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Solvent-Induced Chirality in the Hydroboration of Ketones

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The influence of the systematic variation of chiral solvents and of diverse Lewis acids on the asymmetric induction of the hydroboration of acetophenone has been studied. None of the solvents used could surpass lactic acid methyl ester, and for the Lewis acids, $ZnCl_2$ and ZnI_2 showed positive effects on the enantiomeric excess (*ee*) and the conversion. Also, the effect of the substrate structure was investigated by comparing the conversion and *ee* of eight different ketones. Apparently, the achievable asymmetric induction was higher with aromatic ketones.

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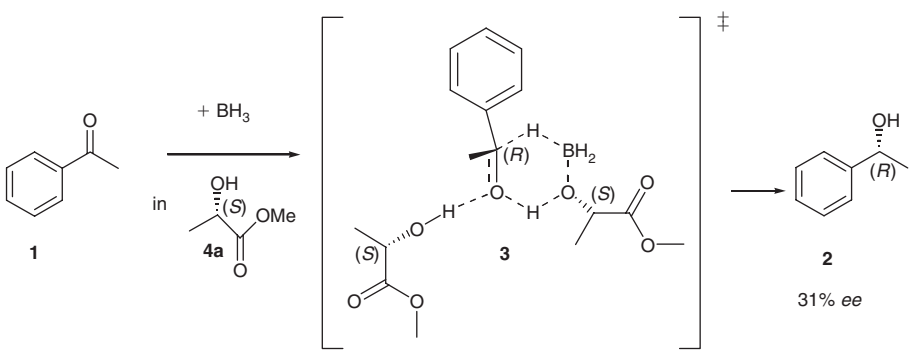
Introduction

Asymmetric induction in chemical reactions, achieved from the inherent chirality of the reactants or from chiral catalysis, is very well known.[1,2] Since the late 1970s, the principles of asymmetric induction by a chiral solvent have been examined.[3–5] Molecules from the natural chiral pool have served as solvents or solvent additives. Because of the low enantiomeric excesses (*ee*s) obtained, interest in this synthetic strategy for an enantioselective reaction was soon lost.

Recently, however, asymmetric induction by chiral ionic liquids (CILs) has become an emerging field of research and impressive examples of highly enantioselective reactions have been described.[6,7] These include the asymmetric Baylis–Hillman and aza-Baylis–Hillman reactions developed by Vo-Thanh and Leitner, as well as the Michael addition of ketones to nitrostyrenes reported by Luo, Cheng and coworkers.[8–10] As the toxicology and ecotoxicology of ILs remain to be clarified at present, we maintained the idea of induction from the natural chiral pool.[11,12] Only recently, we reported our first success in the enantioselective hydroboration of acetophenone in (*S*)-lactic acid esters. Molecular modelling was performed to explain the experimentally observed enantioselectivity, and the calculated *ee* of 37% for the (*R*)-product at 0°C is in striking agreement with the experimentally observed 31% *ee* (Scheme 1). To detect whether a chiral borane formed from lactate and BH_3 is an intermediate in our solvent induced reduction, we had added BH_3 to an equimolar amount of (*S*)-ethyl lactate. When carrying out the reduction of acetophenone in tetrahydrofuran (THF), complete conversion was observed but no enantioselectivity could be detected. The moderate *ee* could be improved up to 60% in the presence of stoichiometric amounts of $ZnCl_2$.[13–15]

From a purely synthetic point of view, these results may have little value compared with the Ru^{II}-based catalytic enantioselective hydrogenations of Noyori and co-workers,[1a] but our focus was on solvent induced chirality. 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.



Scheme 1. Six-membered transition state assumed for the chiral solvent induced hydroboration reaction of acetophenone.

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We herein report the results of systematic variation of the solvent, the influence of diverse Lewis acids, and of substrate structure on the hydroboration of ketones.

Results and Discussion

Our first successful asymmetric induction experiments were carried out using lactic acid ethyl ester as the chiral solvent. It was found later that methyl lactate was a better solvent choice than ethyl lactate. The methoxy modification of the latter only showed asymmetric induction in combination with a Lewis acid. We wanted to learn more about the influence of the chiral centre of the solvent on the asymmetric hydroboration. As the standard reaction, we again examined the hydroboration of acetophenone with boron hydride at 0°C (Scheme 1), this time in chiral solvents with different structures.

It was proposed that the chirality transfer from the solvent to the ketone proceeded by the interaction of the hydroxy group of the lactic acid ester and the carbonyl group. This corresponds to the findings of all other researchers. The results reported by Leitner, Vo-Thanh, Colonna and coworkers showed that the presence of a hydroxy group in the chiral inductors is essential for a reaction with carbonyl compounds. In general, hydrogen bonding can play a functional role in asymmetric catalysis as reviewed recently by Jacobson.[16]

We decided to retain the hydroxy group, the hydrogen, and the methyl group as general structural elements of the solvents. The organic remainder, R, of the general solvent structure **4** was varied and the respective (*S*)-form was always applied (Fig. 1).

Surprisingly, none of the solvents used could surpass lactic acid methyl ester in terms of *ee* and conversion (Table 1). In particular, in the case of propane-1,2-diol **4c** and the respective 1-amino compound **4f**, we had hoped for a closer interaction because of two hydrogen binding functional groups. But neither conversion of acetophenone **1** nor *ee* of the resulting phenylethanol **2** were satisfactory in these solvents. On the one hand, concurrent reaction of the additional acidic protons with the boron hydride could explain the low conversions, and on the other hand, preferred hydrogen bridging from the functional group beside the chiral centre was assumed for the small *ee*. In particular, the amino group in **4f** might have interacted with the boron reagent during the proposed transition state (Scheme 1) mainly by Lewis acid–base interaction. Replacement of the primary hydroxy group in **4c** by a *tert*-butyl ether improved both conversion and *ee*. Despite the bulky remainder, however, the values with **4d** were only half of those we obtained using the lactic acid esters. Less steric hindrance, as in the case of hexan-2-ol **4g**, gave significantly higher *ee* at a similar conversion level.

The unexpectedly poor to non-existent chiral inductions using 1-chloropropan-2-ol **4e** and 4-hydroxypent-1-ene **4h** still remain unexplained.

Next, the positive effect of $ZnCl_2$ on conversion as well as on the *ee* suggested a systematic variation with the Lewis acid. Following the classification by Kobayashi, we chose active aldehyde-selective ($AlCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$) and active aldimine-selective ($FeCl_3$), as well as weak neutral ($ZnCl_2$, ZnI_2) and weak aldimine-selective (CuI) Lewis acids.[17] Again, we used the hydroboration of acetophenone in lactic acid methyl ester this time at −20°C as the standard reaction (Scheme 1).

The results display very clearly that the preferred Lewis acid is weak and neutral. Under these conditions, only $ZnCl_2$ and ZnI_2 showed good to moderate asymmetric induction with simultaneous acceptable conversion. Although iron(III) chloride led to the highest conversion with the lowest *ee*, aluminum chloride gave considerable *ee* but unacceptable conversion. Table 2 summarizes the results.

Theoretically, the role of the Lewis acid still remains unclear and the respective transition state is highly speculative. Thus, from an empirical point of view, it made sense to examine the influence of other combinations of solvents and Lewis acids. We chose propane-1,2-diol **4c** and its 1-*tert*-butyl ether **4d** (Tables 3 and 4).

As can be seen from Tables 3 and 4, the results were poor to moderate. In the case of the alkoxypropanol **4d**, all Lewis acid catalysts lower the *ee*, and conversion was slightly improved solely in the case of $TiCl_4$. The increase of the *ee* from 9 to 22% using $ZnCl_2$ and the diol **4c** was the only real improvement found. Surprisingly, when employing $AlCl_3$ or $FeCl_3$ in this solvent, the ketone was consumed quantitatively, but no phenylethanol could be found after workup. Instead, 70% of **1** had been converted

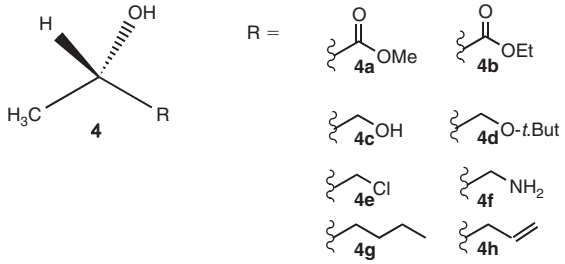

Fig. 1. General structure of the solvents used; only the (*S*)-forms were applied.

Table 1. Conversion and *ee* of the hydroboration of acetophenone to phenylethanol in different chiral solvents; $t = 0°C$

ee, enantiomeric excess

Solvent	Conversion [%]	*ee* (*R*-form) [%]
Lactic acid methyl ester **4a**	41	31
Lactic acid ethyl ester **4b**	35	27
Propane-1,2-diol **4c**	3	9
1-*tert*-Butoxypropan-2-ol **4d**	23	14
1-Chloropropan-2-ol **4e**	24	0
1-Aminopropan-2-ol **4f**[A]	17	0
Hexan-2-ol **4g**	20	25
4-Hydroxypent-1-ene **4h**	36	4

[A] Co-solvent THF 1:1.

Table 2. Influence of different Lewis acids on the hydroboration of acetophenone in lactic acid methyl ester at −20°C (Scheme 1)

ee, enantiomeric excess

Lewis acid	Conversion [%]	*ee* (*R*-form) [%]
$ZnCl_2$	47	46
ZnI_2	43	49
$AlCl_3$	11	39
$FeCl_3$	69	2
$TiCl_4$	36	5
$SnCl_4$	33	4
CuI	27	9
$SbCl_5$	2	5

Table 3. Influence of different Lewis acids on the hydroboration of acetophenone in propane-1,2-diol at −20°C (Scheme 1)
ee, enantiomeric excess

Lewis acid	Conversion [%]	*ee* (*R*-form) [%]
$ZnCl_2$	6	22
ZnI_2	5	13
$AlCl_3$	—	—
$FeCl_3$	—	—
$TiCl_4$	6	2
CuI	4	7

Table 4. Influence of different Lewis acids on the hydroboration of acetophenone in 1-tert-butoxypropan-2-ol at −20°C (Scheme 1)
ee, enantiomeric excess

Lewis acid	Conversion [%]	*ee* (*R*-form) [%]
$ZnCl_2$	4	11
ZnI_2	6	8
$AlCl_3$	24	11
$FeCl_3$	27	3
$TiCl_4$	38	6
CuI	15	7

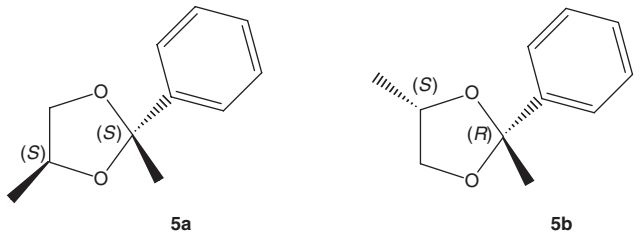

Fig. 2. Diastereomeric acetals formed from acetophenone and (*S*)-propane-1,2-diol using $FeCl_3$ or $AlCl_3$ Lewis acid.

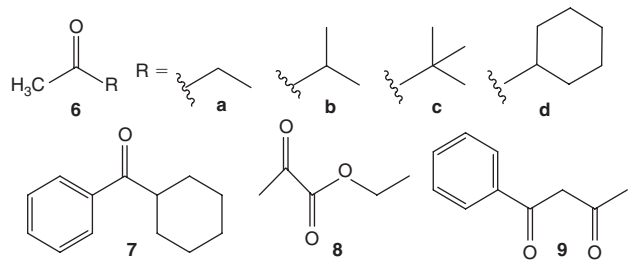

Fig. 3. Different ketones applied in methyl lactate mediated chiral hydroboration.

into the diastereomeric acetals **5a** and **5b** (Fig. 2), which could easily be separated and identified by gas chromatography/mass spectrometry. The substances showed a diastereomeric ratio of 2:1 but we neither isolated nor analyzed them further.

Of particular interest was the influence of the substrate structure on the achievable asymmetric induction (Fig. 3, Table 5).

Reaction in methyl lactate at 0°C without Lewis acid showed higher conversion rates for the alkyl-methyl ketones **6a**–**c** compared with acetophenone **1** but unfortunately lower

Table 5. Hydroboration of different ketones in methyl lactate at 0°C
ee, enantiomeric excess

Ketone	Conversion [%]	Alcohol *ee* (*R*-form) [%]
6a	70	**10** 8
6b	50	**11** 19
6c	87	**12** 19
6d	40	**13** 19
7	22	**14** 26
8	100	**4b** 20
9	73	**15** —[A]
1	41	**2** 31

[A] Elimination product.

Table 6. Distilled yields and ee values of the asymmetric hydroboration of different ketones catalyzed by ZnI_2 in methyl lactate/THF at −78°C
ee, enantiomeric excess

Ketone	Yield [%]	Alcohol *ee* (*R*-form) [%]
6a	61	**10** 35
6b	55	**11** 43
6c	60	**12** 61
6d	82	**13** 39
7		**14** 47
1	72	**2** 63

ee. In particular, butan-2-ol **10** from **6a** showed very poor *ee*, probably because of the insignificant stereo differentiation between the ethyl and methyl groups. The isopropyl remainder of 3-methylbutan-2-one **6b** and the *tert*-butyl group of 3,3-dimethylbutan-2-one **6c** clearly enhanced the asymmetric induction, but 3-methylbutan-2-ol **11** and 3,3-dimethylbutan-2-ol **12** still did not reach the *ee* of phenylethanol **2**.

Amazingly, 1-cyclohexylethanol **13** from ketone **6d** yielded the same *ee* as **11** or **12**. Replacement of the phenyl ring in **1** by a cyclohexyl structure led to a significant drop in selectivity; the *ee* fell from 31 to 19%. As the steric requirements of the cyclohexylmethylketone **6d** seemed to be higher than those of acetophenone **1**, one may speculate about the positive influence of an aromatic structure in the reactant on the selectivity. So we tried cyclohexyl phenyl ketone **7** as a reactant and found significantly increased values for cyclohexyl phenyl methanol **14**. Thus, besides the geometry of the transition state **3**, interaction of the aromatic ring with the solvent, such as π–π stacking with the carbonyl group, may play a major role in induction. We assumed that the more alike the reactant and solvent are, the higher the induction rate may be. Ethyl pyruvate **8**, however, reacted quantitatively but **4b** only achieved 20% *ee*. In the case of benzoylacetone **9**, no hydroxy ketone was obtained but only the elimination product 4-phenylbut-3-en-2-one **15**.

As asymmetric induction was strongly enhanced by ZnI_2 in the parent reaction, we compared its influence on the conversion of **6a** both in methyl lactate and in propane-1,2-diol at −20°C. Whereas the reaction in the latter solvent showed as little as 19% conversion with an improved induction of 14% *ee*, butan-2-one was hydroborated with a chiral induction of 35% *ee* in methyl lactate catalyzed by ZnI_2. The conversion remained at 71%.

Expectedly, low temperatures lead to increased *ee* values and conversions whereas an equivalent volume of THF has to be

added as a co-solvent in order to improve stirrability and enhance mixing at −78°C. So the best results were achieved with the Lewis acid ZnI_2 in a 1:1 solvent mixture of lactic acid methyl ester and THF at −78°C. The respective *ee* values and distilled yields of the alcohols **2**, **4b**, and **10** to **14** are listed in Table 6.

Conclusion

Solvent-induced chiral hydroboration of ketones was strongly enhanced by zinc halides, and less so by other Lewis acids. We believe it is a remote possibility that, before the reaction, BH_3 forms a more selective reagent with the zinc salts. From the results of the influence of the molecular structure of the inducing solvent, we conclude that there should be only one hydrogen bridging functional group – located at the chiral centre. It is likely that further interaction of the carbonyl group is valuable for substances that contain an aromatic ring. π–π stacking may be responsible for its orientation and one may speculate about the influence of the outer sphere of the solvent cage in which the transition state occurs.

Experimental

The chiral solvents **4a**, **b**, **e**, **f**, and **h** were bought from Sigma/Aldrich and used as they were. Substances **4c** and **4d** were made from 1-*tert*-butoxypropan-2-ol and substance **4g** was made from hexan-2-ol according to ref. [18].

The Lewis acids and the boran/THF complex were from Merck and used without further purification.

The ketones **1**, **6a**–**c**, and **9** were bought from Aldrich, **6d** and **7** from alpha aesar, and **8** from Merck.

General Procedure

In a two-necked flask, one closed by a septum, the other equipped with a pressure relief device, 5 mmol of the Lewis acid was dissolved in 5 mL of the respective solvent or 10 mL of the solvent mixture. The ketone (5 mmol) was added. The solution was cooled to the reaction temperature. While stirring, 5 mL of a 1 M solution of BH_3 in THF was added dropwise to the mixture by a syringe (0.5 h). The reaction mixture was kept at that temperature for an additional 0.5 h and then allowed to warm to ambient temperature (1 h). For the determination of conversion and *ee*, 200 μL of the reaction mixture was hydrolyzed with 200 μL of water and the resulting clear solution was added to a Chromabond XTR solid phase extraction tube. Subsequent extraction four times with 1 mL of diethyl ether gave the samples that were analyzed by gas chromatography (GC, HP 5890 II/autosampler 6890 (250°C); He 1 mL min^{-1}, Cyclodex B (Agilent), FID (300°C); **2** isotherm 130°C, retention times (*R*)-(+) 8.384 min; (*S*)-(−) 8.735 min; **4b** isotherm 80°C, retention times (*R*)-(+) 7.766 min; (*S*)-(−) 8.229 min; **10** isotherm 40°C, retention times (*R*)-(−) 7.254 min; (*S*)-(+) 7.484 min; **11** isotherm 70°C, retention times (*R*)-(−) 5.534 min; (*S*)-(+) 5.647 min; **12** isotherm 70°C, retention times (*R*)-(−) 8.072 min; (*S*)-(+) 8.674 min; **13** isotherm 100°C, retention times (*R*)-(−) 19.489 min; (*S*)-(+) 19.885 min; **14** isotherm 150°C, retention times (*S*)-(−) 40.854 min; (*R*)-(+) 41.431 min.

For identification, the homochiral forms (*S*)**2**, (*R*)**10**, and (*S*)**15** were bought from Sigma/Aldrich. For the other alcohols, the reaction mixture was hydrolyzed with 50 mL of water and the aqueous phase extracted twice with 30 mL of ether. The solvent was evaporated, 10 mL of 10 N NaOH was added and the extract stirred for 10 min at 50°C to hydrolyze the remaining lactic acid ester. Again, the mixture was poured onto 50 mL of water and the aqueous phase extracted twice with 30 mL of ether. The organic phase was dried with sodium sulfate and after evaporation of the solvent, the residue was distilled. **14** was crystallized from cyclohexane. The form of the major compound of the respective enantiomeric mixture was determined by measuring the rotational power of the product mixture at room temperature (25°C) (Schmidt+Haensch Kreispolarimeter). **11**: bp 112°C; 170 mg, 40% yield; *ee* 43%; $[\alpha]_D = -2.65$ (*c* 0.068, $CHCl_3$) Lit. $[\alpha]_D = +5°$ neat (*S*)-form.[19] **12**: bp 120°C; 270 mg, 60% yield; *ee* 61%; $[\alpha]_D = -4.63$ (*c* 0.11, $CHCl_3$) Lit. $[\alpha]_D = +8.7°$ neat (*S*)-form.[20]

13: bp 189°C; 515 mg, 82% yield; *ee* 39%; $[\alpha]_D = -3.3$ (*c* 0.206, $CHCl_3$) Lit. $[\alpha]_D = +5.3°$ neat (*S*)-form.[21] **14**: mp 67–68°C (from cyclohexane); 460 mg, 49% yield; *ee* 47%; $[\alpha]_D = +2.3$ (*c* 0.7, $CHCl_3$) Lit. $[\alpha]_D = -29.2°$ *c*(benzene) 0.22 (*S*)-form.[22]

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