Chiral Solvents

DOI: 10.1002/anie.200600327

Highly Enantioselective Aza-Baylis–Hillman Reaction in a Chiral Reaction Medium**

*Rolf Gausepohl, Pascal Buskens, Jochen Kleinen, Angelika Bruckmann, Christian W. Lehmann, Jürgen Klankermayer, and Walter Leitner**

Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

A chemical reaction that leads to enantiomerically enriched products can in principle be carried out with a source of chirality in any of the involved components—starting materi-

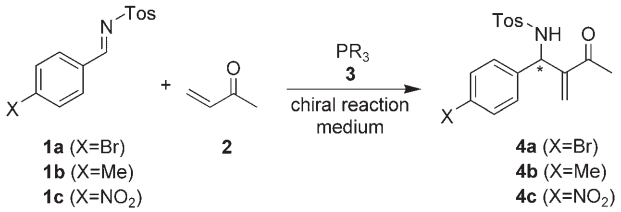
[*] R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, Dr. J. Klankermayer, Prof. Dr. W. Leitner
Institut für Technische und Makromolekulare Chemie
Rheinisch-Westfälische Technische Hochschule Aachen
Worringerweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-80-22177
E-mail: leitner@itmc.rwth-aachen.de
Dr. C. W. Lehmann, Prof. Dr. W. Leitner
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SPP 1179, SFB 380). R.G. and P.B. thank the Fonds der Chemischen Industrie and the Graduate School 440 "Methods in Asymmetric Synthesis", respectively, for PhD stipends. We thank Dr. K. Ditrich (BASF AG) for a generous gift of (*R*)-mandelic acid. Furthermore, we are very grateful to H. Eschmann and T. Steins for their technical support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

als,[1] catalysts,[2] or reaction media.[3] To date, all asymmetric transformations that yield appreciable enantioselectivities are based on the first two strategies. Herein we report the first example of a highly enantioselective asymmetric synthesis in which only the reaction medium contains chiral information.

We focused our investigations on the aza-Baylis–Hillman reaction, a C–C-bond forming reaction of activated alkenes (e.g., **2**) with imines (e.g., **1**).[4] This organocatalytic transformation is catalyzed by nucleophilic Lewis bases such as tertiary phosphines (**3**) and leads to highly functionalized chiral allylic amines (**4**) (Scheme 1). The previously developed methods for enantioselective synthesis of the allylic amine **4** provide the necessary chiral information within the substrate[5] or through catalysts.[6] We have prepared the ionic liquid (IL) **9**, which contains a chiral anion and induces high enantioselectivities (up to 84% *ee*) when used as reaction medium.



Scheme 1. The aza-Baylis–Hillman reaction. Tos = 4-toluenesulfonyl.

The strategy of applying chiral solvents in asymmetric synthesis was pioneered by Seebach and Oei.[7] They used a chiral amino ether as the solvent in the electrochemical reduction of ketones but observed only low enantioselectivities (up to 23.5% *ee*). Since then, all attempts to apply chiral solvents in asymmetric synthesis have resulted in similar or lower enantioselectivities. This led to the generally accepted conclusion that "asymmetric induction caused by chiral solvents is usually rather small".[3]

As ILs have attracted a lot of attention recently as a new class of solvents,[8] the incorporation of chiral information in these media has caught the interest of several groups.[9] Although details of the structure and dynamics of these solvents as well their interactions with dissolved substances remain largely elusive, chiral ILs have already started to emerge for various purposes[9] including asymmetric synthesis.[10] Very recently, Vo-Thanh and co-workers reported the largest presently known asymmetric induction caused by a chiral IL as the only source of chirality in an asymmetric reaction.[10a] In the DABCO-catalyzed Baylis–Hillman reaction (DABCO = 1,4-diazabicyclo[2.2.2]octane) of benzaldehyde and methylacrylate they obtained enantioselectivities up to 44% *ee* (e.r. = 2.6) by using an IL with chiral cations derived from (−)-*N*-methylephedrine. To the best of our knowledge, no significant asymmetric induction has been reported so far for ILs with chiral anions.

Previous investigations on the mechanism of the aza-Baylis–Hillman reaction by our group indicate that a bifunctional stabilization of the zwitterionic reaction intermediates is necessary to obtain high enantioselectivities and to prevent subsequent racemization of the reaction product **4**.[11] In conventional systems, this can be achieved by incorporating both a nucleophilic catalyst and a Brønsted acidic co-catalyst into one chiral molecule. ILs, however, offer the possibility of establishing a bifunctional interaction by incorporating the acidic center into the chiral anion of the solvent, thus allowing monofunctional achiral nucleophiles to be used as catalysts in the enantioselective aza-Baylis–Hillman reaction (Figure 1).

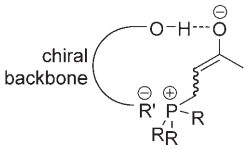
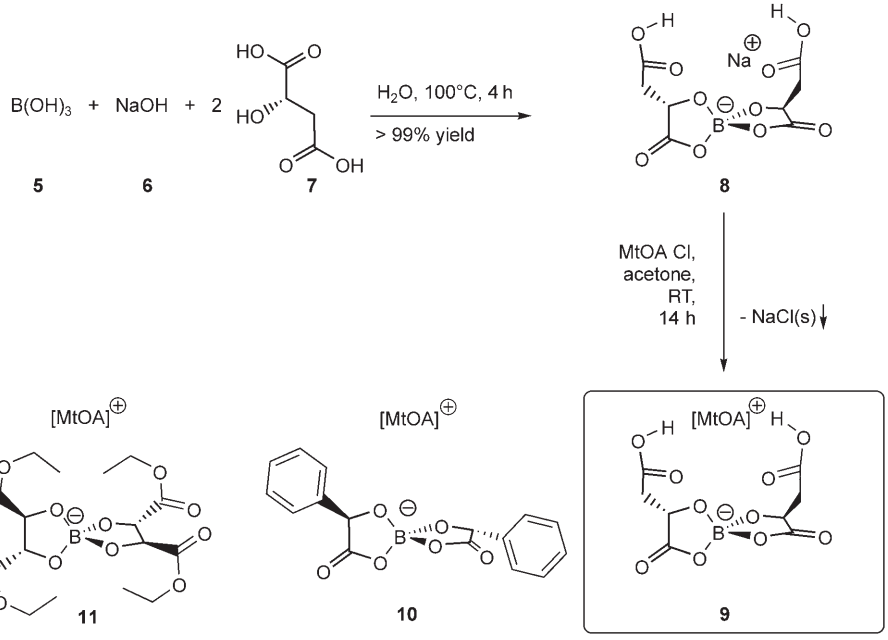


Figure 1. Possible bifunctional interaction of the zwitterionic intermediate of the aza-Baylis–Hillman reaction with the chiral anion of an IL containing a hydrogen-bond donor.

For ions containing hydrogen-bond donor functions, we targeted borate anions based on L-(−)-malic acid, which is available from the chiral pool (Scheme 2). The sodium dimalatoborate salt **8** was prepared by stirring an aqueous



Scheme 2. Two-step synthesis of methyltrioctylammonium dimalatoborate (**9**). Only one of the two possible diastereoisomers is shown.

solution of boric acid (**5**), sodium hydroxide (**6**), and L-(−)-malic acid (**7**) in an open flask at 100 °C.[12] Figure 2 depicts the molecular structure of the anion as revealed by X-ray crystal structure analysis,[13] which proves the connectivity and

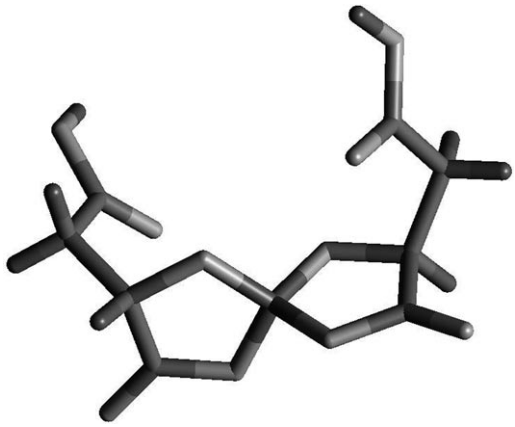


Figure 2. Molecular structure of the dimalatoborate anion in the solid state as revealed by X-ray single-crystal structure analysis of the corresponding sodium salt **8**. Only the *S,S,S* diastereoisomer is present in the crystal lattice. The O-B-O angles range from 103.9 to 105.1° within the five-membered ring and from 109.0 to 113.4° between the rings (see the Supporting Information for details).

configuration indicated in Scheme 2. Multinuclear NMR experiments confirmed the presence of the five-membered ring arrangement also in solution. Two sets of signals are observed in a 1:1 ratio in the ^{1}H and ^{13}C NMR spectra of samples of dissolved single crystals even at low temperature (233 K, $[D_4]$MeOH). This is due to the formation of a 1:1 mixture of the two possible diastereoisomers that result from the fixed chirality at the asymmetric carbon atoms and the labile chirality at the boron center of this spiro-type compound.[14]

The exchange of the sodium ions with methyltrioctylammonium (MtOA) was carried out with aliquat 336 (MtOACl) in acetone. Filtration of the precipitated NaCl and evaporation of the solvent yielded a colorless liquid with a melting point of −32 °C.[15] The related ILs **10** and **11**, which lack a potential hydrogen-bond donor, were prepared in a similar manner.

To assess the efficacy of the IL **9** for chiral induction, the aza-Baylis–Hillman reaction between methyl vinyl ketone (**2**) and *N*-(4-bromobenzylidene)-4-toluenesulfonamide (**1a**) was studied in the new reaction medium using PPh_3 (**3**, R = Ph) as the nucleophilic catalyst (see Experimental Section). The chiral allylic amine (*R*)-**4a** was obtained in this model reaction with reasonable conversion and high enantiomeric excess.[16] In a series of four independent experiments using various batches of **9**, conversion varied between 34% and 39% and the enantioselectivity ranged from 71–84% *ee*. The highest enantiomeric excess (84% *ee*) observed in these experiments corresponds to an enantiomeric ratio of 11.5 and hence a difference in activation energies $\Delta\Delta G^{+}$ of 6.05 kJ mol^{-1} for the formation of the two enantiomers. This is by far the highest asymmetric induction obtained with a chiral solvent as the sole source of chirality.

Several experiments were carried out to investigate the mechanism of the chirality transfer by the chiral reaction medium.[17] Notably, the structurally related ILs **10** and **11** resulted in lower conversions (15% and 14%, respectively) and the formation of racemic product, which indicates the necessity of a Brønsted acidic moiety within the chiral ion.[11] Dilution experiments with one equivalent of **9**, **8**, or **7** per molecule of **3** in THF or CH_2Cl_2 also resulted only in the formation of small amounts of racemic product. These results show that neither **9** nor any of its chiral precursors can be used as an additive for the asymmetric aza-Baylis–Hillman reaction in conventional solvents. Consequently, the use of **9** as a reaction medium is crucial for effective asymmetric transformation in this system.

Almost identical results were obtained with substrate **1a** using other aryl phosphines (**3**) as the achiral nucleophilic catalyst in **9** as the reaction medium ($P(o\text{-tolyl})_3$: 35% conversion, 74% *ee* (*R*); $(C_6F_5)PPh_2$: 9% conversion, 71% *ee* (*R*)). The catalyst PPh_3 also led to reasonable conversion (39%) and a high level of enantioselectivity (64% *ee*) for the *p*-methyl-substituted substrate **1b**. With the less electron-rich substrate **1c**, however, product **4c** was obtained in only 10% *ee*. A control experiment showed that this results from a lower level of intrinsic asymmetric induction, as no racemization of **4c** occurred under turnover conditions. A similar decrease in asymmetric induction was described by Vo-Thanh and co-workers for the mechanistically related Baylis–Hillman reaction of *p*-nitrobenzaldehyde and methylacrylate in ILs with chiral ephedrinium cations.[10a] They explained the drop in enantioselectivity by the formation of a hydrogen bond between the OH group of the chiral ion and the NO_2 function of the substrate.

In conclusion, we reported the first example of an asymmetric reaction in which a chiral reaction medium induces a high level of enantioselectivity. Using a specifically designed ionic liquid with a chiral anion as the only source of chirality, enantioselectivities of up to 84% *ee* ($\Delta\Delta G^{+} = 6.05$ kJ mol^{-1}) were obtained in the aza-Baylis–Hillman reaction. This is the highest enantioselectivity induced to date by a solvent as the sole source of chirality. These results are comparable with the values obtained with the best catalysts for the asymmetric aza-Baylis–Hillman reaction in conventional solvents (94% *ee*,[6e] 83% *ee*[6c,d]).

The results described herein demonstrate that, contrary to popular opinion, the strategy of applying chiral solvents in asymmetric synthesis can result in appreciable enantioselectivities. The key to effective chirality transfer lies in strong intermolecular interactions such as electrostatic attraction and hydrogen bonding between the solvent molecules and the intermediates or transition states of the enantioselective reaction step (see Figure 1). Functional ionic liquids offer unique possibilities to create such arrangements for a wide range of transformations.

Experimental Section

8: **7** (10.73 g, 80.0 mmol, 2.00 equiv) was dissolved in water (10 mL) and treated with boric acid (**5**, 2.47 g, 40.0 mmol, 1.00 equiv). A solution of sodium hydroxide (**6**, 1.60 g, 40.0 mmol, 1.00 equiv) in

water (30 mL) was then added. The reaction mixture was stirred in an open flask at 100 °C. After evaporation of the water (ca. 4 h), **8** was isolated as a white powder (11.92 g; 40.0 mmol, > 99 % yield).

9: Methyltrioctylammonium chloride (3.54 g, 8.75 mmol, 1.00 equiv) was dissolved in acetone (20 mL) and treated with a solution of the sodium borate salt **8** (2.61 g, 8.75 mmol, 1.00 equiv) in acetone (20 mL). The reaction mixture was stirred at room temperature overnight. During this period, sodium chloride precipitated as a white solid. The reaction mixture was filtered and the solvent was removed in vacuo to yield **9** as a highly viscous, hygroscopic colorless liquid.

Typical procedure for the aza-Baylis–Hillman reaction: **4a**: Imine **1a** (0.125 mmol, 1.00 equiv) and catalyst **3** (12.5 μmol, 0.10 equiv) were dissolved in **9** (1.0 mL, 6.7 mL per mmol **1**). After addition of **2** (12.5 μL, 10.5 mg, 0.150 mmol, 1.20 equiv), the reaction was stirred at room temperature for 24 h. Excess **2** was removed in vacuo, a small sample of the reaction mixture was dissolved in [D_6]DMSO, and the conversion was determined by ^{1}H NMR spectroscopy. The rest of the reaction mixture was dissolved in water/methanol (1:1, 5 mL). Further methanol was added to obtain a clear solution of the reaction mixture. After (partly) exchanging the cation on an ion-exchange resin (contact time approximately 5 min), all volatile substances were removed in vacuo. The resulting solid was extracted with heptane/*i*PrOH (85:15, 1 mL), and the solution was directly analyzed by HPLC on a chiral phase to determine the enantiomeric excess of **4a**.

Received: January 25, 2006
Revised: March 10, 2006

Keywords: asymmetric synthesis · C–C coupling · chiral solvents · ionic liquids · organocatalysis

[1] G. H. Roos, *Compendium of Chiral Auxiliary Applications*, Academic Press, San Diego, **2001**.
[2] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**.
[3] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2003**.
[4] For a recent review on the Baylis–Hillman reaction, see: D. Basavaiah, A. J. Rao, T. Satayanarayana, *Chem. Rev.* **2003**, *103*, 811 – 891.
[5] X. Liu, J. Zhao, G. Jin, G. Zhao, S. Zhu, S. Wang, *Tetrahedron* **2005**, *61*, 3841 – 3851.
[6] a) M. Shi, Y.-M. Xu, *Angew. Chem.* **2002**, *114*, 4689 – 4692; *Angew. Chem. Int. Ed.* **2002**, *41*, 4507 – 4510; b) D. Balan, H. Adolfsson, *Tetrahedron Lett.* **2003**, *44*, 2521 – 2524; c) M. Shi, L.-H. Chen, *Chem. Commun.* **2003**, 1310 – 1311; d) M. Shi, L.-H. Chen, C.-Q. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790 – 3800; e) K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680 – 3681.
[7] D. Seebach, H. A. Oei, *Angew. Chem.* **1975**, *87*, 629 – 630; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 634 – 635.
[8] a) P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *112*, 3926 – 3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772 – 3789; b) P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, **2003**.
[9] For recent reviews on chiral ILs, see: a) C. Baudequin, D. Brégeon, J. Levillain, F. Guillen, J.-C. Plaquevent, A.-C. Gaumont, *Tetrahedron: Asymmetry* **2005**, *16*, 3921 – 3945; b) J. Ding, D. W. Armstrong, *Chirality* **2005**, *17*, 281 – 292.
[10] a) B. Pégot, G. Vo-Thanh, A. Loupy, *Tetrahedron Lett.* **2004**, *45*, 6425 – 6428; b) J. Ding, V. Desikan, X. Han, T. L. Xiao, R. Ding, W. S. Jenks, D. W. Armstrong, *Org. Lett.* **2005**, *7*, 335 – 337; c) Z. Wang, Q. Wang, Y. Zhang, W. Bao, *Tetrahedron Lett.* **2005**, *46*, 4657 – 4660.
[11] P. Buskens, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2005**, *127*, 16762 – 16763.
[12] The corresponding Li salt: P. H. Cunningham, F. L. Warren, Jr., H. O. Marcy, M. J. Rosker (Rockwell International Corp., USA), EP-95-109113 693704, **1996**.
[13] Crystal data for **8**: $C_8H_8BNaO_{10}$, $M_r = 297.9$, crystal dimensions $0.36 \times 0.34 \times 0.25$ mm^3, monoclinic $P2_1$ (No. 4), $T = 100$ K $a = 5.40160(10)$, $b = 11.6781(2)$, $c = 9.4451(2)$ Å, $\beta = 105.0590(10)$, $V = 575.340(19)$ Å^3, $\rho_{calcd} = 1.720$ Mg m^{-3}, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å. CCD scans yielded 10760 (1906 unique) reflections, $R_{int} = 0.038$. Multi-scan absorption correction, $\mu = 1.719$ mm^{-1}, $T_{min} = 0.85$, $T_{max} = 1.0$. Structure solution (direct methods) SHELXS-97, full-matrix least-squares refinement against F^2 SHELXL-97, 213 parameters, hydrogen atoms in idealized geometry (riding model) R = 0.025, wR = 0.077, highest residual electron density peak 0.2 Å^{-3}. Complete lists of atom coordinates and anisotropic displacement parameters as well as tables of bond lengths and bond angles are available as supplementary material. CCDC-297143 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[14] a) J. Boeseken, J. A. Mijs, *Recl. Trav. Chim. Pays-Bas* **1925**, *44*, 758 – 762; b) S. Green, A. Nelson, S. Warriner, B. Whittaker, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4403 – 4408; c) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373 – 382.
[15] The melting point was determined by differential scanning calorimetry; 72 ± 2 % conversion (determined from ^{1}H NMR spectroscopy); impurities: octanol (from aliquat 336, up to 6 %), water (200–2800 ppm, determined by Karl Fischer titration).
[16] The absolute configuration of **4a**–**c** was assigned as *R* by comparison with the work of Shi et al.[6d]
[17] The possibility of enrichment of one enantiomer during workup was excluded by subjecting a scalemic mixture of **4c** to the same experimental procedure. This control material had 74 % *ee* (*S*) before and 76 % *ee* (*S*) after the workup procedure.

