Solvent-Dependent Stereoselectivity in a Still–Wittig Rearrangement: An Experimental and ab Initio Study

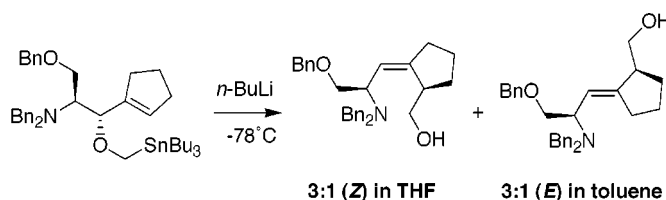Scott A. Hart,[†] Carl O. Trindle,[†] and Felicia A. Etzkorn*,[‡]

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ABSTRACT

The Still–Wittig rearrangement gave opposite selectivities for (*Z:E*)-alkenes in THF (3:1) vs toluene (1:3) in the synthesis of serine–proline dipeptide amide isosteres. Four transition states leading to (*Z*)-and (*E*)-alkenes with THF and without (representing toluene) were identified by ab initio calculations at the 3-21G* level. The calculated (*Z:E*)-ratios with THF (4.7:1) and without THF (1:3.2) suggested that the transition state geometries and energies were well-represented by the calculations.

In the synthesis of *cis*-proline dipeptide mimics,[1] we have used the Still−Wittig [2,3]-sigmatropic rearrangement[2] to form trisubstituted (*Z*)-alkenes selectively. Others have similarly synthesized disubstituted (*E*)-alkene dipeptide mimics.[3] The general [2,3]-sigmatropic rearrangement has been studied extensively,[2,4] providing detailed accounts of how substitution of the allylic ether precursor determines the stereochemical outcome of the rearrangement in a predictable fashion; the tabular survey compiled by Nakai gives an excellent overview of these effects.[4b] While (*E*)- or (*Z*)-alkene selectivity of [2,3]-sigmatropic rearrangements can be predicted by conformational analysis of the expected transition state, little has been demonstrated regarding solvent effects on selectivity, since these rearrangements are usually performed in THF or mixtures containing THF.[4b] We report here an example of solvent-dependent stereoselectivity in this rearrangement and provide an ab initio theoretical analysis of the possible transition states to account for the stereoselectivity.

Solvent variations in the Still−Wittig rearrangement include examples where the use of THF resulted in either reduced yields[3c] or reduced yields coupled with significant [1,2]-rearrangement.[3a,b] In these cases, hexane was found to be a superior solvent, leading to [2,3]-rearrangement in higher yields. However, these examples were in systems where (*E*)-alkene formation was significantly favored by sterics and thus provided little information concerning the role of solvent in (*Z*)- or (*E*)-selectivity. In solvents other than THF, the alkene geometry was not variable as a result of formation of a cyclic product.[4e]

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Most conformational analyses of the [2,3]-sigmatropic rearrangement have excluded the role of the counterion for simplicity, with some exceptions. One specific proposal was that the presence of a methoxymethyl ether protecting group allowed the substrate to act as a tridentate ligand, chelating the Li+ counterion and forcing a locked conformation in the transition state. While this proposal accounts for the observed results, theoretical analysis was not performed.[5] The effect of counterion chelation in the transition state on the outcome of [1,2]-sigmatropic rearrangements was analyzed recently, though solvent was not at issue.[6] Computational studies on the minimal, nonsubstituted [2,3]-rearrangement substrate found that a five-membered ring saddle point was located without the cation present, but the Li+ counterion had to be included in energy calculations in order to locate a true transition structure.[7] In these cases solvent effects were not examined. A review by Collum that discusses the chelation of Li+ by TMEDA vs THF is particularly relevant for our results.[8]

Still–Wittig Rearrangement. Beginning with tributyl-stannane **1a**, our system favored the (Z)-alkene upon treatment with n-BuLi in THF,[1] as expected when a pseudoaxial transition state is preferred (Scheme 1).[2] However, in **1b**,

Scheme 1. Solvent-Dependent Stereoselectivity.

1a: R = H
1b: R = OBn

(Z)-2   (E)-2

solvent	ratio of products	
THF	3	1
toluene	1	3
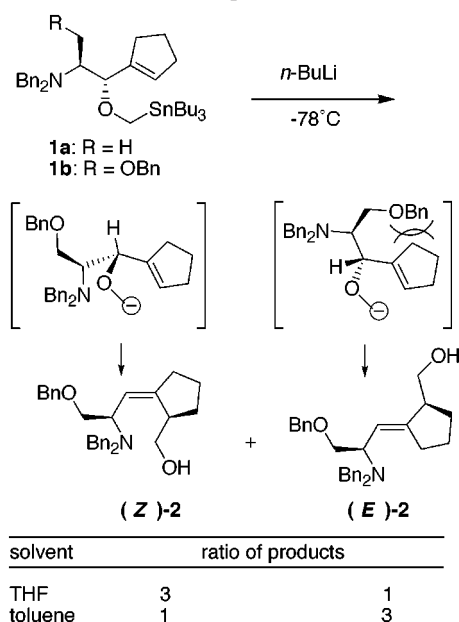
the case where R = OBn, (Z)-selectivity was only 3:1 in THF at −78 °C (Scheme 1).[1c] The rearrangement was thus performed in toluene to examine the effect of solvent on (E)- or (Z)-alkene selectivity. A reversal of selectivity was observed when toluene was the solvent at −78 °C, giving

3:1 (E:Z)-**2** (Scheme 1). Rearrangement at +50 °C yielded a 1:1 mixture of (Z)- and (E)-alkenes in each solvent.[9]

This selectivity difference led us to examine possible transition states in an effort to explain these results. The transition state proposed by Still[2] leading to the (Z)-trisubstituted homoallylic alcohol (Scheme 1) was expected to be favored over the analogous transition state leading to the (E)-trisubstituted alkene as a result of unfavorable steric interactions in the equatorial plane. This simple analysis is consistent with our results in THF but not in toluene. Because of these differences, we used ab initio calculations to clarify the geometries and energies of the transition states leading to the (Z)- and (E)-alkenes in the presence and absence of THF.

Calculations. The tributylstannyl group was not included in the calculations after initial results indicated that this group quickly distanced itself from the reacting carbanion once the rearrangement began. The tributyltin may influence the conformation of the ground state, but it was not a factor in comparison of the transition states. The starting structures for calculations were truncated versions of **1b**; methyl groups were used in place of the benzyl protecting groups. This truncation greatly reduced the calculation time while retaining the most proximal steric interactions involved at the benzylic positions. Restricted Hartree–Fock (RHF) calculations at the 3-21G* level located transition state structures on the paths leading to major and minor products in the presence and absence of one coordinating THF molecule. The size of the systems in question limited the sophistication of the calculations we could complete. RHF calculations in the small 3-21G* basis produced reasonable bond distances and angles for the reacting fragments and reproduced to a good approximation the results of Wu, Houk, and Marshall on the simplified system they studied.[7] Although differences in transition state energies were very small, the transition states being compared were stereoisomers and we expected major basis set errors to cancel out. The energy ranking of the four transition states was consistent from MNDO through RHF/3-21G* levels.

The effect of counterion chelation in the Wittig rearrangement was found to be crucial in our system. Because THF is capable of coordinating Li+, the resulting transition state structure that included a THF molecule was quite different than the transition state structure without THF. The transition state structure was governed by the manner in which Li+ coordinates to the substrate and solvent. Figure 1 shows the resulting structures and relative energies found in each case. For the system with THF present, the solvent molecule chelated the Li+ (Figure 1A). The cation also interacted with the amine and the ether oxygen adjacent to the reacting carbanion, thus forming a five-membered chelated ring that locked the steric interactions of the transition state in a defined orientation. The transition structure leading to the

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(9) The product ratios for the reactions in toluene and the reaction at +50 °C in THF were determined by integration of the appropriate alkene signal in the 1H NMR of the reaction mixture (Supporting Information). Chemical shifts of the alkene protons had been previously determined by isolation and characterization of both alkenes from the reaction in THF at −78 °C.
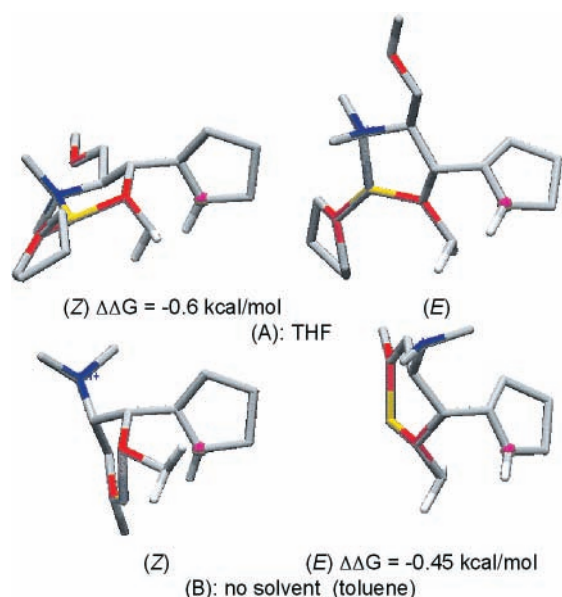
Figure 1. Transition states found leading to (Z)- and (E)-alkenes **2**: (A) with one THF and (B) without solvent, to represent the reaction in toluene. Li⁺ is shown in yellow. The new bond is formed to carbon marked with pink dot. Only hydrogens at the reacting centers are shown. Calculations used Gaussian 98. Graphics were prepared with MacroModel v. 6.0.

(Z)-alkene was more stable by 0.6 kcal/mol than the structure leading to the (E)-alkene. At −78 °C, this value would result in a 4.7:1 (Z:E) ratio, consistent with the predominance of (Z)-alkene experimentally (3:1 Z:E).

Results for the system in the absence of THF revealed a crucial difference in the way the substrate chelated Li⁺. Figure 1B shows the transition structures located in the absence of THF (representing the reaction in toluene). At the 3-21G* level, the transition structure leading to the (E)-alkene was more stable by 0.45 kcal/mol than the structure leading to the (Z)-alkene. In both (E)- and (Z)-transition states without the THF present, the Li⁺ cation lay between the two ether oxygens, constraining the system to a six-membered ring that significantly altered the stereochemistry of the reaction.[10] In this case, the calculated energy difference of the transition states would result in a 3.2:1 (E:Z) ratio, consistent with the observed 3:1 (E:Z) ratio of products.

The only difference in these two sets of diastereomeric transition states was the presence or absence of one THF molecule, which implied that the steric demands of the THF molecule on the system altered the stabilities of the resulting transition states. The striking difference was that, with THF present, the chelation was of the form O−Li(THF)−N, while without THF the cation instead preferred to chelate the two ether oxygens, O−Li−O. There is some evidence that Li⁺ prefers to chelate oxygen over nitrogen (THF over TMEDA).[8] Despite the presence of a tertiary amine in the molecule, our calculations showed chelation to only the two internal oxygen atoms when THF was absent. When THF was present, the internal tertiary amine replaced the methoxy as ligand. In this model, the THF molecule was interacting in a steric manner to determine the conformation of the transition state. The transition structures lacking THF adopted distinct structures, binding only the two internal oxygen atoms. These steric interactions were not obvious in qualitative analysis of this system, but ab initio transition state analysis enabled us to visualize such differences.

In summary, ab initio calculations were consistent with the stereochemical outcome of these Still−Wittig rearrangements. Transition state structures located by Hartree−Fock methods in the presence or absence of a chelating THF molecule demonstrated differences in the manner in which the Li⁺ counterion was chelated by the electronegative atoms of the substrate. Examination of the transition state structures found at the 3-21G* level did not reveal any discrete interactions that might account for the observed selectivity. Beyond the obvious differences in the manner of Li⁺ chelation, the diastereomeric transition structure differences were qualitatively subtle. Despite the approximate nature of the computational level applied, the ab initio calculations were a useful tool for predicting plausible transition states because they yielded subtle structural details that were not obvious by qualitative analysis but they were instrumental in favoring one transition state over another. The solvent-dependent differences in these transition states can be used as a guide in future applications of the Still−Wittig rearrangement where specificity in alkene geometry is desired.

Supporting Information Available: Experimental procedures for the synthesis and analytical data of the (E)- and (Z)-alkenes, calculations and NOE spectra confirming alkene geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Calculations at the 3-21G* level demonstrated that structures containing O−Li−O chelation instead of N−Li−O in the presence of THF were higher in energy by 7.58 kcal/mol (frontside approach to give Z) and 6.01 kcal/mol (backside approach to give E). In the absence of THF, structures containing O−Li−N chelation were higher in energy than those containing O−Li−O chelation by 7.71 kcal/mol (frontside approach to give Z) and 6.17 kcal/mol (backside approach to give E).