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# Theoretical Studies on Reductive Etherification Reactions between Aromatic Aldehydes and Alcohols

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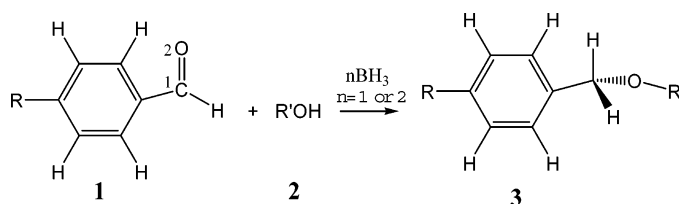
The mechanism of reductive etherification reactions between aromatic aldehydes and alcohols has been investigated with the DFT(B3LYP)/6-31G* method. One or two BH_3 molecules have been used to simulate the role of the catalyst and reducing agent. The solvent effects of the title reactions have been studied by the PCM model. It is found that the reactions between aromatic aldehydes and primary, secondary, and tertiary alcohols can proceed more easily in a polar solvent such as acetonitrile. The results provide evidence in theory to broaden the applications of reductive etherification reactions for the optimization of the radiochemical synthesis process of ^{18}F-labeled ether radiotracers.

Introduction

Interest on the research and applications of ^{18}F-labeled radiotracers for Positron Emission Tomography (PET) imaging agents is growing very fast nowadays. Because of the short half-life of [18]F ($T_{1/2} = 110$ min), it is highly desirable that the total time for radiotracer production, including all radiosynthetic steps, is as short as possible. In the literature, a three-step procedure was reported to synthesize a 4-fluorobenzyl ether with biological interests from ^{18}F-labeled fluorobenzaldehyde.[1,2] Recently, a series of studies on the application of decaborane as a catalyst and a mild, quite stable reducing agent in methanol have been published, for example, reductive reactions of aldehydes,[3a] ketones,[3b,c] carbonyls,[4] nitrobenzenes,[5] al-

kenes and alkynes,[6] anilines,[7] and azides,[8] and deprotection of ethers[9a,b] and acetals.[9c] It is reported that the reductive etherification of aromatic aldehydes with decaborane ($B_{10}H_{14}$) in methanol or ethanol is an efficient way to synthesize the corresponding ethers. But such reactions could only be used to synthesize simple compounds ($R = CH_3$, C_2H_5 in Scheme 1) and performed in neat alcohols acting as reactant as well as solvent.[3a] This may be a disadvantage in special cases. In our previous paper,[10] it is reported that the reactions between 4-fluorobenzaldehyde and primary, secondary, and tertiary alcohols with decaborane can proceed in acetonitrile,

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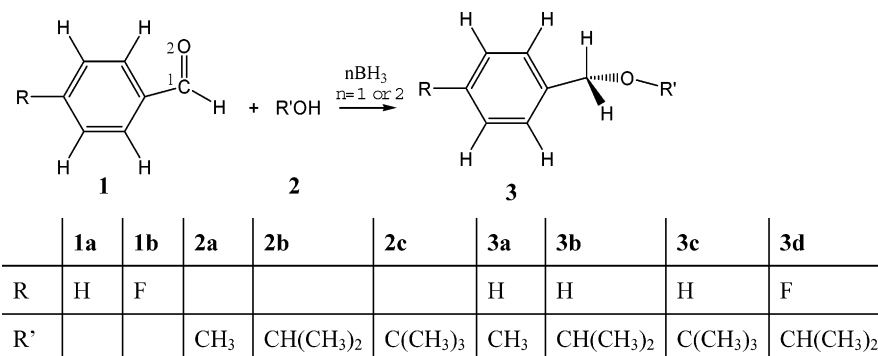[‡] Institute of Interdisciplinary Isotope Research.

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SCHEME 1

	1a	1b	2a	2b	2c	3a	3b	3c	3d
R	H	F				H	H	H	F
R'			CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	CH_3	$CH(CH_3)_2$	$C(CH_3)_3$	$CH(CH_3)_2$

which provides the possibility to synthesize ^{18}F-labeled fluorobenzyl ether with biological interests from 4-[^{18}F]-fluorobenzaldehyde in one step. Moreover, solvents have many effects on the reactions. Although several experimental investigations have been reported, the whole picture of the mechanism for the title reaction is still unclear. Therefore, theoretical studies based on density functional theory (B3LYP) are presented in this paper, which include the location of the possible stationary points along the title reaction paths. In addition, the substituent and solvent effects of the title reactions have also been investigated. The reactions studied are shown in Scheme 1.

Method of Calculation

Density functional calculations are carried out for reductive etherification reactions between aromatic aldehydes and alcohols. The geometries of reactants, products, complexes, intermediates, and transition structures have been fully optimized. All the geometric parameters of the possible stationary points have been located at the B3LYP/6-31G* level and characterized by the number of imaginary vibrational frequencies. As one of referees mentioned about the influence of larger basis sets, we have also performed some single-point calculations at the B3LYP/6-311++G** level. The obtained results show the differences of the relative energies are 2−3 kcal/mol for most of the species and the maximum is only about 5 kcal/mol. Therefore, the 6-31G* basis set is reasonable for the present reaction mechanism study. The solvent effects of the title reactions have been performed with the PCM model[11] with acetonitrile (dielectric constant $\epsilon = 36.64$) or tetrahydrofuran (dielectric constant $\epsilon = 7.58$) as solvent at a temperature of 298 K. One or two borane BH_3 molecules have been used to simulate the roles of decaborane both as the catalyst and as the reducing agent. For all the reactions, only single-point SCRF calculations have been performed with B3LYP/6-31G* geometries. The relative energies of all stationary points in the gas phase are corrected with zero-point vibrational energies. The bonding characters have been investigated with QTAIM theory.[12] All calculations included in this work have

been performed with the Gaussian 98 program package[13] and the AIM2000 program.[14]

Results and Discussions

All the possible stationary points along the reaction paths have been located and verified. The atomic numbering systems of the possible stationary points are shown in Scheme 2 and Figure S1 in Supporting Information (more detailed information). The full geometric parameters are listed in Table S1 in Supporting Information. It is clear that the title reaction has two distinctive steps, i.e., the addition (from reactants to **INT1a2**) and reduction processes (from **INT1a2** to product **3a**), as shown in Scheme 2 for the **1a** + **2a** + 2BH$_3$ case. The following paragraphs will discuss the steps separately in more detail.

Addition Process. In this process, three possible cases were considered, i.e., one BH_3 molecule, two BH_3 molecules, and without the BH_3 molecule. When one BH_3 molecule approaches benzaldehyde **1a**, a complex **COM1a1** (The final "1" means one BH_3 molecule) is formed first, in which the B−O2 bond distance is 1.61 Å. At the same time, the bond length of C1−O2 is changed to 1.24 Å in **COM1a1** from 1.22 Å in reactant **1a**. That is to say, the interaction between the B atom of catalyst BH_3 and O2 of benzaldehyde increases the C1−O2 bond strength. The attack of O3 in **2a** on C1 in **COM1a1** becomes easier. **TS1a1** has a four-member-ring structure, with the bond lengths of C1−O2, C1−O3, O2−H4, and O3−H4 being 1.38, 1.59, 1.33, and 1.18 Å, respectively, indicating that the bond strength of C1−O2 is further weakened and the single bond C1−O3 is almost formed. If two molecules of BH_3 are considered, the bond length of B−O2 in complex **COM1a2** is only 1.55 Å, 0.06 Å shorter than that in one BH_3 case. And the bond length

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SCHEME 2.   Typical Catalytic Model with Two BH₃ Molecules[a]
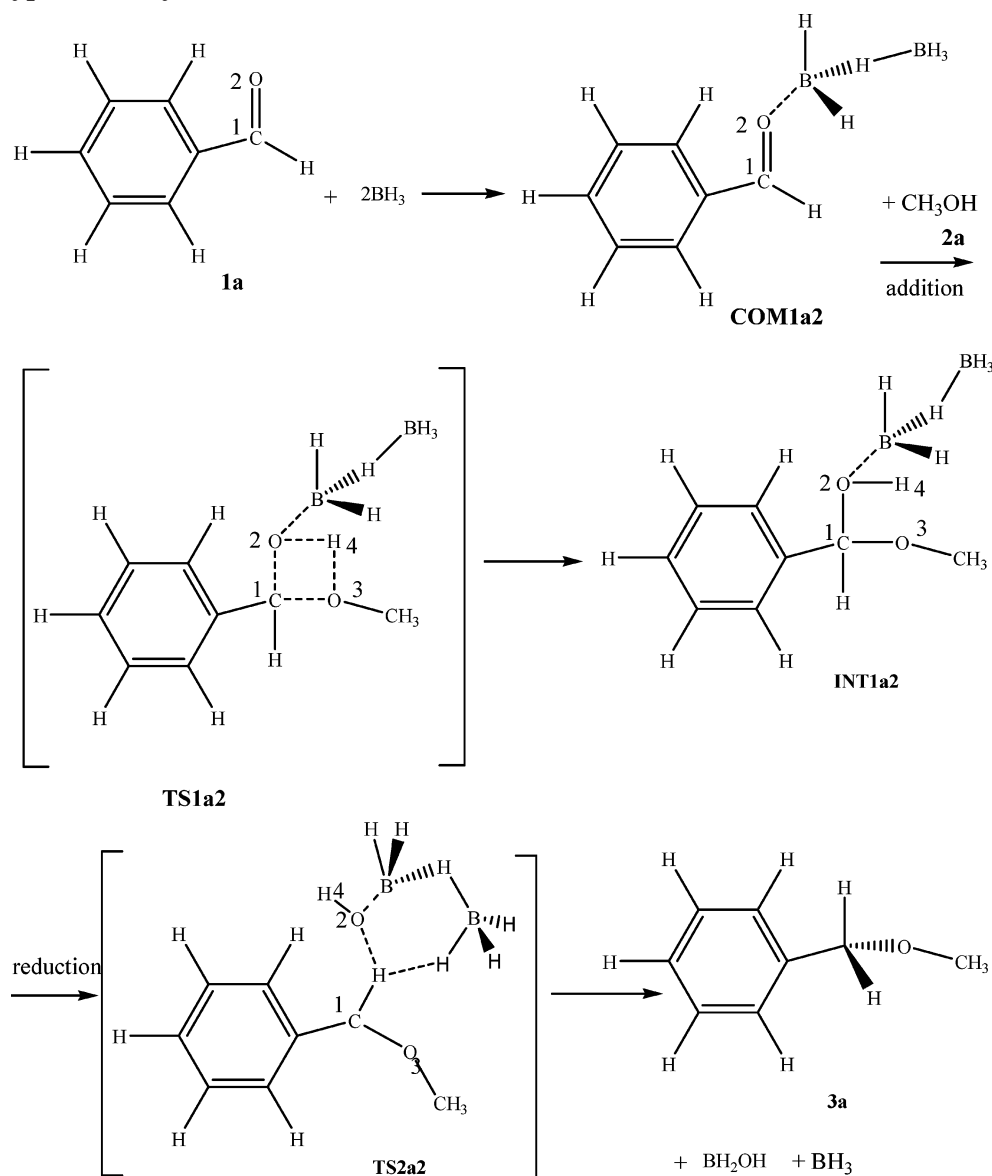
[a] The final "2" in the compound identifiers indicates two BH₃ moieties.

of C1−O2 is 0.03 Å longer than the corresponding bond length in the original reactant. It is interesting that there exists the bonding of B−H−B in **COM1a2**, and the bond lengths of two B−H bonds are 1.27 and 1.37 Å, respectively. As we know, there are four hydrogen atoms involved in the electron-deficient three-center bonding of B−H−B in the structure of $B_{10}H_{14}$, which is relatively loose and might be the active center of the catalyst. There is no direct evidence from the experiments that the catalytic role of $B_{10}H_{14}$ is dependent on the whole molecule or on one or more of its decomposition products. Therefore, in this paper, we only chose one or two BH₃ molecules to mimic the catalytic and reductive roles. In fact, we also considered the B_2H_6 as catalyst first, but there are two B−H−B bonds, one of which must be broken before it could form a complex with benzaldehyde (comparing the structure of **COM1a2**). And the energy of B_2H_6 is about 36.4 kcal/mol (with zero-point energy, ZPE) below that with two BH₃ molecules, even the energy

of **1a** + B_2H_6 is 5.4 kcal/mol (with ZPE) lower than that of **COM1a2**, so we adopt the two-BH₃ model in the present study. The bond lengths of C1−O2, C1−O3, O2−H4, and O3−H4 in **TS1a2** are 1.40, 1.53, 1.32, and 1.23 Å, respectively, slightly different from those in the one-BH₃ case, but quite different from those without catalyst. As shown in Figure 1, the bond distance of C1−O3 in **TS1a0** (without catalyst BH₃) is 0.2 or 0.26 Å longer than that in **TS1a1** or **TS1a2**, and the bond length of C1−O2 is shorter than the corresponding one in **TS1a1** and **TS1a2**, which shows that **TS1a0** is more reactant-like.

The potential energy profile for this process is shown in Figure 2, from which one can clearly see that the energy of **TS1a0** is about 32 kcal/mol above the sum of the energies for the reactants. Such a high energy barrier is very difficult to overcome at the real experimental conditions. For the one-BH₃ molecule to mimic the catalytic effect, the energy of **TS1a1** is only about 12 kcal/mol above those of the reactants, but for the two-BH₃
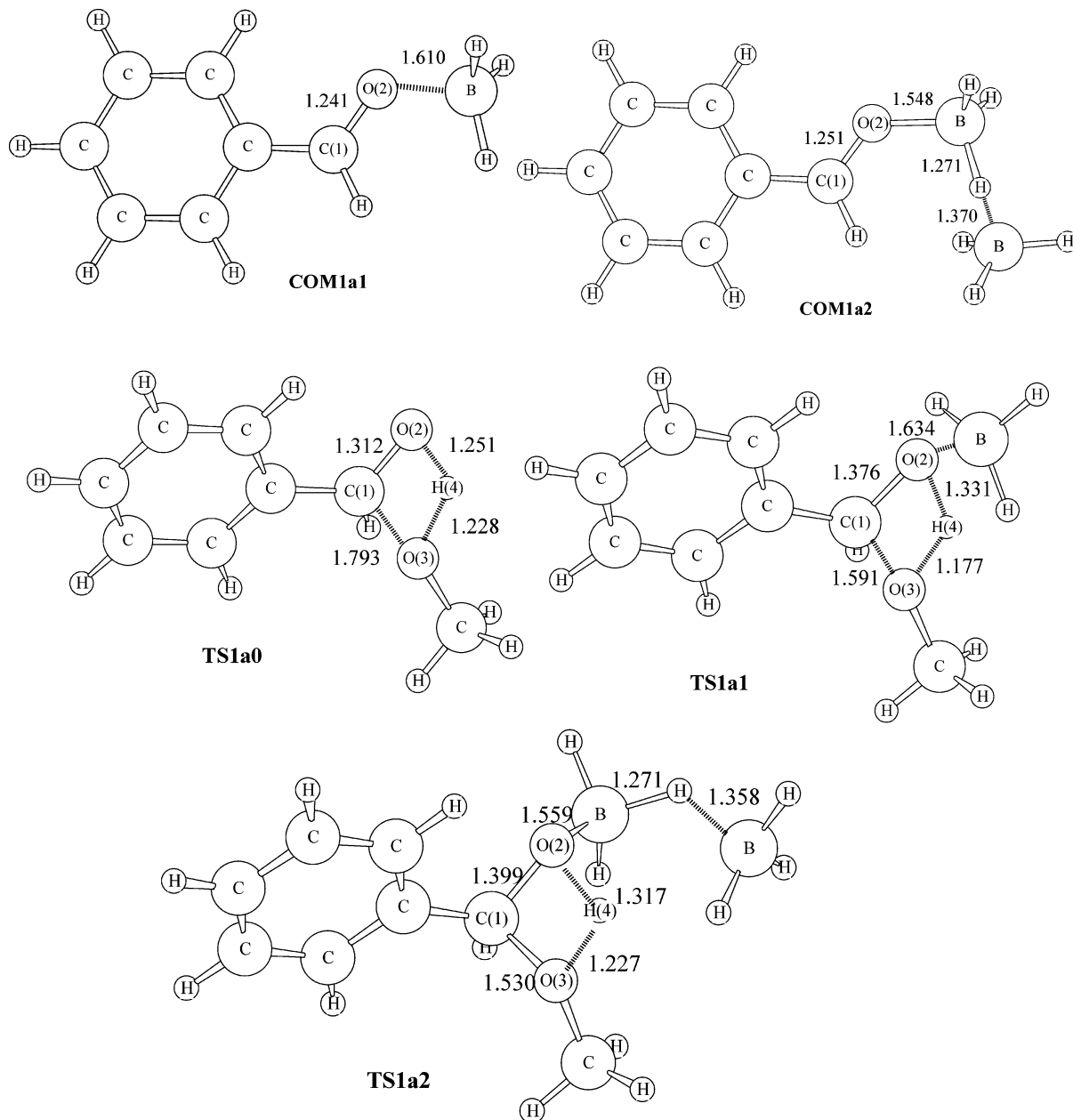
FIGURE 1. The chief geometrical parameters (bond length in Å) for some optimized stationary points of the reductive etherification reactions between benzaldehyde (**1a**) and methanol (**2a**).

case, the energies of all of the possible stationary points are well below the reactant's asymptote. As stated before, because the two-BH_3 model could represent the role of $B_{10}H_{14}$, the following discussion will focus on the results of this two-BH_3 model. In addition, the reaction without BH_3 might stop at **INT1a0** (hemiacetal) because there is no H atom for the reduction process.

   Reduction Process. In general, **INT1a2** should be broken into two pieces of $[OHBH_2-H-BH_3]^-$ and PhCH-$(OCH_3)^+$, but extensive search on this reaction path can only find a transition state **TS2a2** whose imaginary vibration frequency is only $-98i$ cm^{-1}. However, the structure of **TS2a2** shown in Figure 3 seems somewhat unusual. There are three hydrogen–hydrogen bonds and one C–H···O bond in **TS2a2** because there exist bond critical points (see red dots in Figure 3). The electron

densities ρ_b for those dihydrogen bonds at critical points are about 0.01 au, whereas that of the C–H···O bond is 0.02 au. The distances of C1–O2 and C1–H16 bonds are 2.83 and 2.78 Å, respectively, but no bond critical points could be found between these two pairs of atoms. Therefore, the C1–O2 bond in **INT1a2** is completely broken before **TS2a2**, but hydrogen transfer takes place mainly after **TS2a2**, which is verified by the IRC calculation. From Figure 4a, one can realize that the bond length of B15–H16 is mainly changed after $s = 10\sqrt{amu\cdot bohr}$, which leads to the energy change along IRC (Figure 4b) becoming more steep after $s = 10\sqrt{amu\cdot bohr}$. IRC calculation also confirmed that **TS2a2** is indeed connected with **INT1a2** and **3a** + BH_2OH + BH_3 (see Figure 4b). As the distance between C1 and O2 increases, the weaker interactions, such as hydrogen–hydrogen bonding and
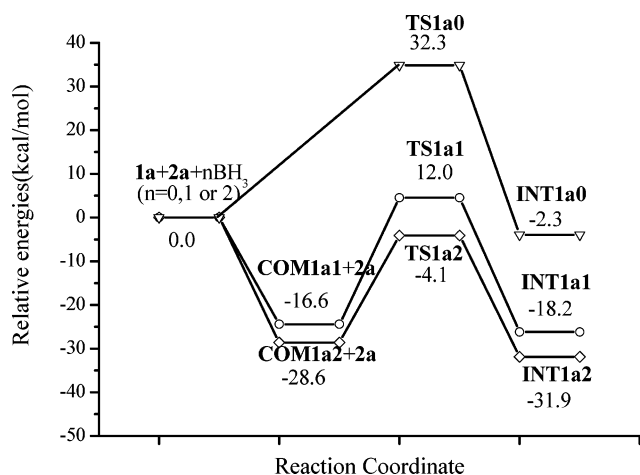
FIGURE 2. The schematic potential energy surface for the addition process under the gas phase (with zero-point energy correction).
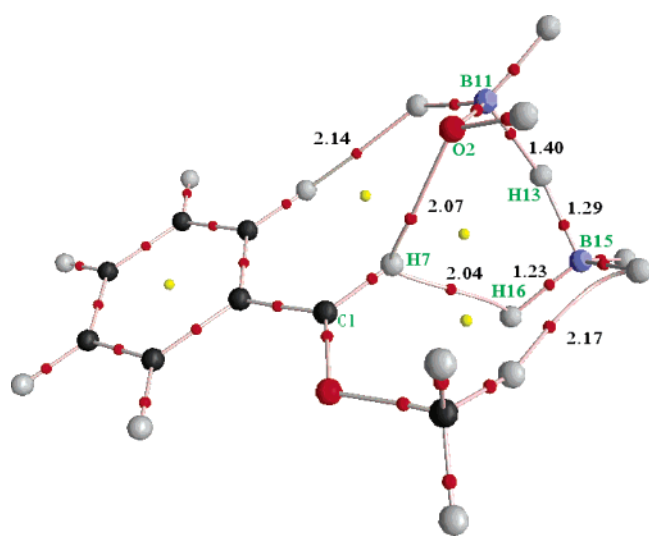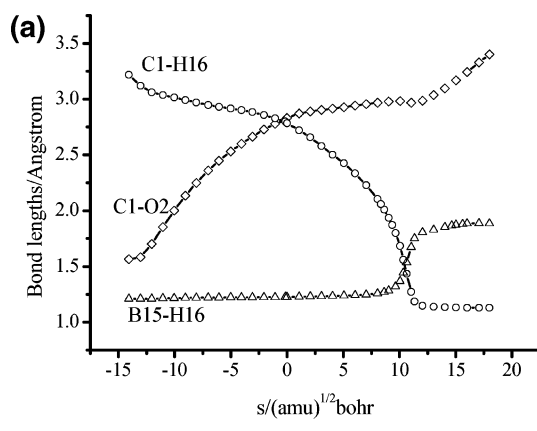

FIGURE 3. Molecular graphs for **TS2a2**, together with the main geometric parameters. Bond and ring critical points are denoted by red and yellow dots, respectively.

C−H···O bonding, will disappear, and the bonding between C1 and H16 will set up. The reaction will stop when the proton H16 is transferred completely from the

HOBH$_3$BH$_3$ fragment to C1 in the PhCHOCH$_3$ fragment. Mulliken population indicates that the charge of the PhCHOCH$_3$ part in **TS2a2** is +0.83e, as it is of zwitterions. As the formation of **INT1a2** releases energy of 32 kcal/mol in the first step, it is not difficult to overcome the energy barrier of 16 kcal/mol for this step. We have also examined the energies of [HOBH$_3$BH$_3$]$^-$ and PhCH-(OCH$_3$)$^+$, and found that they are about 19 or 7.7 kcal/mol (in acetonitrile) higher than those of **INT1a2** and **TS2a2**, respectively, so the present mechanism involving **TS2a2** should be reasonable.

The Solvent Effect. The solvent effect of the present reaction has been investigated by the PCM model with tetrahydrofuran and acetonitrile as solvents, which have been used in the experimental exploration. According to our previous experience,[15] the geometric optimization will not change the relative energy obviously (usually less than 2 kcal/mol), so only single-point SCRF calculations have been performed with B3LYP/6-31G* geometries. The schematic description of the potential energy surface for **1a** + **2a** + 2BH$_3$ is given in Figure 5, together with
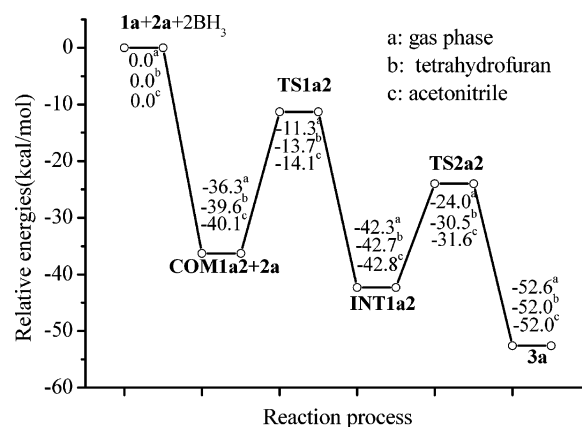

FIGURE 5. Schematic description of the potential energy surface of **1a** + **2a** + 2BH$_3$ (without ZPE).

the values in the gas phase without ZPE corrections. From Figure 5, one can see that acetonitrile and tetrahydrofuran solvents lower the energies of **COM1a2**, **TS1a2**, and **TS2a2** about 2−7 kcal/mol, but they do not change the stabilities of **INT1a2** and **3a**, so the solvents accelerate the reduction process. For example, the energy
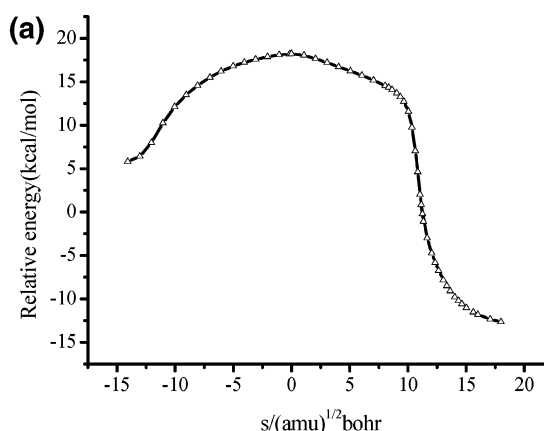

FIGURE 4. (a) The changes of the main geometric parameters along the IRC; (b) energy profile of the step from INT1 (hemiacetal) to the product (benzyl ether).
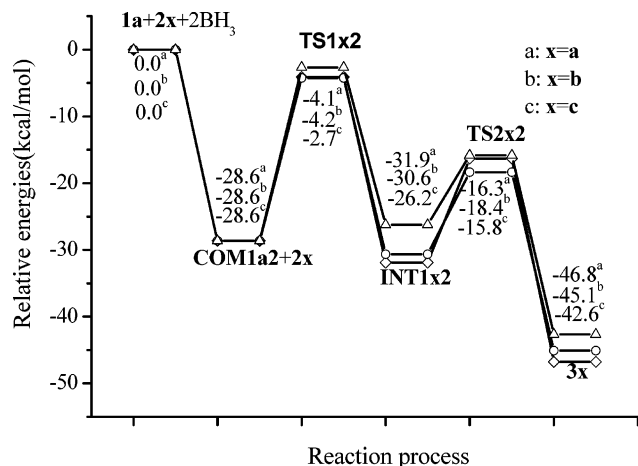
FIGURE 6. Schematic description of the potential energy surfaces for the reactions **1a** + **2a**, **1a** + **2b**, and **1a** + **2c** in the gas phase.

barrier from **INT1a2** to **3a** is 18 kcal/mol in the gas phase, but it becomes 11 kcal/mol in acetonitrile solution. Because the dipole moments of **TS2a2** are 11.4 (in the gas phase) and 13.6 D (in acetonitrile), respectively, the polar solvent lowers its energy. At the same time, the solvent also changes the charge distribution. The charge of the $PhCHOCH_3$ part in **TS2a2** becomes +0.87e from +0.83e (in the gas phase).

Substituent Effects. At fist, we thought that a more crowded alcohol, such as *tert*-butyl alcohol, could not react with benzaldehyde, but our experiments showed that the reaction could proceed almost the same as CH_3OH + PHC(O)H. So it is necessary to investigate the substituent effect on the α carbon of alcohol. The schematic potential surfaces of the reactions for **1a** + **2a**, **1a** + **2b**, and **1a** + **2c** reactions with two BH_3 molecules are shown in Figure 6, from which one can realize that the potential surfaces of the reactions between benzaldehyde and primary, secondary, or tertiary alcohols are quite similar. The relative energies for the stationary points between benzaldehyde and 2-propanol are almost the same as those between benzaldehyde and methanol, and the

largest difference is only 2 kcal/mol for **TS2a2** and **TS2b2**. For the *tert*-butyl alcohol case, all of the stationary points are less stable by a maximum of 5 kcal/mol, but the energy barrier for the reduction step is the least one among these three cases. That is to say, primary, secondary, and tertiary alcohols can be used for the reductive etherification reactions. Substitution on the benzene ring is also considered, in which the reaction between 4-fluorobenzaldehyde and 2-propanol is presented. The obtained geometric parameters are quite close to others, and the relative energies of the stationary points for the reaction **1a** + **2b** and **1b** + **2b** are less than 1 kcal/mol. Therefore, it can be concluded that 4-fluorobenzyl ether may be synthesized from 4-fluorobenzaldehyde in one step, which is in good agreement with our previous experimental fact. [10]

Conclusions

According to the above discussions, the following conclusions could be drawn:

(1) The title reactions include two distinct steps, i.e., addition and reduction, and the addition step is the rate-controlling one.

(2) Two BH_3 molecules could mimic the catalytic effect, which obviously lowers the reaction energy barrier. The BH_3 molecule is both a catalyst and reductant.

(3) The polar solvents favor the transition state **TS2a2**, i.e., the reduction step.

(4) Substitution effects of alcohol are not obvious. For example, even more crowded *tert*-butyl alcohol could easily react with benzaldehyde.

Supporting Information Available: The optimized Cartesian coordinates, frequencies, and energies of all the stationary points are listed in Tables S1–S16 and the numbering systems are given in Figures S1–S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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