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Fragile asymmetry

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Abstract

Crystallization-assisted asymmetric transformation can be used to prepare single diastereomers of optically pure boron complexes (boroxazolidinones) from amino acids and KBF_3. Conversion into enolates followed by alkylation results in optically pure α-alkyl amino acids after methanolysis of the boron complex.

Crystallization of an equilibrating pair of isomers can result in nearly complete conversion of the mixture into the less soluble isomer.[1] This phenomenon is described in the literature using the term "second order asymmetric transformation", terminology that was taken loosely from the German "asymmetrisches Umlagerung zweiter Art".[2] We have been interested in the possibility of using related techniques for solving problems of asymmetric synthesis. For example, asymmetric transformation might be used to accumulate one of the enantiomers **2a** or **2b**, the adducts of an achiral imine or aldehyde with a prochiral Lewis acid. This might be possible by seeding with the pure enantiomer (kinetically controlled crystallization) or by crystallization from a chiral solvent to differentiate enantiomer solubility (therrmodynamic control). There are some examples where this approach is at least partly successful with simpler substrates,[3] but the spontaneous resolution of sensitive structures such as **2** has not been reported. We are far from a solution to this difficult problem, but it is one of the long range goals of our program.

The classical way to obtain single enantiomers by crystallization is to use reactants that contain an additional stereogenic center. Thus, Lewis acid adducts **3a** and **3b** are diastereomers that should differ in free energy and in solubility. Depending on the location of the second stereogenic center (R*), there may be little or no difference in the solution free energy because intramolecular interactions between R* and the stereogenic boron center may be small while intermolecular interactions are even smaller. However, in the crystal lattice, intermolecular interactions will be far more important. In general, there will be a difference in crystal lattice stability, and therefore, in solubility.[1] The same considerations apply to adducts **4a** and **4b**, derived from a prochiral borane and a chiral Lewis base X*, regardless of the location and nature of the additional stereogenic center. Thus, slow removal of solvent from an equilibrating mixture of **4a** and **4b** should convert all of the mixture into that diastereomer which has the more stable (less soluble) crystal lattice.

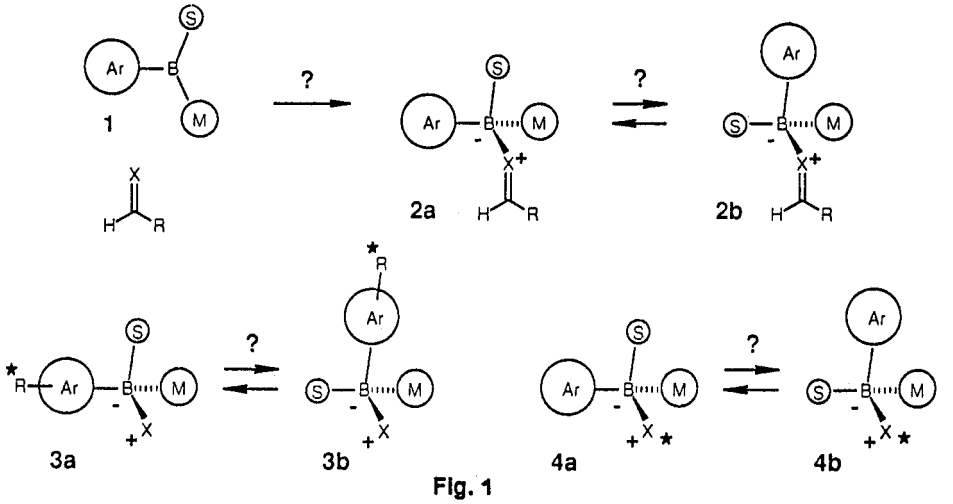


Fig. 1

In contrast to classical resolutions, crystallization assisted asymmetric transformations (hereafter abbreviated as AT) are not limited by a 50% maximum in recovery, and there are a number of examples where yields approach 100%.[1] In cases where the second stereogenic center (*) is derived from an inexpensive source, the AT technique should therefore provide a practical way to obtain optically pure Lewis acid-Lewis base adducts. However, the adducts must be used at temperatures where they do not undergo significant reequilibration. It is essential for the boron center to retain "asymmetric memory", and to store the stereochemical information derived from the crystallization event.

One possible application is illustrated in the case of a cyclic boron complex **5**, derived from an α-heteroatom-substituted carboxylic acid. If **5a** can be crystallized, then conversion into a chiral enolate **6** provides an opportunity to test asymmetric memory. We selected this specific example for investigation because the same concept has already been explored in a carbon-based system by Seebach *et al.*.[4] Thus, oxazolidinone **8** is available from a protected α-amino acid, and alkylation of the chiral enolate affords **10** after hydrolysis. A boron-based analog of the Seebach system is a demanding test for the AT concept. Assuming that **5a** is the less soluble diastereomer in the equilibrating pair, conversion to the enolate **6** followed by alkylation can give optically pure products only if both **5a** and **6** survive this sequence without reequilibration via B--N (or B--O) cleavage.

There are some other helpful analogies for the system chosen for study. Thus, AT is already demonstrated (>90% recovery) in a silicon-based amino acid derivative **12**, available from N-phenyl phenylalanine **11**.[5] Structure **8** is unstable to hydrolysis and does not appear to be suitable for synthetic applications, but analogous boron heterocycles have been prepared and they are hydrolysis-resistant as well as highly crystalline.[6] Asymmetric transformations have been observed in other boron heterocycles,[7] but not in complexes of amino acids similar to **5**.

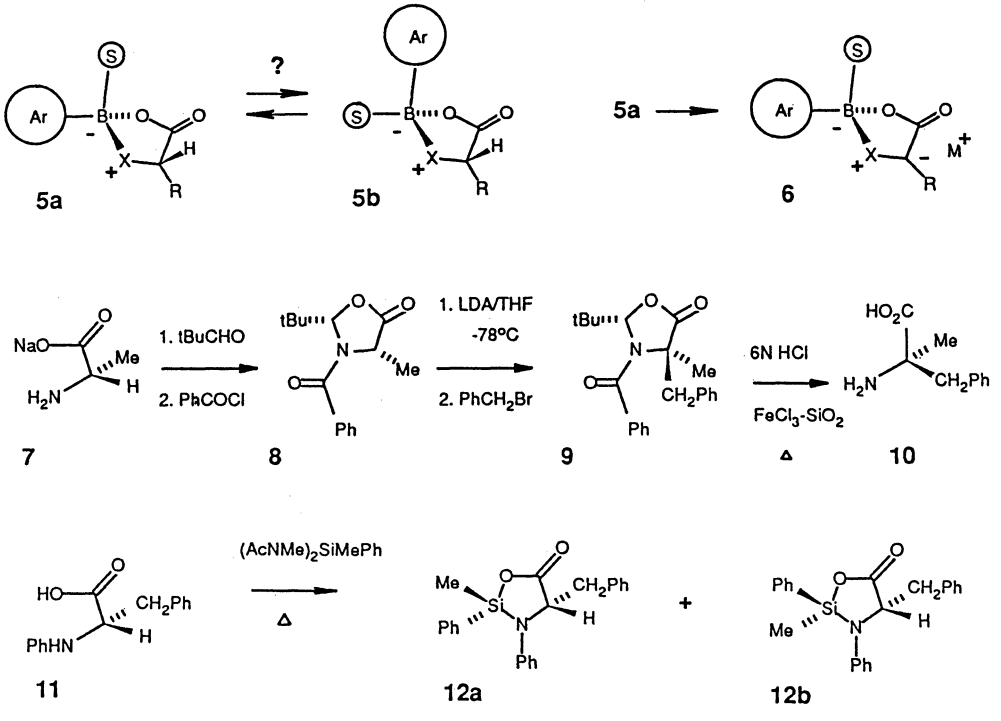


Fig.2

To explore the possibility of AT, we prepared **14** using the reaction of a prochiral borane **13** with phenylalanine. The crude product is a 1:1 mixture in solution, but it crystallizes readily to produce a single diastereomer (>90%). With Ar=C_6F_5, the crystalline diastereomer is reasonably stable in solution, and reequilibrates on a time scale of hours at room temperature. However, the phenyl analog (Ar=C_6H_5) equilibrates completely within an hour because the boron substituents are less electronegative. Under neutral conditions, both systems probably equilibrate via B-N dissociation to **15**, followed by reclosure. However, the rate of diastereomer equilibration is sensitive to the presence of basic catalysts because **14** is readily deprotonated to **16**. Subsequent B-O cleavage provides an additional mechanism for loss of stereochemistry via **17** and equilibration is essentially instantaneous in the presence of triethylamine.

To avoid base-induced equilibration, it is necessary to modify the nitrogen substituent. The dimethylamino group provides one solution to this problem, and the desired complex **18** can be prepared from N,N-dimethylphenylglycine by reaction with a source of $PhBF_2$. After crystallization of the mixture of diastereomers, **18** is obtained as a single diastereomer (X-ray structure proof) in 92% yield.

To demonstrate asymmetric memory, **18** was deprotonated using mesityllithium. After quenching with DCl and recrystallization of the recovered boron complex, deuterium-containing **19** was converted into the α-deuterated N,N-dimethyl phenylglycine, >95% ee according to NMR assay using a chiral shift reagent. Thus, asymmetric memory has been maintained throughout this sequence.

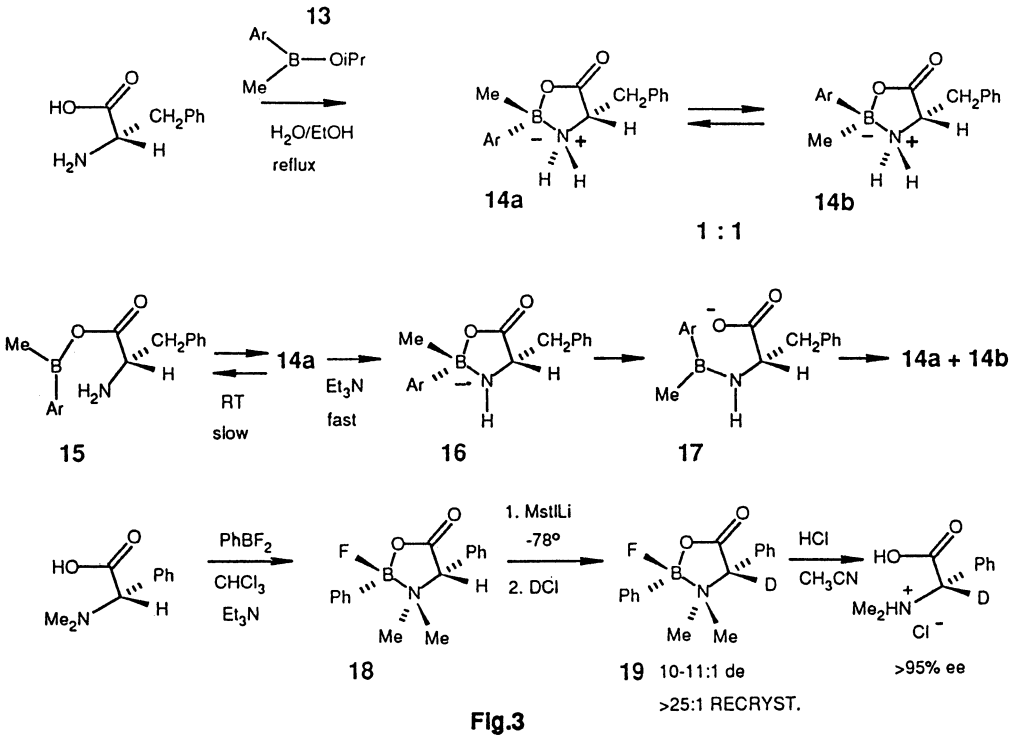
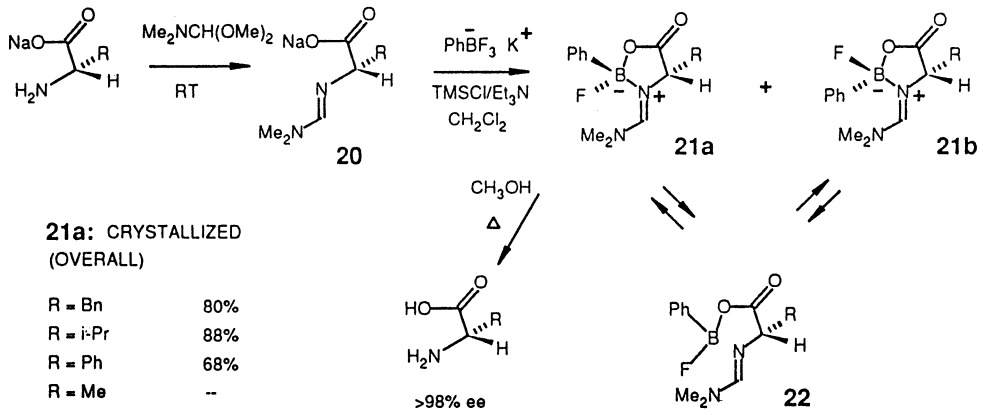


Fig.3

Boron complexes can also be made from amidine-protected amino acids **20**, available from the sodium salts and N,N-dimethylformamide acetal. Conversion into the boron complexes **21** is possible using preformed $PhBF_2$, but a simpler and more convenient method has been developed. The highly crystalline salt $PhBF_3K$[8] is easy to prepare from $PhB(OH)_2$ and KHF_2. When $PhBF_3K$ is exposed to fluoride scavengers such as Me_3SiCl, the $PhBF_2$ reagent is generated reversibly, and conversion to **21** proceeds in high yield. Several derivatives of **21** have been prepared in this way with R=alkyl. Once crystallized, they are stable compounds that can be handled without special precautions. Complexes **21** survive aqueous workup, but they undergo



21a: CRYSTALLIZED (OVERALL)

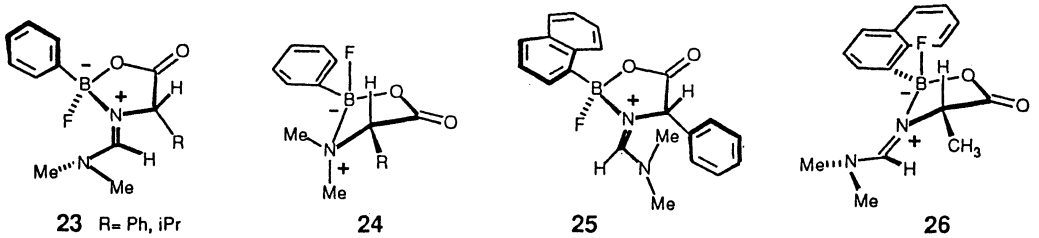
R = Bn	80%
R = i-Pr	88%
R = Ph	68%
R = Me	--

Fig.4

slow cleavage upon warming in hydroxylic solvents. Complete removal of the boron residue as well as the amidine can be effected with <1% racemization simply by refluxing **21** in methanol for several hours.

Crystallization of **21** follows the pattern expected for the AT phenomenon. So far, diastereomer **21a** has always been the crystalline isomer when a phenyl group is attached to boron (X-ray analysis). The same isomer is usually favored in solution, but the stability difference between **21a** and **21b** can be modest, as in the case of phenylalanine (R=CH_2Ph, **21a**:**21b** = ca. 3:1). Initially, we had used a conventional crystallization method to isolate the phenylalanine complex. Individual crops were collected at room temperature, and the mother liquors were concentrated to yield additional crops. In this way, 85% of **21a** was recovered in 5 crops. However, the best way to achieve AT is to allow crystallization to proceed at a temperature where the equilibration process is reasonably fast. Thus, slow evaporation of ethyl acetate from a ca. 3:1 mixture of **21a** + **21b** at 60°C affords >90% of **21a** in a single crop! Since recovery exceeds the amount of **21a** present at equilibrium, AT is clearly demonstrated.

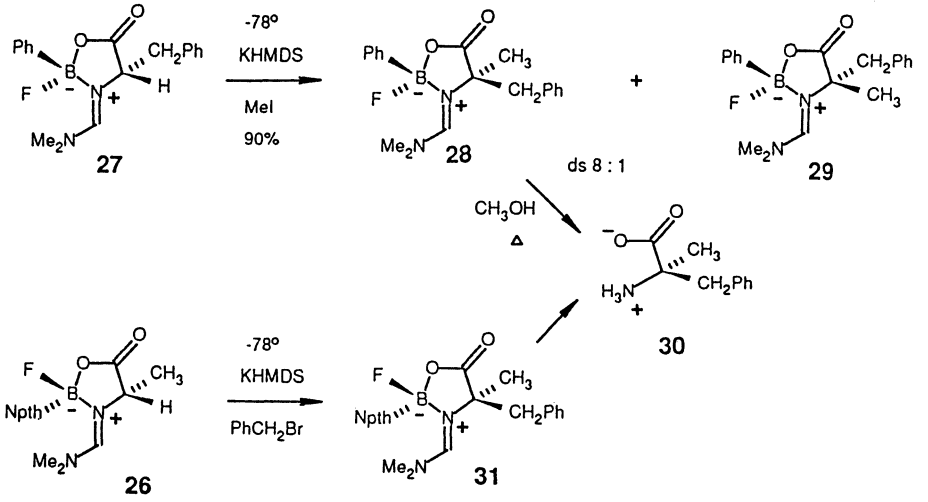
We have encountered examples were AT occurs spontaneously. Thus, solvent removal during workup of crude **21** (R=phenyl or isopropyl) often results in crystallization and nearly total (>10:1) conversion to **21a**. On the other hand, there are stubborn examples such as alanine (R=CH_3) where it is difficult to prevent precipitation of both diastereomers due to low solubility. We have not yet developed successful conditions for the crystallization of the alanine complex in the B-phenyl series. On the other hand, the B-naphthyl derived alanine complex crystallizes without difficulty. Surprisingly, the stereochemistry at boron is inverted by comparison with **21a**, as illustrated by the perspective drawing **26** (B-naphthyl and C-methyl groups cis). One other B-naphthyl complex has been investigated (**25**), but this substance has the same boron stereochemistry as does **21a** (see structure **23** for a sketch of the X-ray structure). Furthermore, the N,N-dimethylphenylglycine complex **24** corresponds to **26** in relative stereochemistry (cis B-phenyl and C-phenyl groups). Apparently, the crystal lattice preferences are controlled by subtle substituent effects. In any event, practical routes to the boron complexes have been developed, and AT has been demonstrated in a number of examples.



23 R= Ph, iPr 24 25 26

Fig.5

Our studies have focused on the enolization and alkylation of phenylalanine and valine-derived boron complexes. Valine tends to be a difficult substrate for many of the alternative chiral amino acid enolate equivalents,[9] but it is the best substrate so far for our AT process. Phenylglycine complexes have also been explored, but many experiments remain to be done before the techniques are fully optimized. The principal features of the alkylations are summarized for the preparation of **30**. Thus, conversion of **27** to the potassium

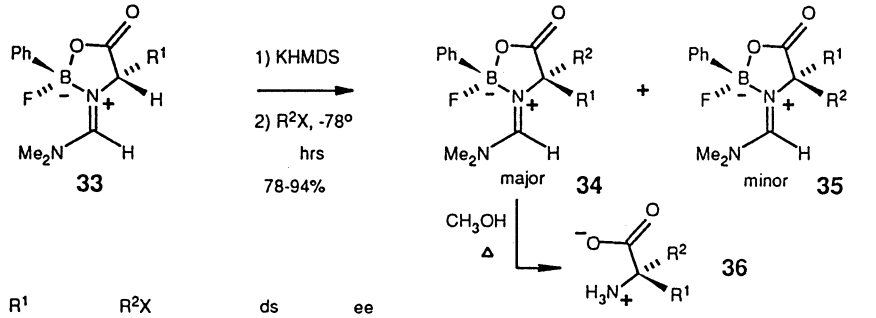


27 28 29 30 26 31

Fig. 6

enolate followed by methylation affords **28** as the dominant diastereomer. After separation from **29**, the complex is cleaved efficiently by refluxing methanol to give **30** with >95% ee, measured according to the method of Kellogg et al.[10] The same enantiomer **30** can also be obtained by benzylation of the B-naphthyl alanine complex **26** followed by methanolysis of **31**. Since **26** differs in boron stereochemistry compared to **27**, enolate benzylation from the less hindered side should give the same stereochemical result as does methylation of **27**.

Valine alkylations also proceed uneventfully. Thus, **33** (R=i-Pr) affords α-alkyl derivatives in good yield via the potassium enolate. We have proved that enantiomer excess (ee) corresponds exactly to diastereomer excess (de) in the methylations and that asymmetric memory has been maintained. The purified alkylation product **34** (R^1=iPr; R^2=CH_3) affords α-methyl valine with >95% ee after cleavage in refluxing methanol. All of these results are summarized in Fig. 7.



R^1	R^2X	ds	ee
CH_2Ph	MeI	87%	>95%
iPr	MeI	81%	>95%
iPr	n-C_3H_7I	87%	
iPr	$PhCH_2Br$	>95%	
iPr	allyl-Br	>95%	

R^1	R^2X	ds	ee
Ph	MeI	67%	40%
Ph	allyl-Br	92%	30%
CH_3	$PhCH_2Br$	98%	--

Fig. 7

In contrast to the valine and phenylalanine complexes, the phenyl glycine complex affords a product with significantly different levels of de vs. ee. Thus, purification of **34** (R^1=Ph; R^2=CH_3) followed by methanolysis affords **36** with an ee of only 40%. This result probably reflects the decreased reactivity of the phenyl-substituted enolate, a factor that increases the risk of B-N bond cleavage, as shown from **37** to **40**. Once achiral **40** is formed, alkylation will produce racemic products. Subsequent diastereomer separation can no longer produce optically pure products because **38** and **39** will be contaminated by **ent 38** and **ent 39**,

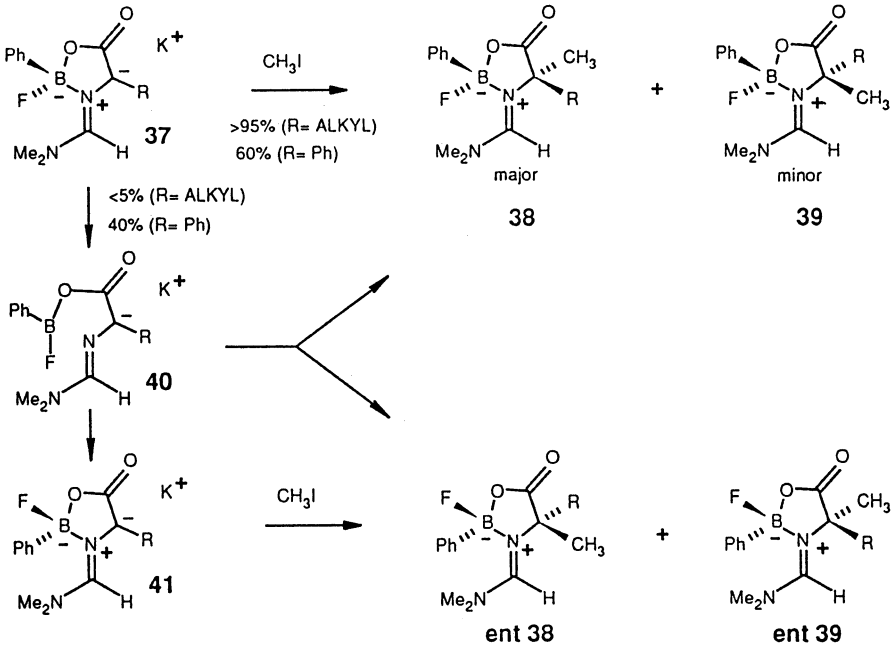


Fig. 8

respectively. Alanine also remains a troublesome substrate because the corresponding B-phenyl boron complex has not yet been crystallized in acceptable purity. On the other hand, the alkylation chemistry works very well, as shown by the last example tabulated in Fig. 7.

In summary, we have established that crystallization assisted asymmetric transformation is a viable means for controlling the stereochemistry at stereogenic boron in complexes of amino acids. The technique allows the synthesis of chiral α,α-dialkyl amino acids with high levels of optical purity. Interconversion of the isomeric boron complexes is easily controlled, and survival of asymmetric memory at boron has been demonstrated for the valine and phenylalanine complexes.

Asymmetric transformations are among the oldest known stereochemical phenomena,[1] but they have seldom been systematically exploited. The preliminary studies presented in this account are intended to develop practical Lewis acids that will routinely allow the crystallization of optically pure adducts. We believe that some progress in this direction has been made.

Acknowledgements

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