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Solvent effects on the diastereoselection in $LiAlH_4$ reduction of α-substituted ketones

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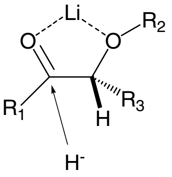
ABSTRACT

Based on high-level DFT calculations including solvent molecules, it was found that steric effects of solvent may be responsible for the diastereoselection in $LiAlH_4$ reduction of acyclic ketones substituted by an oxygen-containing functional group at the α-position to the carbonyl. It was concluded that the conventional chelated transition state models lead to the predominance of the R^*,S^*-diastereoisomers against experimental observation.

π-Facial diastereoselective hydride reduction of ketones is one of the most important reactions in organic synthesis. The origin of π-facial diastereoselection has been the subject of intense debate for half a century and still remains a controversial issue.[1–17] Although our previously developed EFOE model successfully predicted the correct stereoselectivity of $LiAlH_4$ reduction of cyclic ketones,[7,9,18–22] comprehensive understanding of the π-facial diastereoselection in acyclic ketone is still needed. In this Letter, we report theoretical investigation on the origin of π-facial diastereoselection of some acyclic ketones.

It has long been known that most $LiAlH_4$ reduction of acyclic ketones substituted by σ-electron-withdrawing substituents, such as an oxygen-containing functional group at α-position, gives predominant R^*,S^*-diastereoisomer products.[23,24] Nelson et al. proposed the chelated transition state model **1** by extending the Cram rule[23,25] and described the course of the reduction which leads to the R^*,S^*-diastereoisomers.[24]



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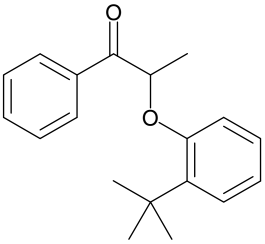
On the other hand, it is also known that in the case of large substituents, such as 2-*o*-*tert*-butylphenoxylpropanone (**2**), R^*,R^*-diastereoisomers are predominant product (more than 99%).[24]



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Nelson et al. explained that the reversion of diastereoselection might be the result of destablizing the chelated transition state because of the steric hindrance of large substituents. Here, to verify the Nelson's proposal, we have located the transition state structure of $LiAlH_4$ reduction of ketone **2** by DFT method.[26] For the sake of simplicity, we deal with one enantiomer of **2** in following calculations, in which the configuration of the α-carbon is *R*. To calculate correct selectivity for both sides of the diastereo-face all conformers of the transition states are fully located. Table 1 shows the relative stability of all these transition state structures.

Seven conformers of *Re*-face attack (give R^*,S^*-diastereoisomer) and eight conformers of *Si*-face attack (give R^*,R^*-diastereoisomer) are located. In each face, most stable conformer **a-1** or **b-1** is a chelated structure (Fig. 1).

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Table 1
Relative stability of possible transition states in LiAlH$_4$ reduction of (*R*)-2-*o*-*tert*-butylphenoxylpropanone[a]

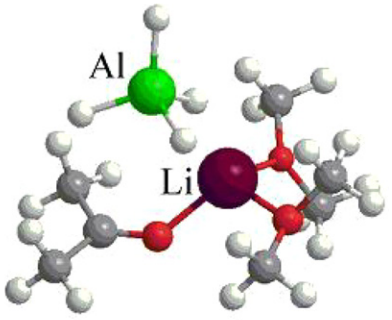
TS	Facial selection	Rel. E^{b} (kcal mol^{-1})	Population[c] (%)
a-1	*Re*-face	0.00	99.96
b-1	*Si*-face	4.68	0.04
c-1	*Si*-face	6.45	0.00
d-1	*Si*-face	7.04	0.00
e-1	*Re*-face	8.36	0.00
f-1	*Re*-face	8.77	0.00
g-1	*Si*-face	8.98	0.00
h-1	*Si*-face	9.34	0.00
i-1	*Re*-face	9.39	0.00
j-1	*Si*-face	11.73	0.00
k-1	*Si*-face	12.07	0.00
l-1	*Re*-face	12.12	0.00
m-1	*Re*-face	12.26	0.00
n-1	*Si*-face	13.20	0.00
o-1	*Re*-face	13.55	0.00

[a] All transition state structures were located at the B3LYP/6-31+G(d) level.
[b] All energies were ZPE-corrected.
[c] Ratios of TSs were calculated assuming the Boltzmann distribution at 25 °C.

Table 2
Calculated relative energy of possible initial complexes in LiAlH$_4$ reduction of acetone[a]

Initial complexes	Number of coordinating dimethyl ether	Rel. E^{b} (kcal mol^{-1})
a-2	0	18.56
b-2	1	4.86
c-2	2	0
d-2	3	0.38

[a] B3LYP/6-31+G(d)//B3LYP/6-31+G(d).
[b] All energies were ZPE-corrected.



c-2

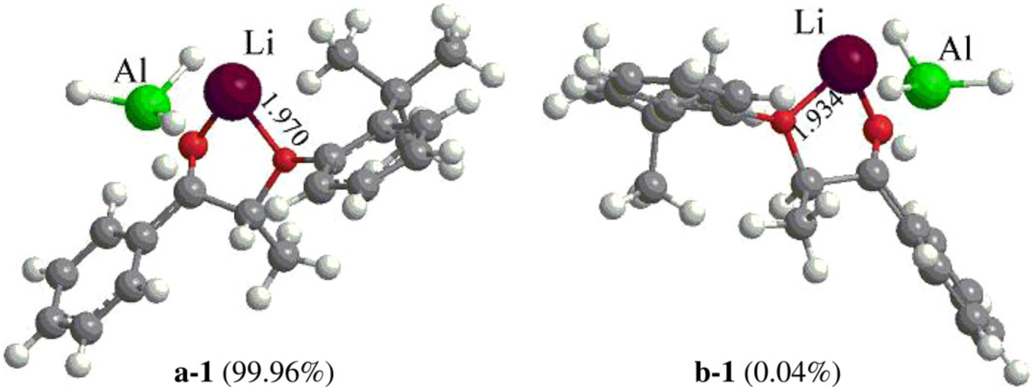
Figure 2. Most stable initial complex structure in LiAlH$_4$ reduction of acetone.

The *Re*-face-attack chelated transition state structure **a-1** is highly stable compared with other structures and calculated diastereoselectivity is 99.96% *Re*-face attack. It is completely opposite to the experimental diastereoselectivity (more than 99% *Si*-face attack), showing that Nelson's hypothesis is not correct.

To this end, we consider the possibility that solvent effect might affect the diastereoselectivity of LiAlH$_4$ reduction. It is well known that lithium ion is a strong Lewis acid, and solvates very well in polar solvents. LiAlH$_4$ reduction is mainly performed in ethereal solvents such as diethyl ether or tetrahydrofuran, so ethereal oxygen should coordinate to lithium atom of LiAlH$_4$. In spite of this possibility that solvent molecules may play important role, there have been few theoretical studies that deal with solvent molecule in an explicit way. However, some studies of stereoselectivity have recently pointed out the importance of the solvent coordination to the reagent or reactant,[27,28] and in 2005 Estrin et al. performed QM-MM simulations for the system which includes LiAlH$_4$ and dimethyl ether explicitly and obtained the result that dimethyl ether oxygen coordinates at the lithium of LiAlH$_4$ in stationary point.[29] Herein we propose the possibility that solvent molecules coordinated at lithium might prevent chelation of the phenoxyl oxygen in LiAlH$_4$ reduction of ketone **2**. To verify this hypothesis, we first located possible forms of initial complexes in LiAlH$_4$ reduction with explicit inclusion of dimethyl ether. Acetone was used as a simple substrate. We calculated the energy of optimized initial complex structure varying the number of dimethyl ether molecules coordinating at the lithium, and adding the energy of individual dimethyl ether properly so that each system has the same number of dimethyl ether. Table 2 shows the relative energy of possible initial complexes. We found that the structure with two dimethyl ether molecules **c-2** (Fig. 2) is most stable.

From this result, we conclude that in dimethyl ether solvent most predominant initial complex of LiAlH$_4$ reduction is the structure in which two dimethyl ether molecules coordinate lithium ion. Consequently, it is necessary to consider the transition state structure in which two dimethyl ether molecules coordinate to lithium ion when we discuss diastereoselectivity. So we have again located all the transition state structures of LiAlH$_4$ reduction of (*R*)-2-*o*-*tert*-butylphenoxylpropanone with two dimethyl ether molecules at the lithium. The results are shown in Table 3.

Ten conformers are located in each diastereofacial process. The most stable transition state structure **a-3** arises from *Si*-face attack and it is not a chelated structure (Fig. 3). The calculated diastereoselectivity is 98.7% *Si*-face attack in excellent agreement with experiment. It is concluded that the structures in which the phenoxyl oxygen faces the lithium (**k-3**, **l-3**, **m-3**, **n-3**, **o-3**, **p-3**, **q-3**, **t-3**) are not chelated structures and thereby not stable compared



a-1 (99.96%) **b-1** (0.04%)

Figure 1. Most stable transition state structures of *Re*-face attack (**a-1**) and of *Si*-face attack (**b-1**) (bond lengths are in Å).

Table 3
Thermodynamic stability of possible transition state structures in $LiAlH_4$ reduction of (*R*)-2-*o*-*tert*-butylphenoxylpropanone in which lithium is coordinated by two dimethyl ether[a]

TS	Facial selection	Rel. E^b (kcal mol^{-1})	Population[c] (%)
a-3	*Si*-face	0.00	66.26
b-3	*Si*-face	0.44	31.34
c-3	*Re*-face	2.69	0.69
d-3	*Si*-face	3.03	0.39
e-3	*Si*-face	3.07	0.36
f-3	*Re*-face	3.19	0.30
g-3	*Re*-face	3.48	0.18
h-3	*Si*-face	3.51	0.17
i-3	*Si*-face	3.85	0.10
j-3	*Re*-face	3.98	0.08
k-3	*Re*-face	4.40	0.04
l-3	*Si*-face	4.40	0.04
m-3	*Si*-face	4.48	0.03
n-3	*Si*-face	4.97	0.01
o-3	*Re*-face	5.60	0.00
p-3	*Re*-face	5.73	0.00
q-3	*Re*-face	6.61	0.00
r-3	*Re*-face	6.89	0.00
s-3	*Re*-face	7.02	0.00
t-3	*Si*-face	8.58	0.00

[a] All transition state structures were located at the B3LYP/6-31+G(d) level.
[b] All energies were ZPE-corrected.
[c] Process ratios of TSs were calculated assuming Boltzmann distribution at 25 °C.

with other conformers in which the phenoxyl oxygen faces opposite to the lithium. It is presumed that steric repulsion between dimethyl ether and large *o*-*tert*-butylphenoxyl group prevents chelation of phenoxyl oxygen with lithium from Figure 3, demonstrating the validity of our proposal.

To prove the appropriateness of the transition state structures in which two dimethyl ether molecules coordinate lithium, we must demonstrate that it can explain the case where the α-substituents are small and diastereoselectivity is R^*,S^* predominant. For this purpose, we then performed the same calculation which uses the transition state structure with two dimethyl ether coordinate lithium about $LiAlH_4$ reduction of (*R*)-2-methoxyphenylpropanone (**3**), the substituent of which is a small methoxyl group and another structure is the same as that of (*R*)-2-*o*-*tert*-butylphenoxylpropanone (**2**). Relative stability of all possible transition structures is summarized in Table 4.

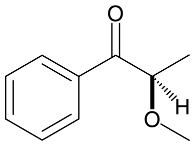


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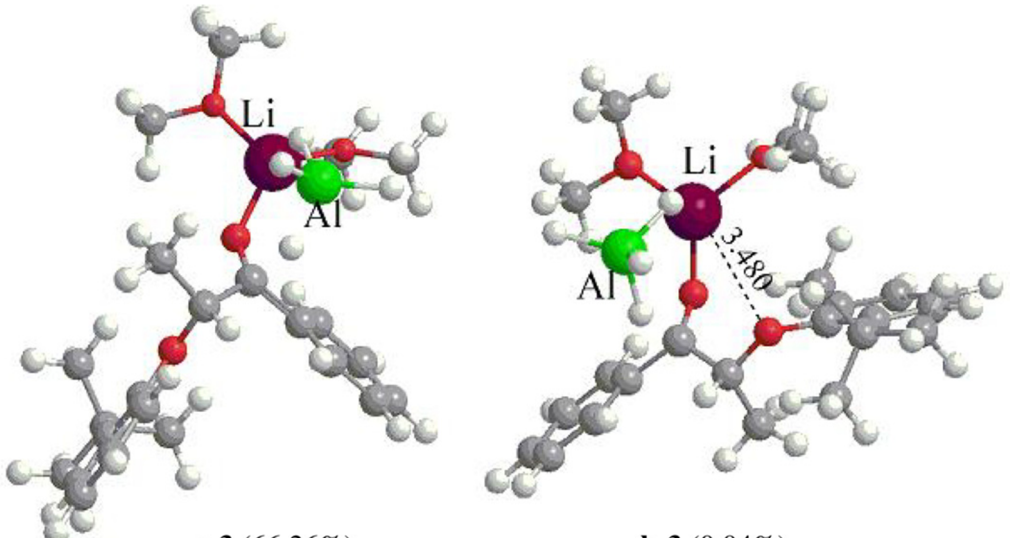
Table 4
Thermodynamic stability of possible transition state structure in $LiAlH_4$ reduction of (*R*)-2-methoxyphenylpropanone in which lithium is coordinated by two dimethyl ether[a]

TS	Facial selection	Rel. E^b (kcal mol^{-1})	Population[c] (%)
a-4	*Re*-face	0.00	64.6
b-4	*Re*-face	0.52	26.9
c-4	*Si*-face	1.69	3.70
d-4	*Si*-face	2.21	1.52
e-4	*Si*-face	2.25	1.41
f-4	*Si*-face	2.58	0.81
g-4	*Si*-face	3.01	0.39
h-4	*Re*-face	3.42	0.19
i-4	*Re*-face	3.53	0.16
j-4	*Si*-face	3.65	0.13
k-4	*Re*-face	3.97	0.07
l-4	*Si*-face	4.03	0.07
m-4	*Re*-face	4.24	0.04
n-4	*Si*-face	5.13	0.01
o-4	*Re*-face	5.74	0.00
p-4	*Re*-face	6.18	0.00
q-4	*Re*-face	6.24	0.00
r-4	*Re*-face	6.38	0.00
s-4	*Si*-face	6.96	0.00
t-4	*Si*-face	7.23	0.00

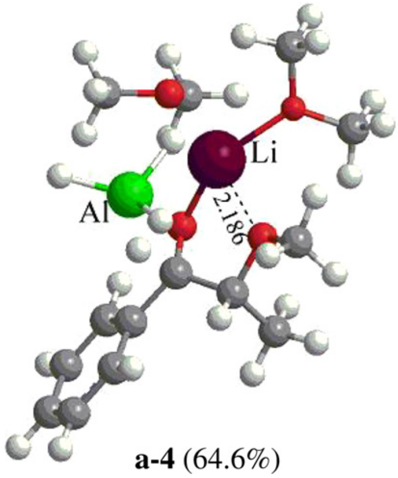
[a] All transition states structure were located at the B3LYP/6-31+G(d) level.
[b] All energies were ZPE-corrected.
[c] Process ratios of TSs were calculated assuming Boltzmann distribution at 25 °C.

Ten conformers are located in each diastereofacial process. The most stable structure **a-4** arises from *Re*-face-attack chelated structure (Fig. 4). It is suggested that when substituents are small, steric hindrance between solvents and substituents is also small and chelated structure can be stabilized. The calculated diastereoselectivity is 91.9% *Re*-face attack in good agreement with the experi-



a-3 (66.26%) **k-3** (0.04%)

Figure 3. Most stable transition state structures (**a-3**) and the structure in which the phenoxyl oxygen does not interact with lithium (**k-3**) (bond lengths are in Å).



a-4 (64.6%)

Figure 4. Most stable transition state structure (**a-4**) in $LiAlH_4$ reduction of (*R*)-2-methoxyphenylpropanone (bond lengths are in Å).

mental data[30] (93% *Re*-face-attack diastereoselectivity). From these results, it can be stated that the transition-state structure model in which two dimethyl ether molecules coordinate lithium can explain the diastereoselectivity in $LiAlH_4$ reduction of a series of acyclic ketones which are substituted for by oxygen-containing functional groups.

In conclusion, we have shown that the diastereoselectivity of $LiAlH_4$ reduction of acyclic ketone substituted for by oxygen-containing functional groups is influenced by the steric effect of solvent molecules which coordinate lithium. Comprehensive studies about reductions of various other acyclic ketones will be disclosed in a later paper.

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