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Chiral induction from solvents—lactic acid esters in the asymmetric hydroboration of ketones

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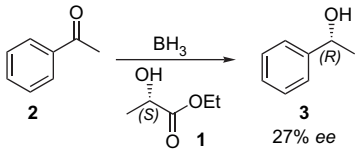
Abstract—The hydroboration of acetophenone in the chiral solvent (*S*)-methyl lactate exhibits moderate enantioselectivities. A six-membered transition state involving the ketone, the borane, and the lactate as the only chiral source is proposed. Molecular modeling explains the experimentally observed enantioselectivities. Calculated ee-values are in accordance with those experimentally observed. Improved ee-values (up to 60%) can be obtained in the presence of stoichiometric amounts of Lewis acid at lower reaction temperatures.

1. Introduction

Solvents can influence organic reactions and the respective product distribution in many ways.[1] In the case of chiral solvents as reaction medium, asymmetric induction can be observed and the products obtained can show enantiomeric excess (ee). The first successful experiments in this field were accomplished in 1975 by Seebach and Oei. They reported the synthesis of 2,3-diphenyl-2,3-butanediol from acetophenone by photolysis or electrolysis.[2] Using the amino ether (*S*,*S*)-(+)-1,4-bisdimethylamino-2,3-dimethoxybutane (DBB) as a chiral solvent the pinacol product could be isolated with 23% optical activity. A further example for the use of chiral solvents was reported by Furia et al., who used menthol in the asymmetric oxidation of sulphides and alkenes.[3] However, the enantioselectivities observed were only moderate (10% ee). Laarhoven and Cuppen irradiated 2-styrylbenzo-phenanthrene in various chiral solvents, such as ethyl lactate, ethyl mandelate, and their *O*-benzoyl-derivatives. The procedure afforded hexahelicenes with an optical yield of 0.2–2%.[4] As a consequence of the generally low enantioselection obtained the use of chiral solvents for asymmetric induction was neglected. However, recently asymmetric induction by chiral ionic liquids (CIL) has become an emerging field of research and impressive examples of highly enantioselective reactions have been described.[5,6] These include the asymmetric Baylis–Hillmann and aza-Baylis–Hillmann reactions developed by Vo-Thanh et al.[7] and Leitner et al.,[8] as well as the Michael addition of ketones to nitrostyrenes reported by Luo, Cheng and co-workers.[9] In the latter reaction, however, only 30 mol % of the task specific ionic liquid (TSIL) was employed.[10] Recently, we reported our first success in the enantioselective sodium borohydride reduction of acetophenone using chiral solvents for the asymmetric induction. Surprisingly, when we performed the reactions in (*S*)-lactic acid esters as solvent the (*R*)-enantiomer of phenylethanol was obtained in 27% ee (Scheme 1).[11]



Scheme 1. Solvent induced asymmetric borohydride reduction.

From a purely synthetic point of view, these results may so far have little value when compared to the Ru(II) based catalytic hydrogenations of Noyori and Ohkuma.[12] However, our interest lay in the development of solvent induced asymmetric reactions, at present an undoubtedly more multifaceted and complex research topic to address and to understand. Here, we report our further studies on the chiral solvent induced asymmetric reduction.

2. Results and discussion

Our continued studies of the solvent induced asymmetric borohydride reduction started by varying the ketone substrate.

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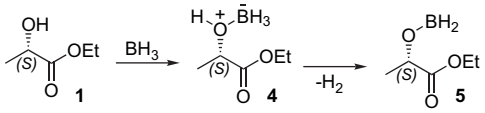
Table 1. Chiral solvent induced borane reduction of different ketones in (*S*)-lactic acid esters at 0 °C

Ketone	(*S*)-Ethyl lactate		(*S*)-Methyl lactate		Configuration of the product
	Conversion	ee	Conversion	ee	
Acetophenone	35	27	41	31	(*R*)
Butanone	75	6	70	8	(*R*)
3,3-Dimethylbutanone	80	14	87	19	(*R*)

Similarly to the hydroboration of acetophenone in (*S*)-ethyl lactate, the reduction of butanone and 3,3-dimethyl-2-butanone resulted in the corresponding products with increased conversion but the ee-values were considerably lower. However, by changing the chiral solvent from (*S*)-ethyl lactate to (*S*)-methyl lactate the enantioselectivities slightly increased (Table 1).

In order to gain a better understanding of the chiral (*S*)-lactate induction, we decided to prepare the *O*-methyl ether of lactic acid ethyl ester, ethyl 2-methoxypropionate. Performing the reaction using this chiral ether as solvent under otherwise same reaction conditions we observed insignificant enantioselectivities, indicating that the free hydroxyl group of (*S*)-ethyl lactate must be involved in the asymmetric induction. When BH_3 is added to lactic acid ester **1** a donor–acceptor adduct **4** is formed, which is presumably the active species in the hydroboration procedure (Scheme 2).



Scheme 2. Reaction of $BH_3 \cdot THF$ with ethyl lactate.

Subsequently, adduct **4** may undergo dehydrogenation to form the chiral borane **5**. In order to detect whether the chiral borane **5** is an intermediate in our solvent induced reduction, we prepared **5** by the addition of BH_3 to an equimolar amount of (*S*)-ethyl lactate and tested **5** in the reduction of acetophenone. When carrying out the reaction in THF, complete conversion was observed but no enantioselectivity could be detected; whereas performing the reaction in (*S*)-ethyl lactate as solvent only 3% conversion occurred but the product **3** was obtained with 7% ee. Hence, the borane **5** should be ruled out as the intermediate or chirality inducing reagent. From these results we can conclude that the presence of the free hydroxy group is crucial for the asymmetric induction. This is in agreement with previous findings of Vo-Thanh et al., Leitner et al., and Colonna et al.[7,8,13] However, the earlier reports on the mechanism of the hydroboration of carbonyl groups describe a four-membered transition state **TS 1** (Fig. 1a).[14] Applying this transition state model to our chiral solvent induced reduction would mean that the methyl lactate would not be sufficiently involved in the transition state and hence enantioselectivities should be low to zero, which is in contrast to the experimental observations. Consequently, (*S*)-methyl lactate, which is the only chiral source, must be involved in the transition state of asymmetric borohydride reduction of acetophenones.

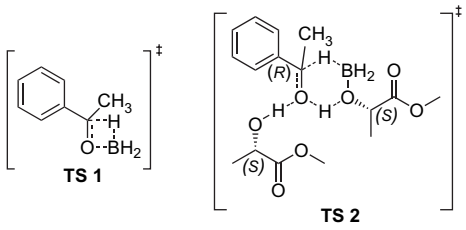


Figure 1. (a): Four-membered transition state.[14] (b) Six-membered transition state assumed for the chiral solvent induced hydroboration reaction of acetophenone.

A plausible transition state model **TS 2**, based on our observations, is given in Figure 1b. We assume a six-membered ring transition state for the investigated solvent induced borohydride reduction of acetophenone. In this transition state the borane acts as a Lewis acid and coordinates to the hydroxyl group of the (*S*)-methyl lactate causing the hydrogen of the O–H bond to become more acidic. This in turn allows the formation of a hydrogen bond to the oxygen atom of the acetophenone and as a consequence the carbonyl group is activated. Due to the ability of carbonyl groups to accept two hydrogen bonds, a second hydrogen bond from a different lactate molecules to the acetophenone acceptor is formed.[15] Through the coordination of the borane to the hydroxyl group of the methyl lactate, the B–H bond becomes activated: the electron density on the hydrogen atom increases, and it coordinates to the carbonyl C-atom of the acetophenone.

Molecular modeling was performed to explain the experimentally observed enantioselectivity. The calculations were carried out on the initial coordination state, which is assumed to be similar to the transition state. We used the parameterization of the Dreiding's force field,[16] which has been proven to give good results for organic compounds. Atomic charges were calculated by the semi-empirical method AM1[17] and all minimizations were performed with the Cerius[2] programs.[18] For calibration, initial test calculations on a set of lactate crystal structures and those of boranes were carried out and showed the applicability and reliability of the force field used. Hence, we started to analyze our system. At first the geometries of the involved molecules were optimized individually. Then the molecules were arranged in the six-membered ring (Fig. 1b). The molecular conformations and the possible arrangements in space were set up according to geometries found in crystal structures of similar compounds.[15] To assure close proximity of the reacting molecules the distance between the hydride of the BH_3 group and the carbonyl C-atom was restrained to a value of 270 pm, which corresponds to a close van der Waals contact.[15,19] Energy minimizations were carried out on various arrangements with the hydride attacking from both the *re*- and the *si*-faces of acetophenone. For the addition from the *si*-face the most favorable arrangement was found with a total energy of 88.53 kJ/mol (Fig. 2).

In contrast, the minimum total energy for the *re*-face attack amounted to 90.75 kJ/mol. Hence, an attack from the *si*-face yielding the (*R*)-alcohol is preferred by about 2.2 kJ/mol. As such, the (*R*)-alcohol should be the kinetically preferred product, which is in accordance with the experiment.

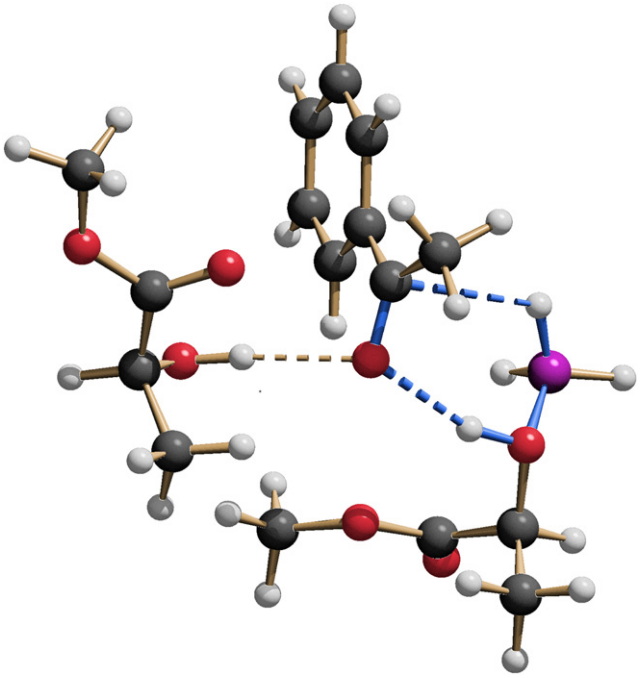


Figure 2. Calculated structure for the initial state for the enantioselective reduction of acetophenone with BH_3 in methyl lactate. The six-membered ring is shown in blue. The formation of the (*R*)-alcohol (as shown) is energetically preferred.

Applying the Boltzmann formula the calculated energy difference corresponds to an enantiomeric excess of 37% for the (*R*)-product at 0 °C, which is in striking accordance with the experimentally observed 31% ee. Within the limitation of theoretical methods and experimental errors, the accomplished calculations afforded astonishing conformity with the experimentally obtained enantioselectivities. As calculated, the experimentally determined ee increases with decreasing temperature down to −40 °C. For temperatures lower than −40 °C, calculations predicted a further increase in enantioselectivity, whereas the experimentally observed ees were reduced. This is probably due to the increasing viscosity of the reaction mixture, which eventually crystallized at temperatures below −60 °C. Hence, we performed the chiral solvent induced reductions by adding a solution of $BH_3 \cdot THF$ to acetophenone in methyl lactate at low temperatures. Addition of THF as a co-solvent lead to a considerable increase of reactivity most probably due to the better solubility and stirrability. However, with the dilution the enantioselectivity decreased significantly. This might be a consequence of weakening of the hydrogen-bond activation.

In the presence of a Lewis acid, closer interaction between the ketone and chiral solvent can be expected. Therefore, we added the $BH_3 \cdot THF$ solution to a mixture of acetophenone and $ZnCl_2$ in methyl lactate at −78 °C. This resulted in 78% conversion and the product was obtained with 50% ee. In comparison, an experiment without Lewis acid resulted in 44% conversion and 9% ee. Addition of an equivalent volume of the co-solvent THF to the methyl lactate at −78 °C improved the solubility and the conversion indeed becomes quantitative. Additionally, the enantioselectivity increased to 59% ee (Table 2).

Table 2. Conversion and enantiomeric excess observed in the reduction of acetophenone to (*R*)-phenylethanol in (*S*)-lactic acid methyl ester at −78 °C

Entry	Hydride source	Co-solvent	Lewis acid	Conversion (%)	ee (%)
1	BH_3	—	$ZnCl_2$	78	50
2	BH_3	THF	—	44	9
3	BH_3	THF	$ZnCl_2$	100	59
4	2/3 BH_3	THF	$ZnCl_2$	93	60
5	1/3 BH_3	THF	$ZnCl_2$	54	59

Conversion of the lactate induced reaction, however, was only quantitative when a threefold excess of hydride was added. Standard reaction conditions employing ketone to hydride ratios of 1:2 and 1:1 showed conversion of 93 and 54%, respectively, and the corresponding products were isolated in 60 and 59% ees. Presumably the reactivity of the three hydride equivalents of BH_3 is different due to the initially produced chiral borinic ester. A more detailed examination at −78 °C clearly displays a difference in the hydride transfer reactivity. Figure 3 shows the first-order kinetic plots with regard to the acetophenone concentration. In the case of equivalent amounts of ketone and BH_3 (a threefold excess of hydride) a clear slope for first-order kinetics is found. For the reactions with equal and twofold amount of hydride (2/3 BH_3 and 1/3 BH_3, respectively), it is not possible to determine which kinetics apply but each plot shows a clear two-slope behavior; the intersection points of the linear regression at about 4.2 and 3.5 indicate a change of the reaction kinetics at about 34 and 65% conversions, respectively.

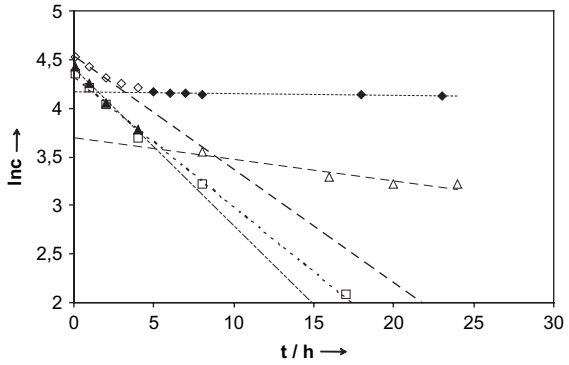


Figure 3. First-order plot of the reaction of acetophenone with different amounts of BH_3 in (*S*)-methyl lactate. BH_3 (1 equiv) (□), BH_3 (2/3 equiv) (△/▲), BH_3 (1/3 equiv) (◇/◆).

It can be concluded that the reaction rate of the first hydride is sufficiently high at −78 °C, whereas the rate of the second one is obviously slower. The rate slows down but by warming the reaction media up to ambient temperatures the second hydride's reactivity is increased. Presumably under these conditions it reacts at an appropriate rate with the ketone. Particularly noteworthy is the fact that this leads to the same enantioselectivity. This indicates that no detrimental effects on the enantioselection arise from the reaction of the primarily formed borinic ester. This is in contrast to the observations made without catalyst.

3. Conclusion

In summary, we here report a chiral solvent induced asymmetric hydroboration of ketones. Performing the borohydride reduction in (*S*)-lactic acid esters as the chiral solvent the resulting (*R*)-configured alcohol was obtained. The reaction outcome and enantioselectivity can be explained by a six-membered transition state **TS 2** (Figs. 1 and 2) which, in contrast to the earlier reported four-membered transition states **TS 1**, considers (*S*)-methyl lactate as the solvent and as the only possible chirality inducing source in the reaction medium. Addition of a Lewis acid to the chiral solvent even increased the enantioselectivities in the hydroboration procedure. Experiments to establish a more detailed mechanism of activation are currently in progress.

4. Experimental

In a three-necked flask, equipped with an adapter for N_2 and a pressure relief device, 10 mmol (1.3 g) $ZnCl_2$ were molten under N_2 and dissolved in 10 mL of the respective solvent or solvent mixture. The ketone (10 mmol) was added. The solution was cooled down to the reaction temperature. While stirring, 10 mL of a 1 M solution of BH_3 in THF were added dropwise via syringe to the mixture. The reaction mixture was kept at that temperature for at least 5 h and then allowed to slowly warm up to ambient temperature over night. In the case of the kinetic studies, the reaction was kept at −78 °C for the whole time. For the determination of conversion and enantiomeric excesses, 200 μL of the reaction mixture were hydrolyzed with 200 μL of water and the resulting clear solution was added onto a solid phase extraction tube Chromabond® XTR. Subsequent extraction using four times 1 mL of diethyl ether gave the samples, which were analyzed by GC. HP 5890 II/autosampler 6890 (250 °C); He 1 mL/min, Lipodex E, isotherm 100 °C, FID (300 °C).

Acknowledgements

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