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Lewis acid–aldehyde–solvent interactions. A computational approach for determining the critical amount of THF molecules necessary for achieving a high enantioselection in chiral oxazaborolidinone-promoted asymmetric aldol reactions

Ryoji Fujiyama,* Kazuki Goh and Syun-ichi Kiyooka

Department of Material Science, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan

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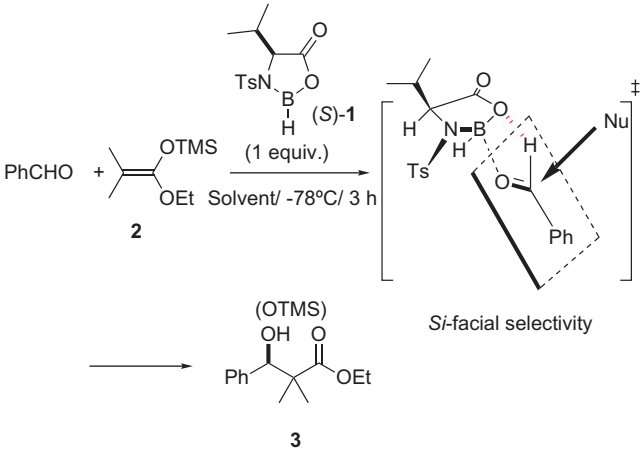
Abstract—The effect of THF as a solvent on the enantioselectivity of oxazaborolidinone-promoted asymmetric aldol reactions of aldehydes with silylketene acetals was investigated. The use of 4–5 M equiv of THF, relative to the chiral borane, was required to achieve a high enantioselectivity. A solvent-modeling study, based on ab initio calculations of intermolecular interactions, revealed the existence of an extended hydrogen bonding network in the resulting assembly, which was composed of THF molecules, the aldehyde, and the oxazaborolidinone. The model rationally provides a spatially suitable active site for controlling the stereochemical outcome of the reaction.

Chiral oxazaborolidinone-promoted asymmetric aldol reactions of aldehydes with silylketene acetals are widely used in the construction of macrolide skeletons, having 1,3-polyhydroxy stereocenters, because of the high resulting enantioselectivity.[1] Stoichiometric reaction conditions in CH_2Cl_2 are typically used in the laboratory in reproducing the level of enantioselectivity.[2] The high facial selectivity can be explained satisfactorily by assuming a transition state model, as shown in square brackets in Scheme 1. Nontraditional hydrogen bonding between the ring oxygen and the formyl hydrogen, as proposed by Corey, plays an important role in effectively fixing the face being attacked by a silyl nucleophile along with the cooperative coordination of the borane to the aldehyde carbonyl function.[3] A theoretical study with coordination models between aldehydes and the related simplified boranes indicated that a different conformer has a lower energy minima.[4] In spite of these previous studies, questions concerning this high selectivity continue to remain because the front side of the chiral borane is extensively exposed. The use of THF was investigated in the course of a search for a more appropriate solvent to replace CH_2Cl_2 in the reaction from an environmental point of view, and, as a result, a remarkable solvent effect was found. We propose herein an explanation of the origin of the high enantioselectivity in asymmetric aldol reactions that require a critical amount of THF. Our conclusions are based on ab initio calculations of an appropriate model system and involve the participation of THF molecules.



Scheme 1.

* Corresponding author. Tel.: +81 88 844 8300; fax: +81 88 844 8359; e-mail: fujiyama@cc.kochi-u.ac.jp

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In preliminary studies[5] of enantioselective Diels–Alder reactions with chiral oxazaborolidinones, Helmchen pointed out that ca. 12 equiv of THF are initially involved in a typical procedure for the preparation of the oxazaborolidinones as the result of adding BH_3·THF (1 M equiv in THF) to a suspension of *N*-arylsulfonyl-α-amino acid in CH_2Cl_2 and that the quantity of the donor additive is necessary for achieving a high enantioselectivity in the reaction and the lowering of selectivity in reactions without such a donor solvent is caused by an association of the catalysts used, that is, a unique species multiplicity.[6a] In the case of the chiral oxazaborolidinone-catalyzed 1,3-dipolar cycloaddition of a nitrone to ketene acetals, contrary to the results of the above Diels–Alder reaction, a high degree of enantioselection could be achieved by excluding donor solvents (such as THF) from the reaction mixture.[6b] We first confirmed THF solvent effects in the chiral oxazaborolidinone-promoted asymmetric aldol reaction of benzaldehyde with silylketene acetal **2** (Table 1): the reaction, under normal conditions, gave the aldol with 88% ee in the presence of (*S*)-**1**, prepared from *N*-*p*-toluenesulfonyl-(*S*)-valine and a 1 M THF solution of BH_3·THF in CH_2Cl_2, while the reaction without THF resulted in a low enantioselection of 28% ee. No deuterium solvent (THF-d_8) effects on the selectivity were observed. Further, no deuterium isotope effects were observed in control reactions using deuterium benzaldehyde (CDO). Thus, the THF molecules in question do not appear to participate in bond-breaking and -forming processes at the transition state, where the selectivity is determined.[7] Therefore, the effects of THF on selectivity might be attributable to the formation of a type of solvent cluster by the coordination of THF molecules around the borane in the reaction. The corresponding reaction in using only THF as the solvent proceeded smoothly to give the aldol product of 82% ee in high yield. This small but significant decrease in selectivity indicates that a large excess of THF disturbs the optimal structure of the solvent cluster slightly. However, THF is clearly a good substitute solvent for CH_2Cl_2 in this aldol reaction. In addition, when sterically bulky ether solvents, which allow free rotation around the C–O–C bond, for example, diisopropyl ether, diphenyl ether, and dibenzyl ether, were used, significant reductions in enantioselectivity were observed (20–30%). THF is the most advantageous solvent for such reactions among these ethers, presumably because of its inherent compact cyclic structure.

Table 1. A typical THF solvent effect in the chiral oxazaborolidinone-promoted asymmetric aldol reaction of benzaldehyde with **2** in the presence of a stoichiometric amount of (*S*)-**1** (Scheme 1)

Entry	Promoter formation conditions	% ee	Yield (%)
1	(*S*)-**1**, prepared from BH_3·THF in CH_2Cl_2	88	76
2	(*S*)-**1**, prepared from BH_3·$S(CH_3)_2$ in CH_2Cl_2	**28**	75
3	(*S*)-**1**, prepared from BH_3·THF in THF	82	85

Control experiments on the proportion of THF to (*S*)-**1** were performed in order to determine the precise quantity of THF required to achieve a high enantioselectivity in the reaction. Unless otherwise noted, the asymmetric aldol reactions described herein were carried out at −78 °C for 3 h under stoichiometric conditions because accurate ratios of the borane–aldehyde complex to THF molecules must be correctly determined.[2] An interesting behavior related to the dependence of enantioselectivity on the quantity of THF present was found in the reaction of benzaldehyde with **2** to give aldol adduct **3**, as shown in Figure 1. Initially, (*S*)-**1** was prepared under THF-free conditions from BH_3·$S(CH_3)_2$ in CH_2Cl_2. Under THF-free conditions, the reaction resulted in a low enantioselectivity of only 28% ee. The complex (*S*)-**1** was prepared in situ with an aliquot of THF added into the starting CH_2Cl_2 solution in each run.[8] When the molar equivalent of THF molecule approached 5, the levels of enantioselectivity became constant at 86–88% ee.

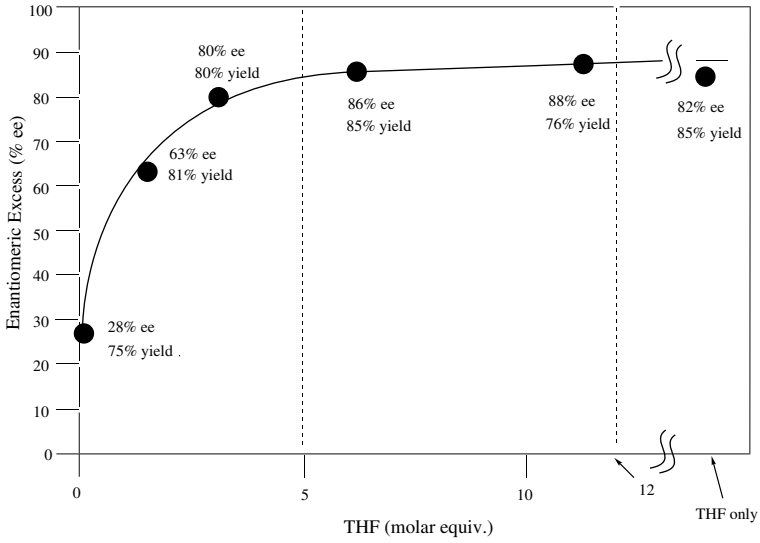

Figure 1. Enantioselectivity as a function of the quantity of THF in the reaction of benzaldehyde with **2** to give aldol adduct **3** (Ref. 8).

Thus, the presence of only a 4–5 M equiv of THF appears to be the critical quantity necessary for satisfying the inherent enantioselectivity. Presumably, this quantity of THF permits the formation of an effective solvent cluster around the chiral borane–aldehyde complex. This interesting dependence of enantioselectivity on THF concentration in the borane-promoted aldol reaction is the first quantitative example indicating the importance of Lewis acid–solvent interactions.

THF molecules clearly surround the chiral oxazaborolidinone–aldehyde complex and might control the efficient approach of a silyl nucleophile to the core center involving a boron atom. At this stage, however, it appeared to be difficult to obtain additional new experimental information concerning the Lewis acid (the borane)–Lewis base (THF) interaction. A computational approach represents an alternative to resolve such an ambiguous problem. Thus, calculations were performed to obtain a rational model for the THF solvent effects. In the calculation, acetaldehyde was used as a model aldehyde in order to reduce the time required for the computation. Two structures (**A** and **B**), optimized in advance, were selected as valid models for the borane (*S*)-1-aldehyde complex, as shown in Figure 2. Structure **A** has been frequently employed to explain the enantioselectivity in our aldol reaction.[1] The facial selectivity is thought to be enhanced by hydrogen bonding of the formyl hydrogen to the ring oxygen[3] and the increasing importance of a cooperative C–H···O interaction of the aldehydic proton (formyl hydrogen) with the oxygen of other substrates also should be considered.[9] Structure **B**, in which a hydrogen bonding between the hydrogen of B–H and the formyl hydrogen is present, was selected as an alternative because it has been calculated to be 3–4 kcal mol^{-1} lower than structure **A** at the B3LYP/6-31G** level by Salvatella and Ruiz-López.[4] Preliminary calculations of the assemblies, consisting of the complexes (**A** or **B**) and one THF molecule, were performed in order to estimate the nature of the interactions of one THF molecule with **A** and **B** at the HF/3-21G* level. As expected, the optimization of the assemblies formed from the complexes (**A** or **B**) and one THF molecule indicates a nucleophilic interaction of the oxygen of THF to the borane-activated carbonyl carbon of the aldehyde. The assemblies are not adequate as a precise model because the nucleophilic interaction of the oxygen atom of one THF molecule to the coordinated carbonyl carbon completely prevents the approach of the silyl nucleophile in the subsequent asymmetric aldol reaction process. On the other hand, the optimization of the assembly formed from **A** and one THF molecule also resulted in the geometry of structure **A′** with a unique additional hydrogen bonding of the formyl hydrogen to the oxygen of THF where the length of the hydrogen bonding is 2.096 Å.

An assembly was computed as spatially plausible model, consisting of the borane–aldehyde complex **A** and four THF molecules in ascertaining the minimal structure of the THF cluster around the complex at the B3LYP/6-31G** level. The optimized geometry is clearly demonstrated by the important interatomic distances in Figure 3. In the geometry, four THF molecules surround the borane–aldehyde complex. Two THF molecules (THF #3 and THF #4) are located above the top side of the oxazaborolidinone ring with a low stabilization energy of 2–3 kcal mol^{-1}. One THF molecule (THF

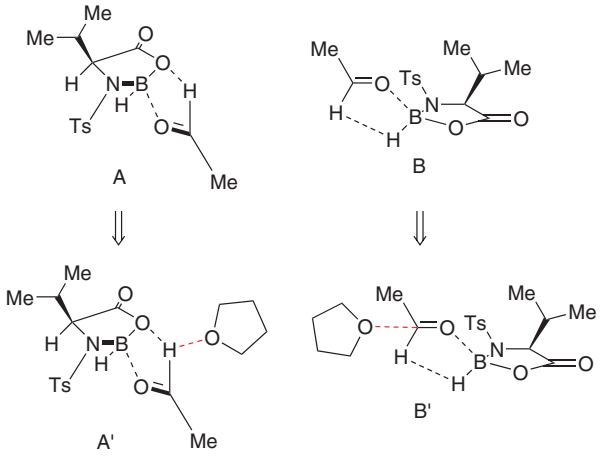

Figure 2. Complex **A** is our model leading to a satisfactory explanation of the stereochemical outcome in the asymmetric reaction. An alternative complex **B** is the Ruiz-López model having the lowest binding energy in a simplified system. The geometry of the assemblies **A′** and **B′** from the complexes (**A** and **B**) and one THF molecule was obtained by preliminary HF/3-21G* calculations.

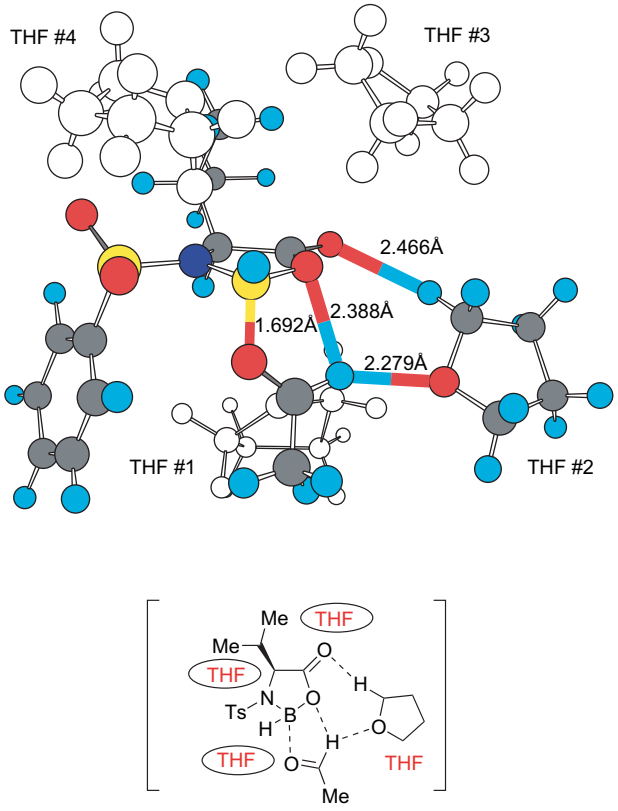

Figure 3. The geometry optimized from the oxazaborolidinone–acetaldehyde complex and four THF molecules by a B3LYP/6-31G** set and intermolecular hydrogen-bonding interactions.

#1) is present within a cavity formed by the ring substituents at the bottom side and blocks the approach of the silyl nucleophile leading to the opposite facial selectivity. The stabilization energy of borane–aldehyde complex and this THF was calculated to be 8 kcal mol^{-1}. The most important THF molecule (THF #2) is situated to the right of the borane–aldehyde complex with a high stabilization energy of 8 kcal mol^{-1}. As expected, this THF molecules (THF #2) plays a specific role in the enatioselectivity. The originally assumed hydrogen bonding between the formyl hydrogen and the ring oxygen of the complex was exactly reproduced and the bond length was found to be 2.388 Å. Furthermore, an additional and interesting intermolecular interaction between the formyl hydrogen and the oxygen of THF was found to be 2.279 Å, which is shorter than the former one. This suggests that the newly found hydrogen bonding is stronger. The structure is additionally stabilized by the additional interaction between the carbonyl oxygen of the complex and one of THF hydrogens (2.466 Å). These H···O distances are well below the sum of the van der Waals radii of 2.72 Å (H = 1.20 Å and O = 1.52 Å).[10] Thus, the resulting assembly is electrostatically stabilized by three cooperative C–H···O hydrogen bonding interactions along with the original Lewis acid–base interaction. The THF molecule (THF #2) occupying such a position might be able to play a role in controlling the approach of the silyl nucleophile. That is to say, the front-side space formed by the borane–aldehyde complex and the THF molecule would be maintained at the sequential transition state assembly suitable for achieving a high enantioselectivity. The THF cluster model obtained is consistent with the experimental results presented above.

In conclusion, the use of 4–5 equiv of THF molecules at the stage of oxazaborolidinone-catalyst formation was found to be essential for satisfying the enantioselectivity in oxazaborolidinone-promoted asymmetric aldol reactions of aldehydes with silylketene acetals. The solvent participates stereochemically in the tuning of an optimal chiral field at the active site. A spatially plausible model for the assembly of the borane–aldehyde complex with four THF molecules was calculated and resulted in a rational interpretation of the experimentally observed THF solvent effects. This modeling study in searching for the role of the THF solvent in question is an example that justifies the utility of ab initio calculations in determining the nature of such solvent effects in considering reactivity and selectivity in various types of reactions involving Lewis acids.

Method of calculation: The calculations were performed with a Gaussian 98 rev. A.11, using the HF and B3LYP methods with 3-21G* and 6-31G** basis sets for geometry optimizations.[11]

Acknowledgements

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8. Experimental procedure: To a solution of *N*-*p*-toluenesulfonyl-(*S*)-valine (326 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added an aliquot of THF (0.1, 0.2, 0.5, and 1.0 mL). A 1 M solution of $BH_3{\cdot}S(CH_3)_2$ in CH_2Cl_2 (1.0 mL, 1.0 mmol) was added over 5 min at 0 °C and the resulting solution was stirred for 30 min. At −78 °C, benzaldehyde (1 mmol, 0.5 mL of a CH_2Cl_2 solution) and silylketene acetal **2** (1 mmol, 0.5 mL of a CH_2Cl_2 solution) were

successively added and the reaction mixture was then stirred for 3 h. After the usual workup, the aldol adduct **3** was obtained in high yields (80–90%). The % ee was determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column.

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