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Asymmetric Induction by a Remote Chiral Substituent – Computationally Determined Stereodifferentiation in Michael Additions of α-Lithiated Allyl Sulfones

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The mechanism of stereoselectivity has been elucidated for the formation of two stereogenic centers in the products of Michael addition to ethyl crotonate by lithiated α-anions of allylic sulfones bearing a remote chiral *N*-substituent. In order to single out reactive carbanion structures, their conformational analysis was performed by ab initio calculations, finally at the B3LYP/6-31+G(d) level. Low-energy reactant structures were aligned taking intermolecular steric contacts into account. It appeared that only two cyclic conformers of the sulfone nucleophile in which the Li cation is chelated by the anionic carbon, as well as the S=O and NH moieties, are sterically accessible to the crotonate approach. Chiral discrimination of one of these conformers is due to an additional Li–π interaction provided by the remote Ph group of the *N*-substituent. The enantioselectivity for the formation of the second stereocenter is due to a different asymmetry of the molecular electrostatic potential (calculated ab initio) in nucleophile–electrophile interactions. Thus, the observed diastereoselectivity is the result of a Ph–Li^+ interaction, as well as a combination of steric and electrostatic factors.

Introduction

Asymmetric induction caused by a chiral molecular unit is a function of the proximity of the chiral fragment to the reaction center, leading to differentiation of diastereotopic stereofaces by an approaching reagent. In this context, the high stereoselectivity that has been observed for reactions of allylic α-sulfonyl carbanions containing a *neighboring* chiral auxiliary with different electrophiles[1a–1e] has been convincingly explained[1d] by modeling the electrophile approach to anion substrates of optimized geometry.

Recently we found a rather unexpected high diastereoselectivity during the addition of lithiated carbanions to α,β-unsaturated esters generating two new chiral centers as in **2** (Scheme 1).[2] These nucleophilic species each bear a chiral substituent four bonds removed from the anionic center. Remarkably, the presence of an aromatic group in the chiral unit is crucial: diastereoselectivity as high as 90:10 was observed for **1a** and **1b**, while **1c** demonstrated no stereoselectivity at all.

There are many examples of remote asymmetric induction (e.g., 1,4-additions of unsaturated carboxylic acids containing chiral *O*-alkyl substituents to esters, nucleophilic reactions of ester enolates bearing chiral *O*-substituents, Enders's α-modification of nonracemic hydrazones, etc.).[3a,3b] In such cases the mechanism of stereodifferentiation is case-specific.

In order to explain the high stereoselectivity of Michael addition products **2** possessing the (3*S*,4*R*) configuration,[2] here we analyze the structural factors involved by computational modeling.

Results and Discussion

In order to reveal how the distant amino fragment of the phenyl sulfones **1** is capable of controlling the reaction stereochemistry during the Michael addition, we first performed a computational conformational analysis of the α-lithiated sulfone **1a**. Our computational study focuses on whether there are low-energy conformers of Li anion **1a**, which a) hinder one of the stereofacial approaches of the crotonate molecule, and b) distinguish between enantiotopic stereofaces of electrophile **3**. This assessment of reagent structures contains a non-explicit assumption that early stages in the reaction coordinate contribute significantly to the free energy of activation.[4]

Conformational Analysis of Carbanion 1a

It is reasonable to assume that only low-energy conformers are involved. Therefore we have considered the steric hindrances involved in *Re* and *Si* approaches of crotonate **3** (see below) for low-energy conformers of **1** lying in the 4 kcal mol^{-1} energy range over the most stable conformer

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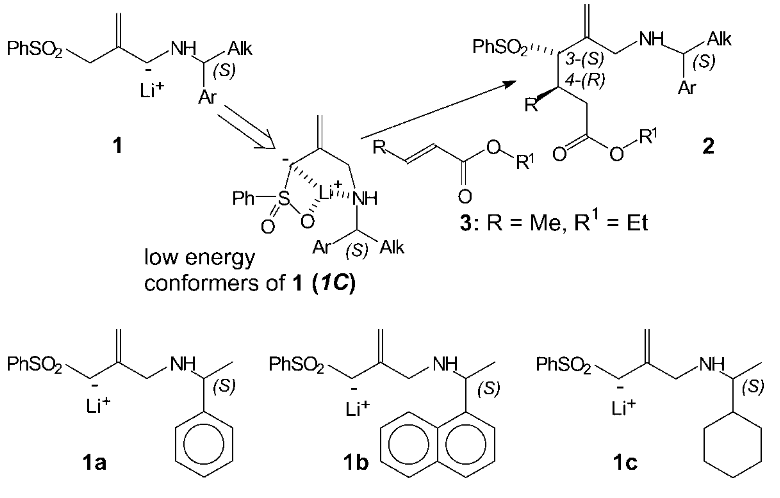

Scheme 1.

found. In other words, we put a sufficiently high upper ΔE limit that should cover reacting conformers. Higher-energy conformers were excluded from further consideration.

Reasonable geometries together with relative stability of conformers of Li anion **1a** can be supplied *reliably* only by ab initio quantum mechanics methods. However, the number of possible conformations for the flexible system **1a** is too big for an ab initio-supported screening. Therefore we used an indirect methodology to locate low-energy conformers of anion **1a**, utilizing the geometries of conformers of the parent non-lithiated sulfone as rough templates. Conformers of this sulfone were located by means of a Monte–Carlo-based conformational search followed by energy minimization (the Amber* force, MacroModel calculation package[5a–5c]). Their structures were transformed to structure **1a**, with replacement of either of the α-protons by a Li atom. Finally, ab initio-provided geometry optimization of these starting anion structures afforded a large set of conformers of the anion (for a more detailed description of the methodology see the Supporting Information).

Among these conformers, our calculations indicate a highly preferred bicyclic structure ***1C*** with an endocyclic Li cation (Scheme 1; see also Table S1 in the Supporting Information for interatomic distances for some low-energy conformers of ***1C***). Structure ***1C*** adopts different conformations of the Li-containing bicycle. These conformers are significantly more stable than extended structures of **1a** (without an O–Li–N interaction) and only they populate the conformational space of 8 kcal mol^{-1} [as the difference (ΔE) of ab initio-calculated total energy] above the lowest energy minimum. The Li$^+$ bridging indeed brings the anionic center and the amino group into close proximity and, as suggested,[2] can lead to asymmetric induction by the chiral "remote" amino fragment.

One of the cyclic conformations, with *cis*-fused four- and five-membered rings of a bent and an envelope shape, respectively (see Figure 1), strongly predominates over other conformations of the bicycle. The lone electron pair

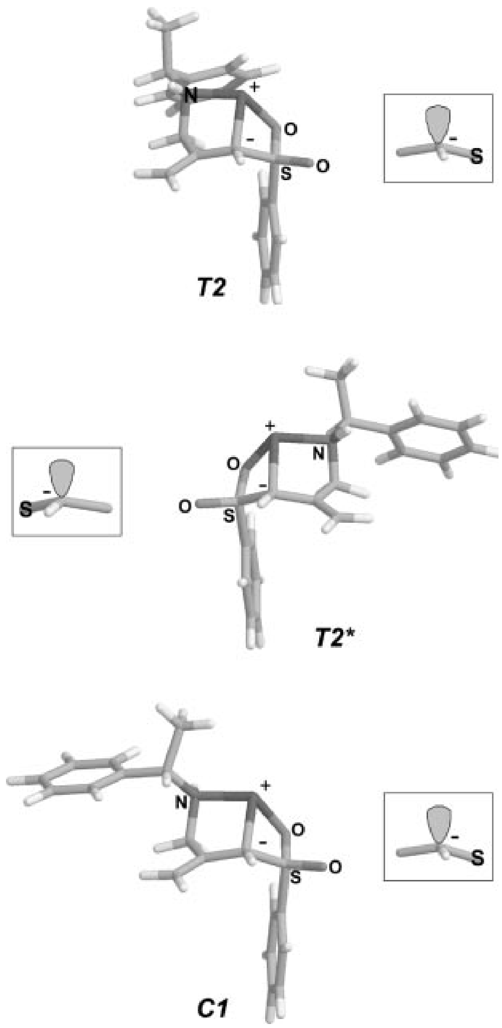

Figure 1. Low-energy conformers *T2*, *T2** ("*trans*") and *C1* ("*cis*") of Li anion **1a** [geometries optimized at the B3LYP/6-31+G(d) level]. The sp^3 orbital of a pyramidal anionic carbon is shown schematically in the frame; the Li cation does not lie on the orbital axis.

of the C anion may be regarded as a ring substituent since the axis of its sp^3 orbital is oriented distinctly from the C^-–Li^+ bond (Figures 1 and 2).[6a] Depending on the relative orientation of ring substituents and the configuration of the carbanion, there are four types of conformers – *T*, *T**, *C*, and *C** (Figure 1) – that are important for the stereodifferentiation analysis.[6b] For convenience, conformers of the *T* and *T** families (e.g., *T2* and *T2**) are labeled here as "*trans*", in view of a *trans* orientation of the *N*-substituent to the lone electron pair of the anionic carbon. Consequently, conformers of the *cis* orientation (e.g., *C1*; Figure 1) are labeled as "*cis*".

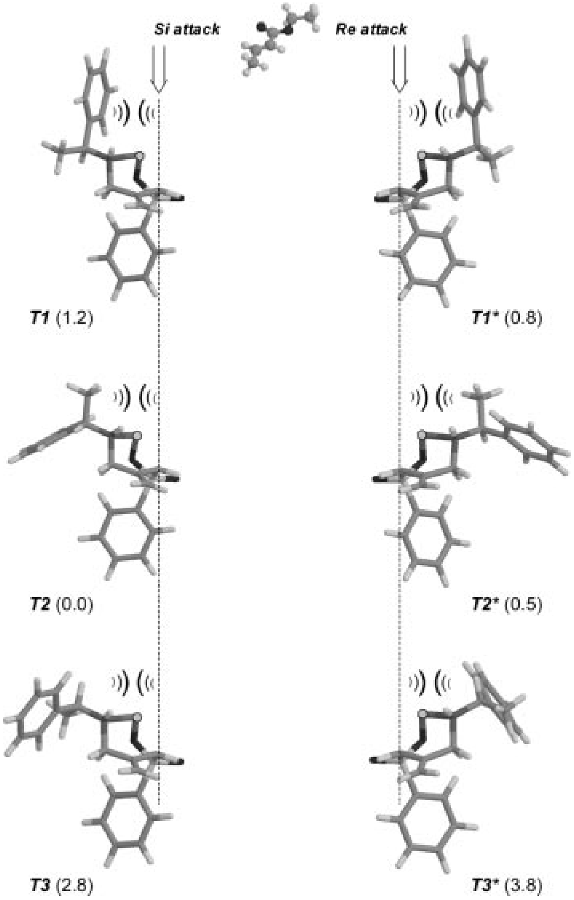

Figure 2. Diastereomeric rotamers ***T1–T3*** and ***T1*–T3**** [geometries optimized at the B3LYP/6-31+G(d) level; Li atom marked by a gray circle; Li–C bond not shown for clarity]. Relative stabilities (as ΔE; kcal mol^{-1}) of the rotamers are shown in parentheses. Dotted lines depict the trajectory of the approach of the crotonate molecule, while arrows show the direction of the electrophilic attack (*Si* and *Re* relate to the carbanion stereofaces). Arcs indicate steric interactions between the crotonate and the substituent oriented "in parallel" to the trajectory.

Values of ΔE for most *T* and *C* conformers lie below a 4 kcal mol^{-1} limit of ΔE relative to the located global minimum (see below). For all other Li-containing bicyclic structures of **1a**, ΔE lies above the 4 kcal mol^{-1} limit; therefore only conformers belonging to the *T*, *T**, *C*, and *C** families shall be regarded as potentially reactive.

These structures possess rotational freedom for the *N*-substituent, allowing three stable (staggered) conformations when this group is rotated around the exocyclic C–N bond. For instance, rotamers *T2* and *C1* each represent one of such conformation for the *T* and the *C* family, respectively, while *T1–T3* and *T1*–T3** are rotamers of the *T* and *T** families, respectively (Figure 2).

Almost all rotamers are low in energy. The global energy minimum corresponds to "*trans*" conformer *T2*. The ΔE values both for the other *T* rotamers and for all *T** rotamers are less than 4 kcal mol^{-1} relative to *T2* (see Figure 2). ΔE for *C1* is 1.2 kcal mol^{-1}, and it is 2.8 and 5.8 kcal mol^{-1} for two other *C* rotamers.

The anionic centers are pyramidalized in conformers *T1–T3*, *T1*–T3** (see Figures 1 and 2, as well as Table S1 in the Supporting Information for molecular geometry parameters) and *C1–C3* (see Figure 1 for *C1*); that is, the hybridization of the carbanion is near sp^3. The lone electron pair of the carbanion is oriented axially (the *H*-substituent is equatorial). No energy minima correspond to the opposite orientation with an axial H and equatorial electron pair: energy minimization at the B3LYP/6-31+G(d) level again led to *T* and *C* conformers. Obviously there is no binding interaction of Li with the electron pair if equatorial, due to a strong chelation of the lithium cation in the *T*/*T** and *C*/*C** conformers in the position favored for the axial electron pair. In addition, in such a case there is an intolerable overlap of van der Waals (VDW) radii of the axially oriented proton and the Li atom. When the Li cation was relocated to stabilize the equatorial electron pair (i.e., the O–Li–N bridge was destroyed in these cyclic conformers), geometry optimization led to extended conformations of high energy. We conclude that the Li-bonded C- and N-pyramids in the bicyclic conformers *T*/*T** and *C*/*C** are configurationally stable[6c] and that each electron pair has a single (axial) orientation relative to the *T*/*T**- or *C*/*C**-shaped lithiabicycle.

Molecular structures of lithiosulfones have been studied in depth.[1d,6d–6g] These species are dimeric, without Li^+–C bonding; eight-membered S–O–Li–O–S–O–Li–O rings are central fragments in these dimers. The structures of the bicyclic conformers *T*/*T** and *C*/*C** are unusual. The Li cation is chelated by the C anion, the amino, as well as the sulfone groups; a monomeric lithiabicycle (Figure 1) is formed as a result. The Li^+–C distance of a magnitude of 2.2 Å (see Table S1 in the Supporting Information) indicates a partially covalent character of the Li^+–C bond.[6g] As a chelate, this cyclic structure should be very stable, which would explain the drastic difference in ΔE (see above) for the bicyclic and the open-chain structures. Due to this stabilization of the C-pyramid in the *T*/*T** and *C*/*C** states ("ground states"), the *detectable* inversion barrier for the C anion should be significantly increased: the inversion takes place in pyramidal open-chain forms of high energy[6c] and requires additional energy to reach a planar transition state. Remarkably, inversion of Li sulfonyl carbanions is rarely slow.[6h]

Analysis of the Mechanism of Stereoselectivity – Configuration at the Anionic C Atom

Let us formally consider the approaching electrophile (ethyl crotonate, **3**) to be the fourth ligand of the tetragonal anionic center. Then the position (or the attack; see Figure 2 for an example of *T* and *T** conformers) of **3** is *Si* or *Re* relative to the heterofacial stereocenters in pairs *T*/*T** and *C*/*C**.

The observed stereoselectivity[2] of the addition of the allylic sulfone carbanion **1a** is the result solely of a discrepancy between the diastereomeric conformers of the carbanion (i.e., *T*/*T** and *C*/*C** conformers) and not of different hindrances for the axial vs. equatorial attack. Then, only *Si* attack of **3** on conformers of the *T* or *C* families leads to formation of the (*S*)-configured 3-carbon of **3**. Correspondingly, only *Re* attack on *T** or *C** conformers affords the (*R*) configuration of this asymmetry center (see Figure 2 for *T* and *T** conformers).

In order to estimate the preference for *Re* or *Si* attack of crotonate **3** on anion **1a** *qualitatively*, we analyzed the steric accessibility of the two heterofacial stereocenters of the cyclic systems of all *T*, *T**, *C*, and *C** rotamers for the crotonate using visual fitting of optimized structures of the reagents (Figure 3).[7a–7g] The electrophile was oriented relative to the anion by being positioned above the lithiated cycle satisfying three conditions: *a)* providing a *Si* approach of **3** to the *T* or *C* conformers and a *Re* approach of **3** to the *T** or *C** conformers, *b)* placing the anionic center of **1a** and the β-carbon atom of **3** at a distance of ca. 3 to 4 Å in a perpendicular line connecting the anionic C-3 and the plane of the crotonate C=C bond, and *c)* maximally avoiding intermolecular steric contacts of other fragments of

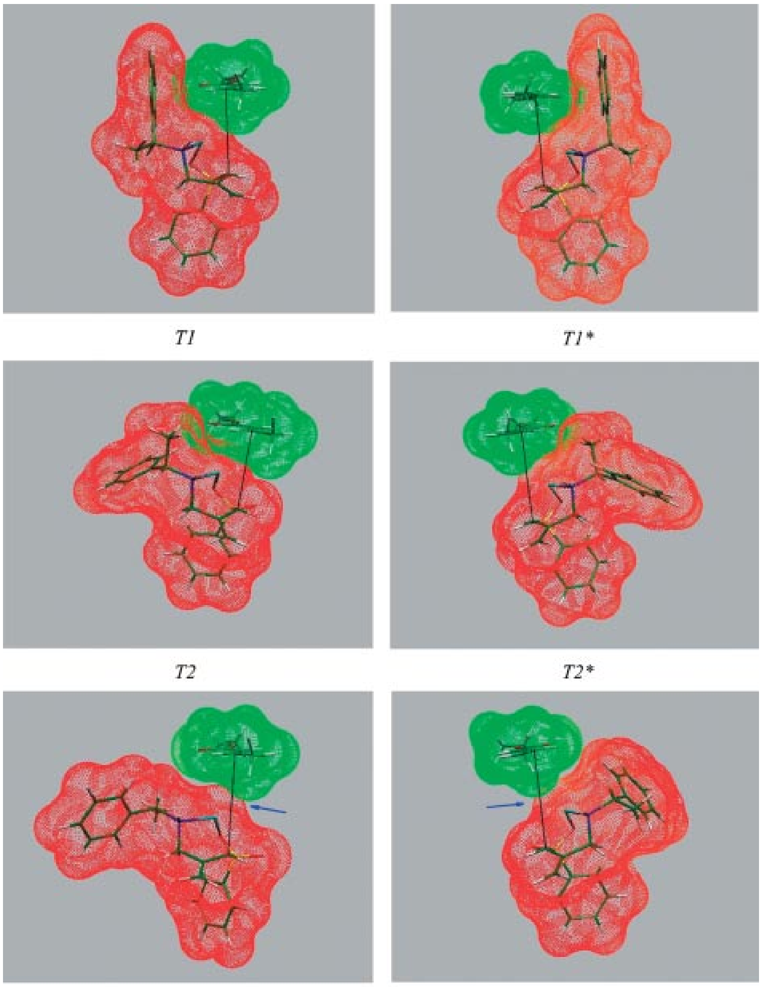
T1 *T1**
T2 *T2**
T3 *T3**

Figure 3. Optimal *Si* (on the left; the *Si* stereoface of the carbanion is attacked) and *Re* (on the right; the *Re* stereoface of the carbanion is attacked) approaches of crotonate **3** (in green; shown in *s-cis* conformation) to diastereomeric structures *T1* and *T1**, *T2* and *T2*, *T3* and *T3** (in red). Ab initio optimized geometries of these molecules together with their van der Waals surfaces are shown. The Li–C bond is omitted for simplicity. Other orientations of the electrophile, keeping the defined distance between the reacting centers while rotating **3** around a normal to the plane of the C=C bond connecting these centers (black line) or a 180° turn around the axis of the double bond followed by rotation around the normal (not shown), lead to an appreciable increase in spatial overlap of chemically noninteracting fragments of the molecules. Blue arrows indicate the region of spatial overlap between the Li atom of **1a** and the Me group of **3** in *T3* and *T3**.

both molecules. We chose a relative orientation of reagents that would afford minimal spatial overlap of their VDW volumes, keeping the above restrictions for the distance and stereochemistry. To locate this orientation we used molecular graphics-assisted alignment of the optimized 3-D structures (see ref.[7] for other successful explanations using similar qualitative estimations).

The sterically *optimal* arrangement of the reagents brings the Li cation in the *T1*, *T1**, *T2*, *T2**, *T3*, and *T3** conformations into close proximity to the carbonyl group of the crotonate in the *s-cis* conformation (see Supporting Information for the example of *T3*). This leads to the Li–O binding interaction. On the other hand, if adopting the less stable *s-trans* conformation, the crotonate C=O moiety does not coordinate the Li cation of **1a** (see Supporting Information). Therefore we consider only the *s-cis* conformation of unsaturated ester **3**.

This analysis shows that *C* and *C** rotamers ("*cis*" species) are unreactive because of severe overlap of their molecular volumes (see Supporting Information and ref.[8]). The "*trans*" conformers *T* and *T** are more open for the axially approaching electrophile. Conformers *T1* and *T1**, as well as *T2* and *T2**, expose a relatively bulky Me or Ph substituent "in parallel" to the trajectory (shown in Figure 2), while conformers *T3* and *T3** have only the *H*-substituent in this direction. Indeed, among the *T*/*T** conformers there is an appreciable superposition of molecular volumes for **3** and the Ph or Me fragments of the phenylethyl substituent in rotamers *T1*, *T1**, *T2*, and *T2** even when arranged optimally (Figure 3). For rotamers *T3* and *T3** an optimal approach of the reagents does not meet any steric hindrances due to the *N*-substituent. Hence, there is a steric discrimination of conformers *T1*, *T1**, *T2*, and *T2* in favor of conformers *T3* and *T3**.

Steric contacts between the Li cation in *T3* and *T3** and the 3-Me group of **3** are not avoidable in tight proximity of the molecules; however, the overlaps of VDW volumes of these fragments are approximately the same in the two diastereomers. Hence, the heterofacial stereocenters in *T3* and *T3** are similarly open for an optimal *Si* and *Re* attack, respectively; this leads to the surprising conclusion that steric hindrance alone is not the only factor for the observed[2] stereoselectivity.

There is a remarkable structural difference between diastereomeric structures *T3* and *T3**. The Li cation is apparently bonded to the phenyl moiety of the *N*-substituent in *T3**, being located "above the plane" of the phenyl ring at a short distance of 3.23 Å (see Figure 3 as well as Table S1 in the Supporting Information). There is no such bonding in *T3*. Li^+–aryl interaction should be of considerable strength in *T3**.[9a–9d] Thus, the chelating anionic ligand is tetradentate in structure *T3** while it is tridentate in *T3*. Stronger binding of the Li cation in conformer *T3** provides a higher reaction barrier for *T3** relative to *T3*, so *T3* is the major reacting conformer, which leads to a preference for the *Si* attack and formation of the (3*S*) configuration in the reaction product **3**.

Our modeling correctly predicts the experimental[2] outcome of the reaction. Moreover, it explains the crucial role (see Introduction) of the presence of an aryl group as a structural unit of the chiral fragment. The observed stereodifferentiation is due to a Li^+–Ph (cation–π) interaction. The explanation of the aryl effect is, in our opinion, a solid argument as to the validity of our simple modeling.

Analysis of the Mechanism of Stereoselectivity – Asymmetry Introduced into the β-C Atom of Crotonate 3

We have shown above that *T3* is a preferred reactive form of anion **1a**. Hence, the crotonate *Re*-face or *Si*-face attack on *T3* results in the formation of (*R*)- or (*S*)-configured tetragonal carbon atoms, respectively, in the precursor α,β-unsaturated chain (Figure 4). There is no appreciable dis-

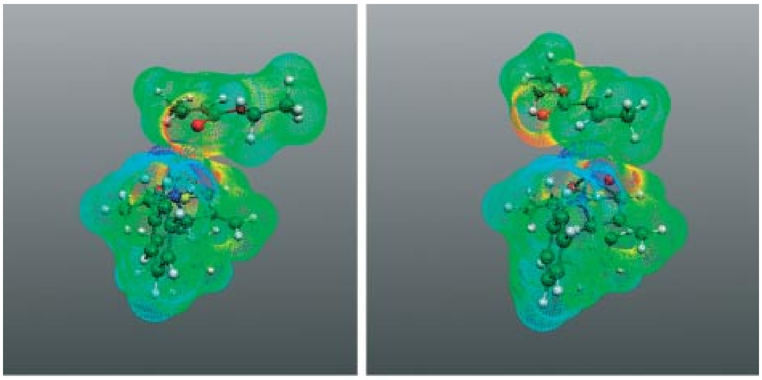
(*R*) configuration (*S*) configuration

Figure 4. Formation of chiral centers of (*R*) or (*S*) configuration (left and right, respectively) in crotonate **3** (shown in *s-cis* conformation) attacking rotamer *T3* via opposite enantiotopic stereofaces (the *Si* face in left and the *Re* face in right; structure *T3* is shown in the same projection). Electrostatic potential, which was calculated at the B3LYP/6-31+G(d) level for optimized structures of each molecule on their VDW surfaces, is shown within the –22 (red) to +22 (blue) limits (kcal mol^{-1}; green color depicts zero potential). There is an optimal relative orientation of the reagents: any rotation (not indicated) of the electrophile around the normal connecting the reacting centers leads to an increase in intermolecular overlap of VDW volumes.

tinction in steric hindrances for **3** approaching the non-crowded conformer *T3* via opposite stereofaces, hence no differentiation of enantiotopic faces of the crotonate caused by steric crowding.

An anisotropic electric field, formed by approaching molecules, orients them to minimize the energy of charge–charge and dipole–dipole interactions[10] before an overlap of the VDW radii of their atoms occurs.[11a–11c] Therefore, for the early reaction stages of *nucleophile* ***1a***–*electrophile* ***3*** interactions, an assessment of charge distribution-related properties[12] – that is, molecular electrostatic potential (MEP) as well as dipole moments – could lead to selection of a favored orientation of the reagents.[13] Indeed, MEP has been employed to choose preferred disposition of interacting molecules even without quantitative estimation of the energy of intermolecular charge–charge interactions.[11a,14a–14d]

We calculated MEP for conformer *T3* as well as crotonate **3** by ab initio techniques using the CHELPG methodology[15] implemented into the Gaussian98 package.[16] On the reacting face of the nucleophile there is a compact region of a high positive potential belonging to the VDW surface of the Li cation (Figure 4). There is also a region of a high negative potential (carbonyl oxygen) on the electrophile surface. This negative region of the crotonate is spatially close to the positive region of the Li cation facilitating Li–O coordination, if the orientation of the reactants is *ul*, which corresponds to the formation of the newly (*R*)-configured stereocenter. This carbonyl MEP region is far from the highly positive MEP region of the nucleophile when the (*S*) configuration is formed. Thus, for sterically optimal pre-reaction disposition, the nucleophile shows charge–charge affinity for the *Si* face of the crotonate electrophile and not for its *Re* face.

Nucleophile **1a** and electrophile **3** carry no net charge, so dipole–dipole interactions between these species should be of higher energy than their charge–charge interactions. In order to estimate how intermolecular dipole–dipole interactions affect the reaction stereoselectivity, we calculated dipole moments for *T3* and electrophile **3** by ab initio methods. These calculations have shown that dipole–dipole interactions do not provide discrimination of one of the enantiotopic faces of the crotonate (see Supporting Information).

Hence, only intermolecular charge–charge interactions lead to a favored pre-reaction orientation of the electrophile that facilitates formation of the stereogenic center of (*R*) chirality. In terms of the Eyring equation, the exponent activation energy is not changed; the orientation accelerates electrophilic attack via the *Si* face of **3** by increasing the transmission coefficient (relative to the coefficient for the attack by the opposite stereoface). Our modeling thus also leads to the correct qualitative conclusion regarding the preferred configuration for the second stereocenter [i.e., (4*R*)] in the product **2**.

We realize that our visually controlled fitting of reactant structures is not a strict methodology. Nevertheless, the well known concept of VDW volumes as a non-interpenetrable molecular space is well established and this feature is easily represented graphically. Attractive and repulsive regions on MEP surfaces as well as vectors of dipole moments are also suitable for visual comparison. In addition, in contrast to energetics estimates, molecular geometries of organic compounds are usually reproduced well by different DFT-based (e.g., B3LYP) calculations employing relatively non-extended basis sets [e.g., 6-31+G(d)]. Our modeling predicts the correct stereochemistry of the reaction for *both* stereocenters. It also explains the unexpected "aryl" effect. In the light of the success of this analysis, we view such mechanistic modeling as a simple tool for routine predictions of reaction stereochemistry when crowded molecules are involved, without any necessity for laborious ab initio calculations.

We also examined these stereochemical conclusions by additionally performing single-point ab initio calculations at the B3LYP/6-31+G(d) level for interaction of conformer *T3* vs. *T3** with crotonate **3**. Exploring the potential energy surface, the anion molecule was rotated around a normal to the plane of the C=C bond of the crotonate by 40º (10º rotation steps) in both directions, starting from the optimal rotational orientation found by our fitting procedure (Figure 3). The system energy is raised for each pair – *T3*/**3** and *T3**/**3** – when the rotation angle is increased (see Supporting Information). It means that steric hindrances are estimated well for rotational orientation of the nucleophile and the electrophile (at least with 10º accuracy for rotation) by visual modeling using exact geometries of the reacting molecules. Furthermore, it appeared that, in successful orientations of *T3* and **3**, as well as *T3** and **3**, the energy difference ΔE is 7.5 kcal mol^{-1} more for the second pair (i.e., electrophilic attack of the crotonate on *T3* is highly preferable by this model). This result is in line with the above visual fitting estimates. Nevertheless, we note that these calculations predict a total predominance in formation of chiral product **2**, whilst the observed diastereoselectivity is less (see Introduction). It is reasonable to assume that this overestimation of ΔE is because of the qualitative character of this modeling as well as the neglecting of solvation.

Conclusions

Our simple computation-supported modeling correctly predicts the preferred diastereoselectivity previously observed for Michael reactions of α,β-unsaturated esters (crotonates) with lithiated allylic α-sulfonyl carbanions bearing remote chiral auxiliaries. This is due to a combination of three factors. A) In terms of VDW distances, only two low-energy conformers of the Michael acceptor are sterically accessible. B) Strong aryl–Li$^+$ bonding, resulting from a 3.23 Å distance, is present in one of these two diastereomeric conformers. This decreases its chemical reactivity and therefore leads to preferential stereochemical selection of the second conformer. The two factors A) and B) two provide an (*S*) asymmetry originating from the anionic carbon of the donor. C) Owing to intermolecular charge–charge interactions, pre-reaction orientation of the reagents is favored when the *Si* enantiotopic face of the crotonate is exposed towards the carbanion. The stereochemical consequence is a predominant formation of the (*R*)-configured center derived from the β-carbon of the crotonate. This demonstrates that, in addition to steric requirements of reacting molecules, electrostatic factors also need to be considered in the stereochemistry of Michael additions.

In view of the above correct prediction of preferred stereochemistry as well as the successful explanation of the aryl effect, molecular graphics-assisted visual fitting of reacting molecules of optimized geometry (see also ref.[1d]), may be a simple method for predicting stereochemistry in reactions of sterically crowded compounds.

Experimental Section

The Amber* and MM3* force field implemented into the Macromodel 6.5 package[5a–5c] were used for the conformational analysis of non-lithiated sulfone and crotonate **3**, respectively. The *no solvent* and *distance-dependent dielectric electrostatics* options as well as the Polak–Ribiere optimization algorithm (a Macromodel component as the *PRCG option*) were employed for the energy minimization. The *Monte-Carlo* option was used for conformational search (generation of 5×10^5 structures with the energy upper limit 3 kcal mol^{-1} from the lowest-energy conformer found).

The geometries of molecular mechanics-derived structures were used as the starting geometries for ab initio calculations (Gaussian98 package[16]) of conformers of **1a** in the gas phase, with replacement of sulfone α-hydrogens with Li atom. Initial ab initio geometry optimization was performed at the restricted Hartree–Fock level using the 6-31G(d) basis set. The resulting geometries of low-energy conformers, as well as the starting geometry for crotonate **3**, were reoptimized at the B3LYP/6-31G(d) and then at the B3LYP/6-31+G(d) level. Starting geometries for rotamers were generated by rotating the *N*-substituent through 120º in conformers *C1*, *T1*, and *T1** of optimized structure. The obtained geometries were subjected to energy minimization at the B3LYP/6-31+G(d) level. No correction of total energy to the zero point was performed. The Newton–Raphson algorithm and Cartesian coordinates were used at the all-minimization levels. In cases of no convergence, the Gaussian's *VeryTight* convergence criterion was recruited.

MEPs for conformers *T3* and *T3** were calculated using the *Cube* option, taking full electron density into account (an $80 \times 80 \times 80$ grid for the electrostatic potential). Atomic charges were calculated according to the CHelpG Scheme[15] implemented into Gaussian (option *Pop=ChelpG* in the Gaussian). Dipole moments were derived for atomic charges which fit the calculated MEP (option *Pop=Dipole*). The 4.2 version of the molecular graphics program Molekel[17] was used for visualization of the VDW volumes of Gaussian-derived structures, their MEP surfaces and vectors of dipole moments, as well as for visually controlled arrangement of 3-D structures.

Supporting Information (see also the footnote on the first page of this article): Description of the methodology for the conformer location, absolute electron energies (au), optimized geometries (Cartesian coordinates), and values of *xyz* components of dipole moment vectors (D) for low-energy conformers, additional projections of the anion–crotonate orientation, as well as parameters of molecular geometries of low-energy conformers of the carbanion.

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[4] This is reasonable due to the exothermic character of Michael additions; namely, based on the Hammond postulate, the structure of the transition state for the interaction of **1a** with **3** should not be very different from the reagent structures.

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[6] a) For consideration of the location of coordinated Li$^+$ relative to sp^3 orbitals of, for example, O atoms see K. B. Wiberg, M. Marquez, H. Castejon, *J. Org. Chem.* **1994**, *59*, 6817–6822; b) There are eight types of conformers for the *cis*-fused bent and an envelope-shaped bicycle ***1C***. Additionally to *T*, *T**, *C*, and *C**, there are four types of diastereomeric structures (with ΔE of 0.2–2.0 kcal mol^{-1} relative to the global minimum) which are different from *T*, *T**, *C*, and *C** only in the opposite configuration of the S asymmetry center; in other words, by an alternative (pseudoequatorial) orientation of the S-Ph substituent. However, assessment of only *T*, *T**, *C*, and *C** is sufficient since the pseudoequatorial orientation of the S-Ph group in the four other structures brings this bulky substituent and the attacking crotonate too close and thus hinders the attack; c) With regard to the C- and N-pyramid of the anion, pairs *T* and *T** as well as *C* and *C** are invertomers. Obviously, there is no one-step interconversion between *T* and *T** or *C* and *C** invertomers. Diastereotopomerization of these forms occurs by a formal pathway *bicycle T (or C)* – ring-opening – *open chain form X1* – carbanion inversion – *open chain form X2* – backbone rotation – *open chain form X3* – N-inversion – *open chain form X4* – ring-closure – *bicycle T* (or C*)*. In other words, both the carbanion and the nitrogen are inverted in an open form of the backbone; d) G. Boche, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277–297; e) M. Linnert, C. Bruhn, C. Wagner, D. Steinborn, *J. Organomet. Chem.* **2006**, *691*, 2358–2367; f) P. Speers, K. E. Laidig, A. Streitwieser, *J. Am. Chem. Soc.* **1994**, *116*, 9257–9261; g) E. D. Jemmis, G. Gopakumar In *The Chemistry of Organolithium Compounds* (Eds: Z. Rappoport, I. Marek), John Wiley & Sons, New York, **2004**, pp. 1–45; h) H.-J. Gais, G. Hellmann, *J. Am. Chem. Soc.* **1992**, *114*, 4439–4440.

[7] A widespread primitive modeling of organic reaction stereochemistry is based on graphical alignment of reagents in their assumed approximate geometries (in other words, on drawing

of perspective projections of common 3-D structures). Obviously, this is often highly speculative. On the other hand, an accurate estimation of relative rates of alternative stereochemical pathways is very laborious for bimolecular reactions of conformationally mobile molecules. In contrast to that of stable conformations, quantitative modeling of transition states using ab initio methods is laborious and computer time-consuming owing to difficulties in location of first-order transition states as well as their great number. Moreover, small differences (0.5–1.0 kcal mol^{-1}) in free energy of activation for alternative pathways are sufficient to provide good stereoselectivity. The accuracy of conventional ab initio calculations is unfortunately of the same order of magnitude even for molecules in vacuo. The inaccuracy may be higher for different solvation models. Thus, quantum mechanics ab initio modeling of transition states, in principle an "absolute" method, is in fact too complex to supply reliable analyses of stereoselectivity in reactions of flexible organic species in reasonable timescales. A combined approach, mechanistic consideration of computationally generated or experimentally derived geometries for starting compounds without quantitative modeling of transition states, has turned out to be successful in many cases. For selected examples see: a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635; b) A. E. Taggi, A. M. Hafez, T. Dubbling, T. Lectka, *Tetrahedron* **2002**, *58*, 8351–8356; c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460; d) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, H.-S. Choi, *J. Am. Chem. Soc.* **2002**, *124*, 2190–2201; e) G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zampori, M. Zema, *Tetrahedron* **2001**, *57*, 10203–10212; f) J. d'Angelo, D. Desmaële, F. Dumas, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505; g) P. Garner, Ö. Şeşenoğlu, H. Burgoon, *Tetrahedron: Asymmetry* **2003**, *14*, 2883–2887 as well as ref.[1d] For instance, in the case of allylic sulfone anions, this approach revealed different accessibility of *exo* and *endo* faces of 2-sulfonyl 2-norbornenyl Li anions upon electrophilic attack. h) Thus, such a relatively simple modeling may be viewed as a fruitful practical compromise between the above mentioned approaches to explain or to predict stereochemistry of reaction products.

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[9] Energy of Li^+–π interaction is estimated as 27–33 kcal mol^{-1} for an optimal disposition of Li cation and a benzene ring (the Li atom is located about 2 Å above the geometrical center of the aromatic cycle; see: a) D. Kim, S. Hu, P. Tarakeshwar, K. S. Kim, *J. Phys. Chem. A* **2003**, *107*, 1228–1238; b) G.-F. Gal, P.-S. Maria, M. Decouzon, O. Mó, M. Yáñez, J. M. L. Abboud, *J. Am. Chem. Soc.* **2003**, *125*, 10394–10401; c) I. Alkorta, J. Elguero, *J. Phys. Chem. A* **2003**, *107*, 9428–9433); d) B. Goldfuss, M. Steigelman, T. Lyschmann, G. Schilling, F. Rominger, *Chem. Eur. J.* **2005**, *11*, 4019–4023. Therefore the energy of Li–Ph interaction for *T3** is not negligible, albeit Li is above the plane of the phenyl ring at a 3 Å distance and shifted to the edge of the ring. Calculations at the MP2/6-31G(d,p) level (this work) showed that the energy of Li^+–π interactions between the Li cation and benzene (a model system) is 13.0 kcal mol^{-1} when arranged as Li^+ and the phenyl ring in conformer *T3**. Hence, destroying this Li–Ph bonding in *T3** should lead to an increase of the kinetic barrier of the addition. Obviously, this increase is probably much less than 13 kcal mol^{-1} since the Li–aryl bonding is not fully disrupted in the early transition state.

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