Asymmetric Synthesis

DOI: 10.1002/anie.200902841

Absolute Asymmetric Reduction Based on the Relative Orientation of Achiral Reactants**

Alexander Kuhn and Peer Fischer*

Most biological molecules are chiral and exist in only one of two possible mirror-image forms. This homochirality of life, the origin of which is still a matter of discussion,[1] has the important consequence that the biological and pharmaceutical activity of chiral molecules is directly related to their handedness. The selective synthesis of only one of the two mirror-image forms of a chiral molecule is therefore of major importance. Although great progress has been made in chemical and biochemical asymmetric synthesis,[2,3] only a few systems permit absolute asymmetric synthesis, that is, enantioselective synthesis from achiral starting materials without the help of chiral reagents or catalysts.[4,5] Absolute means of inducing appreciable handedness are, for example, photochemical reactions with circularly polarized light,[6–8] synthesis in noncentrosymmetric or enantiomorphic crystals,[9,10] reactions in crystals with reduced symmetry as a result of the mixing of different compounds,[11,12] autocatalytic amplification of a chiral bias resulting from small random fluctuations,[13,14] aggregation in supramolecular assemblies,[15] or recrystallization under special conditions.[16,17] As has been suggested on theoretical grounds by Holland and Richardson,[18] absolute asymmetric synthesis should also be possible from achiral reactants by reactions on a selected face of an achiral single crystal. In this case, the orientation and exposure of a selected face of an achiral crystal to the achiral reagent is the "chiral force". The idea was verified experimentally for the stereoselective oxidation of an olefin;[19] however, despite the promising early results, no further report has confirmed or extended these findings to other types of reactions.

This purely geometric approach to absolute asymmetric synthesis from achiral starting molecules in achiral crystals promises higher enantioselectivity than any other absolute asymmetric synthetic scheme. Herein, we demonstrate that this method functions reproducibly. We also introduce a new class of reactions that has not been considered before in this context, namely, reduction reactions. We examined the robustness of the concept by using a different crystal system, a number of different experimental setups, and a new reaction mechanism based on the conversion of a prochiral ketone into a chiral alcohol. This purely geometric approach can provide access to the important class of compounds of tertiary alcohols, which present a challenge for classic stereoselective synthesis.[20] Control of the macroscopic orientation of the nonchiral reactants prior to the reaction and exposure of the appropriate crystal face of the nonchiral starting compound to a reducing agent leads to a product with a high *ee* value. Reversal of the orientation of the crystal generates the product with the opposite molecular handedness.

This reaction scheme based on geometric arguments compares favorably with other absolute asymmetric schemes that are also based on physical principles.[4,5,21] Most other absolute approaches involve circularly polarized light[22] and lead to selective photodestruction,[7] photoresolution,[23,24] and photosynthesis.[25] Light has also been used with a chiral crystal field for asymmetric synthesis from prochiral starting compounds.[10,26] Furthermore, unpolarized light in combination with a magnetic field has been shown to induce a slight excess of one enantiomer.[27,28] Additional approaches are based on spontaneous symmetry breaking in combination with autocatalytic amplification,[13,29,30] and in the case of supramolecular homochirality, the symmetry breaking has been controlled with the help of vortices in a stirred solution.[15] Absolute asymmetric means of controlling the handedness of the product with appreciable enantioselectivity in the absence of an amplification mechanism are asymmetric photolysis[7] and reactions in chiral crystals.[26] However, the serious drawback of photolysis is that, for the product to be formed with a large *ee* value from a racemic mixture, most of the chiral molecules are destroyed in the process,[5] and the limitation of any reaction scheme that relies on enantiomorphic crystals is that only few achiral molecules crystallize in a chiral space group.[5,26] In contrast, most organic molecules crystallize in space groups that are potentially suitable for the completely geometric approach to asymmetric synthesis.[18]

The concept of spatial orientation requires that the orientation of the starting compound is fixed in space, as depicted schematically in Figure 1. If reagent 4 reacts from the left with the central carbon atom, then the resulting structure with a central stereogenic sp^3 carbon atom will be the mirror image of the structure obtained when reagent 4 reacts from the right. The successful implementation of this

[*] Prof. A. Kuhn[+]
Institut des Sciences Moléculaires, ENSCPB
Université de Bordeaux 1, 33607 Pessac (France)
Fax: (+33) 5-4000-6573
http://recherche.enscpb.fr/nsysa/home.asp
E-mail: kuhn@enscpb.fr

Dr. P. Fischer
The Rowland Institute, Harvard University, Cambridge (USA)

[+] On sabbatical leave at:
The Rowland Institute, Harvard University, Cambridge (USA)

[**] This research was supported by the Rowland Institute at Harvard and the French Ministry of Education and Research. We are grateful to Gary Widiger, Chris Stokes, Don Rogers, Doug Ho, Michelle Li, and Jim Foley for technical support and helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902841.

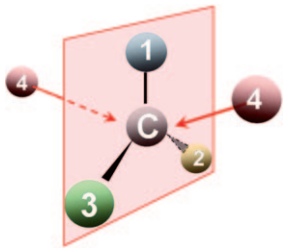
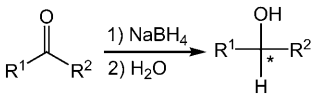


Figure 1. Schematic representation of the concept of absolute asymmetric synthesis based on the preferential orientation of an achiral starting molecule with respect to an achiral reagent 4.

approach for asymmetric synthesis not only requires that the prochiral molecules are prevented from tumbling in space during exposure to the reactant, but also that all molecules in the ensemble have a fixed orientation with respect to one another, so that they give the product with the same handedness. It has been suggested that such an asymmetric synthesis might be possible through the alignment of a monolayer of dipolar prochiral molecules with an electric field while the monolayer is exposed to a directed reagent flux;[31] however, this approach has not been realized experimentally to date.

An alternative approach to fix the orientation of the prochiral starting molecules is based on the natural molecular alignment found in single crystals and enables much larger quantities to undergo the desired reaction. The strategy was first suggested by Holland and Richardson,[18] but the use of achiral single crystals for absolute asymmetric synthesis has neither been confirmed nor explored further, except in initial studies on stereoselective oxidation reactions.[19] Herein, we demonstrate that this simple and general scheme is not only effective, but can also be extended to reduction reactions that provide the product in high optical yields relative to those observed in other approaches to absolute asymmetric synthesis.

In low-symmetry space groups, a lack of mirror planes ensures an overall preferential orientation of the molecules within a crystal, so that an interfacial reaction progressing along one well-chosen direction in the crystal with subsequent dissolution of the product should preferentially lead to one of the two enantiomers. In this case, neither the molecule nor the crystal lattice needs to have chiral features, in contrast to the systems used in other studies.[32,33] Crystals that fulfill this criterion belong, for example, to the two most frequently found achiral space groups, $P1$ and $P2_1/c$. Over 200,000 such organic crystals are listed in the Cambridge Structural Database.[34] The corresponding molecules contain a variety of functional groups; as we wanted to validate the approach for reactions that are complementary to the reported oxidation reactions, we focused on the transformation of a prochiral ketone into a chiral alcohol by reduction. We chose 3-acetyl-6-bromocoumarin (BC) from a number of commercially available candidate molecules as a model system and investigated its reduction with sodium borohydride [Eq. (1)]:



(1)

This reaction is typically carried out in ethanol; however, it also proceeds in aqueous media, as the reducing agent only reacts slowly with water. BC is practically insoluble in water (see the Supporting Information), and so the molecules remain ordered in the crystal until they have reacted. However, the chiral alcohol is slightly water-soluble and can therefore be removed continuously from the crystal face during the reaction.

Needle-shaped crystals of several millimeters in length were grown from saturated solutions in tetrahydrofuran. X-ray diffraction from a single crystal (Figure 2a) showed that

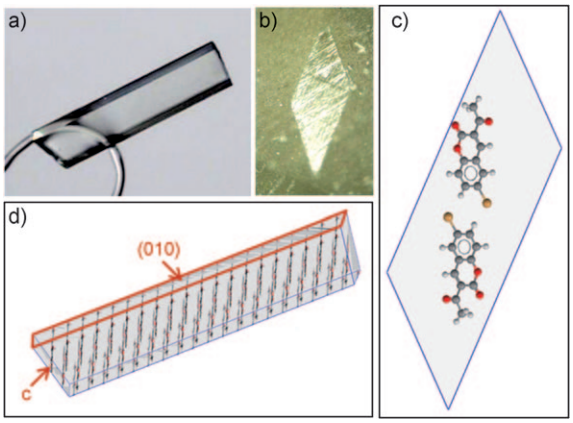


Figure 2. Crystal and crystal structure of 3-acetyl-6-bromocoumarin (BC). a) Single crystal on an X-ray spectrometer holder. b) Crystal sealed in PMMA and polished perpendicular to the main crystal axis prior to reaction (height of crystal is ca. 3 mm). c) Molecular structure of BC molecules and their orientation in the polished crystal face (only two BC molecules are shown). d) Schematic representation of a triclinic BC crystal depicting the stacked orientation of the BC molecules in the bulk crystal. The (010) face is marked, as is the crystal face shown in (c).

the BC molecules lie in planes that are stacked in the direction of the long axis of the needle (Figure 2d), which is along one of the unit-cell axes in this triclinic system. As the molecular planes stack in the direction of the long axis of the needle (the molecular planes are nearly perpendicular to the 010 face of the single crystal), it is possible to deduce the approximate spatial orientation of the molecules by inspection of the macroscopic crystal morphology. The orientation of BC molecules within a plane perpendicular to the long axis of the needle is depicted in Figure 2c. The BC molecules are rotated by 180° with respect to one another, but, importantly, the crystal face in Figure 2c possesses no vertical mirror planes and therefore corresponds to the scenario depicted in Figure 1. It follows that the selective exposure of one of the end faces of the needle to the sodium borohydride solution should lead to only one enantiomer of the chiral alcohol. Exposure of the opposite end face of the needle must result in the opposite enantiomer.

We sealed each crystal in epoxy resin or poly(methyl methacrylate) (PMMA) before removing the sealant at one of the end faces of the needle by carefully polishing perpendicular to the needle axis. The exposed surface (Figure 2b) was

brought into contact with an aqueous solution of the reducing agent. When a visible amount of the crystal had been consumed, the reaction was stopped, and the reaction product was isolated and analyzed by HPLC on a chiral stationary phase (see the Supporting Information). The end face of the crystal was then repolished. Thus, several experiments could be carried out with every crystal.

Table 1 lists some typical results obtained for two crystals that gave the product with opposite enantioselectivity.

Table 1: Enantioselective synthesis at one end of a crystal.

Crystal A	*ee* [%]	Crystal B	*ee* [%]
run 1	+18	run 1	−14
run 2	+21	run 2	−15
run 3	+9	run 3	−10
run 4	+26	run 4	−11

Crucially, the same side of the crystal always generated the product with the same handedness in all repeat experiments. In principle, the product enantiomer that will form in excess can be predicted if one knows which enantiotopic surface is exposed to the solution.[35] The *ee* values are surprisingly high relative to those found in most other absolute asymmetric syntheses, especially if one takes into account that the orientation of the polished end face in the present set of experiments was only controlled by the naked eye (with an uncertainty of approximately 20°) and that the tilt of the molecular planes with respect to the needle axis was not corrected for. We also conducted a number of control experiments in which we exposed either BC powder or unsealed BC crystals to a solution of $NaBH_4$. All control experiments gave racemic mixtures with 0.0 ± 0.5 % *ee* (see the Supporting Information).

To determine which enantiomer should be formed in the reaction, one can select the desired crystal end face by first indexing the crystal with X-rays or with a polarizing light microscope. However, if the sealed needle is polished at both ends, and the two ends are exposed simultaneously to separate reaction chambers (see the Supporting Information), the product must form in both chambers with opposite *ee* values (Figure 3). This reactivity is indeed observed (Table 2). Each end face of the crystal reacts to form one of the two enantiomers. As expected, the *ee* values vary from run to run because the polishing, and therefore also the orientation, area, and reactivity, of the exposed crystal face is not completely identical for each run.

The *ee* values were determined readily by HPLC (Figure 4a; in this case, +15 and −21 % *ee*), and we confirmed by circular dichroism that the two sides of the crystal give chiral products with opposite ellipticities (Figure 4b).

An initially low *ee* value for a nonoptimized reaction could approach 100 % *ee* if the absolute scheme presented herein was coupled to an autocatalytic amplification process. With nonlinear amplification schemes, such as that in the Soai reaction,[36] even a very small initial excess of one enantiomer can drive a chemical reaction to product formation with close to 100 % *ee*.[37] However, none of the nonlinear schemes are

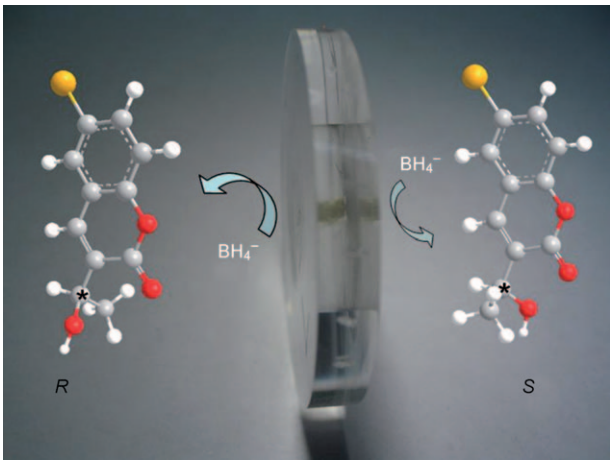


Figure 3. Schematic representation of the reaction. The BC crystal (yellowish, visible at the center of the picture) is sealed in a poly(methyl methacrylate) disk with the long axis of the needle perpendicular to the plane of the disk. Both sides of the disk are polished to expose the opposite ends of the crystal to the reducing agent ($NaBH_4$) in separate reaction chambers (not shown; see the Supporting Information). The *R* and *S* enantiomers of the resulting chiral alcohol form preferentially at opposite end faces of the crystal.

Table 2: Enantioselective synthesis at opposite ends of a crystal in separate reaction chambers.

	Reactor side: right *ee* [%]	Reactor side: left *ee* [%]
crystal C, run 1	+15	−21
crystal C, run 2	+11	−10
crystal C, run 3	+17	−12
crystal D, run 1	+3	−11
crystal D, run 2	+7	−16

themselves absolute. Therefore, a combination of the method described herein with an amplification scheme might be a simple and efficient means of rendering asymmetric reactions absolute without the need for any chiral reagents or catalysts.

We conclude that the directed exposure of selected crystal faces to a reductant enables the reduction of a prochiral molecule with significant enantioselectivity. This example of absolute asymmetric synthesis demonstrates the general validity of this attractive concept for oxidation and reduction reactions. The starting compounds and the crystal are all nonchiral; only their spatial orientation with respect to one another leads to the chiral reaction product. We believe that this strategy can be used widely for the synthesis of single enantiomers, as the number of prochiral molecules that crystallize in low-symmetry space groups is very high, and two different important families of organic reactions have now been shown to be amenable to purely geometric absolute asymmetric synthesis. A particularly promising prospect for this alternative approach to absolute asymmetric synthesis is the possibility of combining it with autocatalytic amplification processes, such as Frank-model reaction networks,[38] which are themselves not absolute. Applications in the production of chiral pharmaceutical compounds may thus be envisioned,

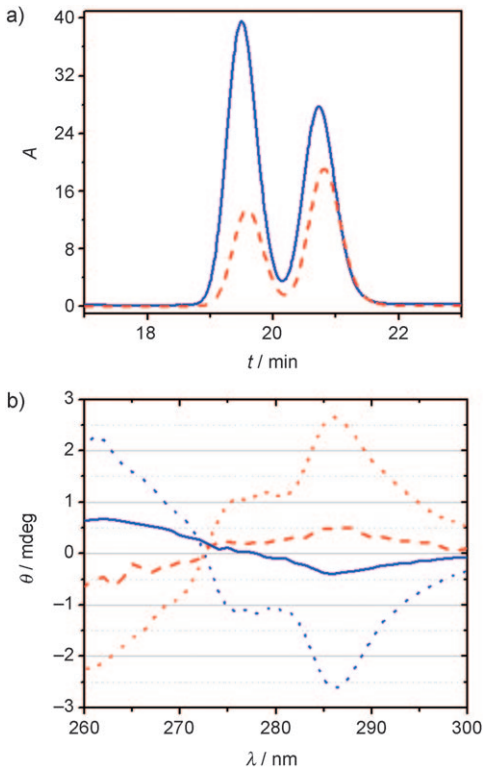


Figure 4. Analysis of the enantioenriched reaction products. a) HPLC on a chiral stationary phase of the products obtained from the opposite ends of crystal C in run 1 (right reactor, solid line; left reactor, dashed line). b) CD spectra of the reaction products from the two reactors (solid and dashed lines) and the two pure enantiomers (dotted lines).

especially if one considers that various other reagents, such as organolithium or organomagnesium compounds, could also be used instead of sodium borohydride.

Received: May 27, 2009
Published online: August 5, 2009

Keywords: absolute asymmetric synthesis · chirality · enantioselectivity · heterogeneous chemistry · single crystals

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