Diego Fernando Montaño. Third row: C. Gabriela Avila-Ortiz, José G. Hernández, Noemi Munguía-Delgado, and Jorge Vargas-Caporali.

technologies, increasing energy efficiency, and lowering emissions in the conversion of fossil fuels ("green" chemistry).[111]

Thus, curiosity, enthusiasm, obstinacy, dedication, and attention to unexpected observations will lead to many new (stereo)chemical discoveries.

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Notes

The authors declare no competing financial interest.

Biography

Eusebio Juaristi was born in Querétaro (Mexico) and studied Chemistry at Instituto Tecnológico de Monterrey (B.Sc.) and at the University of North Carolina in Chapel Hill (Ph.D.). Following a postdoctoral stay at the University of California—Berkeley, he returned to Mexico in 1979 as Professor of Chemistry at CINVESTAV-IPN. He has been Visiting Professor at the ETH-Zurich and UC—Berkeley. In 1998, he received Mexico's Presidential Medal of Science, and in 2006, he became a member of El Colegio Nacional, the highest academic distinction in Mexico.

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(4) Probably because Ernest Eliel noticed how intrigued I was by his "Fieser" molecular models (Aldrich), he gave them to me as a gift, saying he had plenty of them back in his office at Notre Dame. Forty years later, I still use them in my lectures!

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