Crystallization-Induced Asymmetric Transformation vs Quasi-Racemate Formation in Tetravalent Boron Complexes

E. Vedejs,*,‡ R. W. Chapman, S. Lin, M. Müller, and D. R. Powell

Contribution from the Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

Received November 15, 1999

Abstract: Crystallization-induced asymmetric transformation (AT) has been achieved with the salicaldimine complexes **8**/**9**, **11**/**12**, and **14a**/**15a** and with the oxazaborolidinone complexes **22b**/**23b** and **22c**/**23c**. In the case of **22a** and **23a**, the initially formed 3:1 mixture of diastereomers crystallizes under equilibrium conditions to afford a quasi-racemate **24**, containing both diastereomers in the unit cell. Enolate formation from *ent*-**22b** is demonstrated, and methylation occurs to give **26a**. Aldol condensation of the enolate is also feasible, and hindered aldehydes afford adducts such as **27a** or **27b** with good diastereoselectivity. Factors that contribute to quasi-racemate formation are discussed.

Crystallization-induced asymmetric transformation is a promising technique for control of heteroelement configuration.[1−6] One of the earliest examples reports the conversion of equilibrating isomers of a substance containing stereogenic tin into the most stable crystalline diastereomer.[3a] Other intriguing examples include derivatives of stereogenic silicon,[4] boron,[2,5] and phosphorus,[6] as well as relatively numerous examples involving stereogenic carbon as the site that undergoes configurational equilibration.[7] All of these examples share the distinctive feature that defines crystallization-induced asymmetric transformation (abbreviated below as AT): the more stable crystalline diastereomer is obtained with recoveries approaching 100% based on the mixture, regardless of the equilibrium constant in solution.[1] This phenomenon is a consequence of the thermodynamics of phase equilibrium, and provides a powerful technique for control of absolute configuration. The principal requirement is that interconversion (epimerization) of diastereomers must take place faster than crystallization. Another requirement is that one of the diastereomers must be crystalline at a convenient temperature.

In the context of asymmetric synthesis of structures that contain stereogenic heteroelements, the AT approach can be a direct and practical way to access a single configurational isomer. A superficial disadvantage of AT is that it depends on the use of a chiral auxiliary in stoichiometric amounts. However, the auxiliary can be chosen almost at random among inexpensive materials available commercially. The only stringent requirement is that the auxiliary must not interfere with crystallization. No specific intramolecular structural role is required for the auxiliary, and its proximity to the equilibrating stereogenic atom is not obligatory because its crucial role is to define a chiral space group. The chiral environment within the crystal lattice is the reason AT succeeds, so the most important role of the auxiliary is to influence the intermolecular interactions that govern crystal packing.

Given the broad latitude in the choice of a chiral auxiliary in the AT process, the method is probably superior to a total spontaneous resolution of an equilibrating pair of enantiomers. Isolated examples of this latter scenario are known,[8] but the practical requirements are highly restrictive. The enantiomers must be crystalline, capable of interconversion below the melting point, and higher melting (i.e., more stable) compared to the racemic compound. The latter requirement means that the crystallization has to produce a conglomerate (single enantiomers in the unit cell), but this behavior is relatively rare. It is estimated that only 5−10% of crystalline racemic substances afford conglomerates.[9] In most of the examples, the more stable solid phase is a racemic compound (both enantiomers present in the unit cell in a 1:1 ratio). Thus, at least ca. 90% of racemic substances cannot be candidates for total spontaneous resolution due to the requirement of conglomerate formation, not to mention the nontrivial requirements of crystallinity and enantiomer interconversion.

‡ Current address: Department of Chemistry, University of Michigan, Ann Arbor, MI 48109.

(1) (a) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing: Malabar, FL, 1994; Chapter 6. (b) Harris, M. M. *Prog. Stereochem.* **1958**, *2*, 157. Secor, R. M. *Chem. Rev.* **1963**, *63*, 297.

(2) (a) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612. (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460. (c) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *59*, 3020. Vedejs, E.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *59*, 3028.

(3) (a) Pope, W. J.; Peachey, S. J. *J. Chem. Soc. Proc.* **1900**, *16*, 42. (b) van Koten, G.; Noltes, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 5393. van Koten, G.; Jastrzebski, J. T. B. H.; Noltes, J. G.; Pontenagel, W. M. G. F.; Kroon, J.; Spek, A. L. *J. Am. Chem. Soc.* **1978**, *100*, 5021.

(4) Klebe, J. F.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 7255.

(5) Gyori, B.; Emri, J. *J. Organomet. Chem.* **1982**, *238*, 159.

(6) (a) Bader, A.; Pabel, M.; Wild, S. B. *J. Chem. Soc., Chem. Commun.* **1994**, 1405. Bader, A.; Pabel, M.; Willis, A. C.; Wild, S. B. *Inorg. Chem.* **1996**, *35*, 3874. (b) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293.

(7) Mioskowski, G.; Solladié, G. *Tetrahedron* **1980**, *36*, 227. Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 955. Wilen, S. H.; Qi, J. Z.; Williard, P. G. *J. Org. Chem.* **1991**, *56*, 485. For other examples, see ref 1.

(8) Havinga, E. *Biochim. Biophys. Acta* **1954**, *13*, 171. Pincock, R. E.; Perkins, R. R.; Ma, A. S. *Science* **1971**, *174*, 1018. Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.

(9) See ref 1a, p 81.

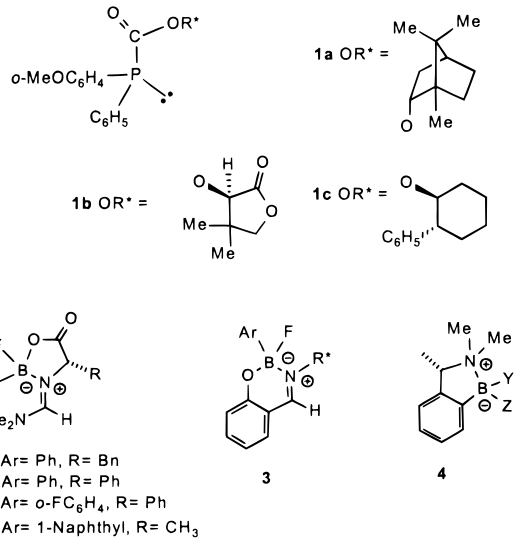
10.1021/ja994023t CCC: $19.00
Published on Web 03/21/2000

Racemic compound formation has a close analogy in the crystallization of diastereomer mixtures. It is possible that two diastereomers would prefer to cocrystallize in an arrangement that places both diastereomers in the unit cell in a 1:1 ratio. Such behavior is termed quasi-racemate formation[10] and several crystal structures of this type are known.[11] If a given stereogenic atom dominates crystal packing for steric or electronic reasons, the crystal lattice tolerates the other stereogenic atom(s) as a minor player that may be present in more than one arrangement with respect to neighboring atoms. In a typical racemate (a racemic compound) each atom of one enantiomer can be paired in centrosymmetric fashion with the corresponding atom of the enantiomer. In a quasi-racemate, the crystal lattice arrangement can resemble a racemate, but the unit cell lacks the formal symmetry elements characteristic of the racemic compound.

One purpose of the work described in this paper was to probe the likelihood of quasi-racemate formation within a group of loosely related structures containing stereogenic boron. This was done by selection of several easily accessible structural types that are related by the presence of C, N, and O substituents at boron. We could find no more systematic basis in the literature to probe or anticipate which structural features are likely to promote quasi-racemate formation. This phenomenon could be a serious obstacle for practical use of AT because it would result in the crystallization of both absolute configurations of a given stereogenic heteroelement within the same crystalline product. If the success rate for AT is well below 50%, as in the case of conglomerate formation, then it would be unwise to pursue AT as an alternative to spontaneous resolution. There are more reports of AT than examples of quasi-racemate formation,[1,12] so it was likely from the outset that the success rate of AT would be reasonably high. On the other hand, in our recent investigation of AT in an organophosphorus environment, one out of the three diastereomer pairs **1a**−**c** crystallized as the quasi-racemate (**1a**).[6b] It seemed possible that the relatively large number of cases where AT affords nearly total conversion to one isomer vs reports of quasi-racemate formation in the literature could be the result of the human element. First encounters with AT are often by accident, and it is striking to find that a mixture of diastereomers is converted with >95% recovery to a single isomer simply by crystallization. Such observations are more likely to be closely investigated than quasi-racemate formation. In the latter, a mixture of isomers crystallizes to give a "mixture", and the phenomenon could easily be dismissed as a failed crystallization.

It was encouraging to learn that none of several closely related oxazaborolidinones **2a**−**d** crystallize as the quasi-racemates,[2] and that AT takes place consistently. Since the latter series constitutes one structural family with minor changes in nonpolar substituents, it could be argued that it is really no more than a single fundamental example. Accordingly, we set out to prepare other tetravalent boron structures containing larger variations of the substituents that are present in **2a**−**d**. A systematic survey was far beyond the intended scope of this study. We were primarily interested in reassurance that quasi-racemate formation

Scheme 1



is not a major concern for the AT concept as structural features of interrelated molecules are varied.

Two classes of stereogenic boron-containing molecules were investigated following prior analogy.[13,14] The first structural type **3** was based on the well-known salicaldimine boron complexes modified by the incorporation of a chiral carbon subunit R*.[13] The second structural type was designed to modify the precedented chiral benzoazaborolidine nucleus **4**.[14] In this case, stereogenic carbon and boron atoms are present within the same subunit, so the substituents Y and Z must be different, but need not be chiral to provide the environment for AT.

Results

Access to representative structures based on **3** was possible using a variation of our previously reported aryltrifluoroborate methodology.[2] Thus, imine **5**[15] was treated with $KPhBF_3$/TMSCl in dichloromethane at room temperature (12 h). After aqueous workup, the complex **6** was isolated by crystallization in 89% yield as an air-stable, water-resistant substance. On the basis of this encouraging result, a similar experiment was performed with the chiral imine **7**.[16] The crude product was obtained as an oil that consisted of two diastereomers **8** and **9** in a 1:1.2 ratio according to NMR assay. When the oil was taken up in hexane, followed by slow evaporation of solvent, a crystalline product was obtained in 80% overall yield as a 38:1 mixture of **8**:**9**. The equilibrium diastereomer ratio of 1:1.2 was restored within 12 h if the crystalline material was dissolved in deuteriochloroform. Since the recovery of **8** in the crystalline product far exceeds the amount originally present at equilibrium, it is clear that the crystallization occurs under AT conditions.

The boron configuration of the crystalline diastereomer **8** is not known with certainty, and the substance was not studied in

(10) See ref 1, pp 100 and 280.

(11) Collet, A.; Jacques, J. *Isr. J. Chem.* **1976**/**1977**, *15*, 82. Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395.

(12) The term "quasi-racemate" also refers to a compound that results from cocrystallization of quasi-enantiomeric substances that differ by the replacement of one substituent (for example, chlorine) by a similar substituent (such as bromine) in the enantiomer. Thus, many of the reported quasi-racemates are not strictly analogous to solids where diastereomer pairs cocrystallize.

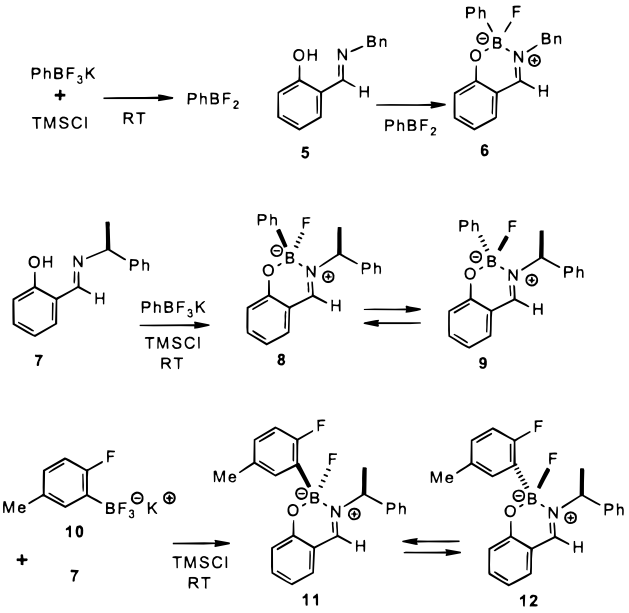
(13) (a) Hohaus, E. *Z. Anorg. Allg. Chem.* **1982**, *484*, 41. Winkler, E.; Hohaus, E.; Felber, E. *J. Chromatogr.* **1988**, *436*, 447. Claas, K. E.; Hohaus, E.; Monien, H. *Z. Anal. Chem.* **1986**, *325*, 15. (b) Korobov, M. S.; Nivorozhkin, L. E.; Konstantinovsky, L. E.; Minkin, V. I. *J. Chem. Soc., Chem. Commun.* **1982**, 169. Korobov, M. S.; Borodkin, G. S.; Borisenko, N. I.; Ryskina, T. A.; Nivorozhkin, L. E.; Minkin, V. I. *J. Mol. Struct.* **1989**, *200*, 61. (c) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063.

(14) (a) Lauer, M.; Wulff, G. *J. Organomet. Chem.* **1983**, *256*, 1. (b) Lauer, M.; Wulff, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 745. (c) Vedejs, E.; Nguyen, T.; Powell, D. R.; Schrimpf, M. R. *J. Chem. Soc., Chem. Commun.* **1996**, 2721.

(15) Brown, N. M. D.; Nonhebel, D. C. *Tetrahedron* **1968**, *24*, 5655.

(16) Takahashi, H.; Suzuki, Y. *Chem. Pharm. Bull.* **1983**, *31*, 4295.

Scheme 2

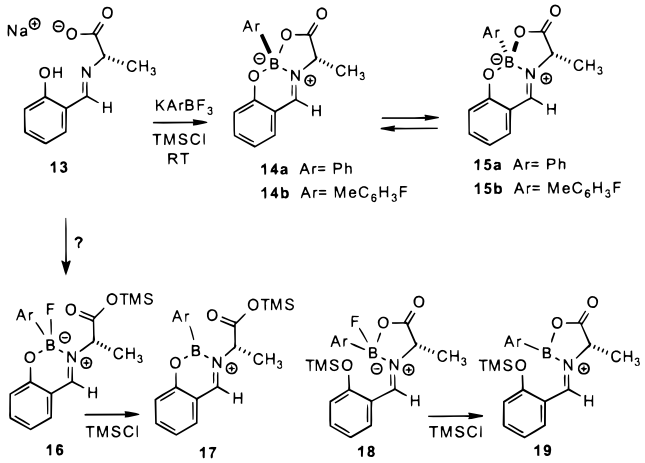


detail because of the facile interconversion of epimers at room temperature. However, supporting evidence for this assignment was obtained from NMR correlations with a closely related structure **11** that was prepared using the *o*-fluoroaryltrifluoroborate salt **10** as an in situ source of reactive trivalent boron.[2b,c] Activation of **10** with TMSCl in the presence of **7** afforded a 1:1.1 mixture of diastereomers **11** and **12**. The initially formed oil did not crystallize at room temperature, but warming the mixture in hexane resulted in the rapid formation of colorless crystals of **11**, 92% overall yield. In this case, the rate of isomer interconversion at room temperature was conveniently slow due to the inductive effect of the *o*-fluorine, and characterization of **11** was easy. Crystals suitable for X-ray crystallography were obtained by conventional recrystallization, and the indicated boron configuration in **11** was confirmed. The crystalline product is the *minor* component of the equilibrium mixture. Since there need be no correlation between solution phase and crystal lattice stability, this result is not surprising. Similar behavior was observed in a previous study.[2]

In view of these promising AT results, we explored a second structural variation related to the salicaldimine complex type **3**. In this case, the "tridentate" salicaldimine carboxylate **13**[17] was used as a substrate. Standard fluorophilic activation of $KPhBF_3$ or the *o*-fluoro analogue **10** with TMSCl in the presence of **13** resulted in displacement of all three B−F bonds and produced the diastereomeric complexes **14** and **15**. This outcome is a logical consequence of conditions where excess fluorophile (TMSCl) is present. One possible interpretation assumes that **16** is formed initially, similar to the events involved with the simpler salicaldimine examples **8** or **11**. Fluorophilic activation of the remaining B−F bond would generate a transient cationic boron intermediate **17** followed by cyclization to **14** + **15**. However, the alternative via **18** and **19** is also precedented[2] and cannot be ruled out. In either scenario, a cationic, strongly electrophilic borane (**17** or **19**) is implicated in the overall conversion. These cationic structures may also be involved in the equilibration of boron configuration, as discussed below.[18]

Conventional room temperature crystallization of the crude oil containing **14a** and **15a** gave **14a** in 73% yield (structure confirmed by X-ray crystallography; nonequilibrating crystallization conditions). Product recovery did not exceed the amount of **14a** present in the initial mixture and the mother liquor was enriched in **15a**. Therefore, AT was probably not involved in the crystallization of **14a**. Indeed, purified **14a** proved to be quite resistant to equilibration with **15a** unless the substance was heated in refluxing toluene. On the other hand, the initial product ratio from **13** was somewhat variable, and did not always correspond to the equilibrium ratio of 5.8:1. These observations suggested that the interconversion of **14a** with **15a** might be a catalyzed process that occurs under the conditions of fluorophilic activation. This was confirmed by treatment of purified **14a** with 10 mol % of TMSCl in dichloromethane or deuteriochloroform. The equilibrium ratio of 5.8:1 **14a**:**15a** was established within 3 days. A preparative version of this experiment was performed with slow evaporation of the solvent, resulting in recovery of a crystalline solid, 26:1 **14a**:**15a**, 96% yield from the 5.8:1 mixture of diastereomers. This result confirms that a typical AT process has taken place under the conditions of catalyzed diastereomer interconversion. Because the catalyst (TMSCl) is easily destroyed in workup or removed by rinsing with solvent, the overall result is especially convenient from a preparative perspective. Once **14a** is isolated, further equilibration of boron configuration does not occur. Therefore, the purified **14a** would be available for chemical transformations that rely on boron to store stereochemical information.

Scheme 3

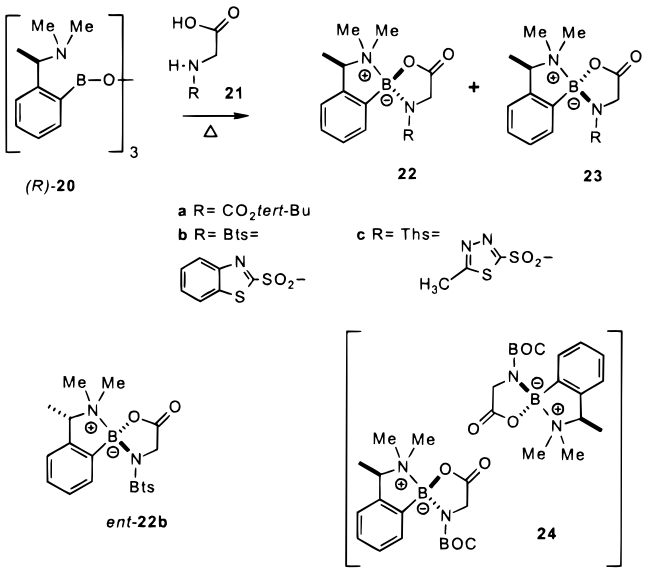


As expected, the *B*-(*o*-fluoroaryl) analogues **14b** and **15b** were considerably more resistant to isomer interconversion. Only partial equilibration of isolated **14b** occurred at room temperature using a full equivalent of TMSCl as the catalyst to produce a 7.4:1 ratio of **14b**:**15b** after 3 days. Complete equilibration required an hour in refluxing chloroform and resulted in a 5.2:1 ratio of **14b**:**15b**. These conditions are not suitable for the optimum AT experiment (slow solvent removal) because the catalyst is volatile, and other AT variations were not pursued in view of the success with **14a**. In terms of mechanistic possibilities, the available evidence is consistent with oxophilic activation of **14**/**15** via **17** or **19** as the intermediates for diastereomer interconversion.

(17) Block, H.; Faulkner, P. J. *J. Chem. Soc. C* **1971**, 329.

(18) Related cationic, trivalent boron intermediates may also play a role in the hydrolytic cleavage of **14a**. The substance is stable in methanol at room temperature, an observation that indicates that trivalent boron is not kinetically accessible under these conditions. Upon addition of catalytic HCl, cleavage proceeded slowly. On the other hand, methanolic KHF_2 cleaves **14a** within 1 h at room temperature. After filtration and evaporation, the residue was extracated with hot acetonitrile to give alanine as the insoluble portion and $KPhBF_3$ as the crystalline product that separated upon cooling the acetonitrile, both formed with >90% recovery. Apparently, cationic boranes are formed under these conditions, and trapping by fluoride ion affords the more stable fluoroborate $KPhBF_3$.

Scheme 4



Further efforts to probe the scope of AT focused on the structural category **4.** Members of this family have been prepared simply be heating an arylboronic acid with a difunctional organic molecule capable of forming two covalent bonds to boron.[13,19] Following these analogies, *N*-*tert*-butoxycarbonylglycine was refluxed with the known *(R)*-**20** in 7:1 toluene:THF for several hours. After solvent removal, the crude product was obtained as a ca. 3:1 mixture according to NMR analysis. The isomers could not be separated by chromatography, but dilution of a concentrated toluene solution with ether gave crystals in 59% yield. However, an NMR spectrum of the solid product indicated a mixture of isomers. In particular, two singlets for the *tert*-butyl groups were observed in a 1:1 ratio, and other signals were consistent with the presence of diastereomers **22a** and **23a**. When the solution was warmed to 60 °C, the isomer ratio slowly changed to the same 3:1 mixture that had been seen prior to crystallization. Multiple attempts to recrystallize the solid or to grow crystals under different conditions always gave the same 1:1 solid. This behavior became clear when X-ray quality crystals were obtained. Both diastereomers corresponding to **22a** and **23a** were present in the unit cell, so the crystalline product is a distinct compound **24**, consisting of equal parts of each diastereomer. The two diastereomers are arranged in a nearly symmetrical fashion with respect to a quasi-center of symmetry halfway between the two boron atoms in structure **24** (Figure 1). Most of the atoms of subunit **22a** are mirrored by corresponding atoms in subunit **23a**, resulting in opposite boron configurations. However, the benzylic carbons have the same absolute configuration, and this feature results in a unit cell that lacks a true axis of symmetry. Thus, **24** is a quasi-racemate. Some other X-ray structures have been reported for quasi-racemates,[11] but we could find no prior example where quasi-racemate formation is accompanied by asymmetric transformation (from a 3:1 to a 1:1 ratio of **22a**:**23a**).

Interactions among the polar boron substituents probably dominate crystal packing to favor the quasi-racemate structure **24** in the solid. Presumably, the benzylic C-methyls as well as the O-*tert*-butyl groups contribute less to the intermolecular interactions in the crystal lattice. In an attempt to perturb the relative magnitudes of these interactions, the CO_2 *t*-Bu subunit

(19) The potassium trifluoroborate/TMSCl method can also be used starting from **20** and KHF_2 in methanol (ref 14c), but there is no advantage in overall yield.

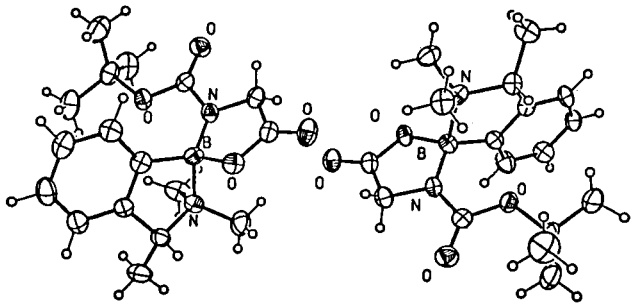


Figure 1. X-ray crystal structure of **24** (quasi-racemate).

was replaced by the relatively polar and bulky benzothiazole-2-sulfonyl (Bts) group.[11] The conversion from *(R)*-**20** and **21b** was performed as before, and the crude product was formed in a 20:1 ratio of diastereomers. The larger isomer ratio allowed facile product isolation by conventional crystallization, and the major diastereomer **22b** crystallized exclusively. Mother liquors partially enriched in **23b** were obtained, but further manipulations resulted in the equilibrium mixture (20:1 isomer ratio) and the minor isomer **23b** could not be isolated. When the mixture was crystallized under AT conditions (warming; slow evaporation of solvent), a crystalline residue consisting of a 40:1 ratio of **22b**:**23b** was obtained. These results indicate that interconversion of **22b** and **23b** takes place and that AT is responsible for the increase in the diastereomer ratio.

A variety of crystallization conditions were explored in the course of these experiments, but a quasi-racemate containing **22b** and **23b** was never obtained. This finding suggests that crystalline **22b** is more stable than the quasi-racemate. However, the possibility remained that **22b** had crystallized under kinetic (not thermodynamic) control due to adventitious seeding. As a precaution against this scenario, the enantiomeric diastereomer pair *ent*-**22b**/*ent*-**23b** was prepared starting from *(S)*-**20**. Crystallization proceeded as before and gave a single diastereomer of *ent*-**22b**. Therefore, it is likely that crystallization of **22b** from the mixture of **22b** and **23b** is a thermodynamically controlled process.

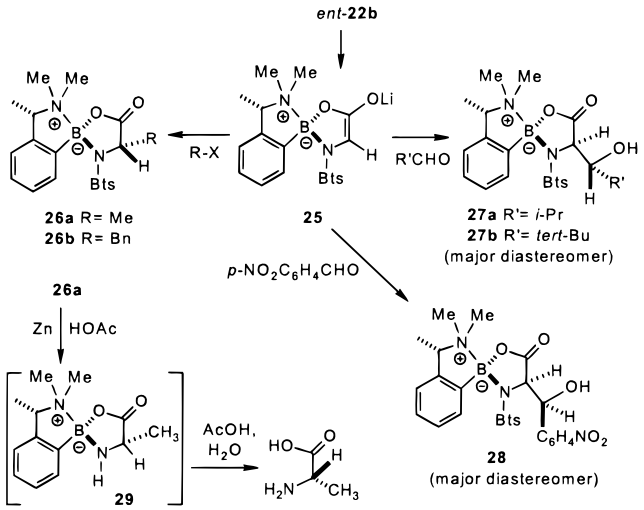
One additional variation was explored using *N*-(5-methyl-1,3,4-thiadiazol-2-ylsulfonyl)glycine (Ths-Gly; **21c**) in place of **21a** in the reaction with **20**. The experiment was performed as in the case of **22b**, and very similar results were obtained. The crude product consisted of a 10:1 mixture of diastereomers **22c**:**23c**. Conventional crystallization afforded **22c** together with mother liquors enriched in **23c**, but warming converted the mother liquor fraction into the same 10:1 equilibrium mixture and slow evaporation of solvent (AT conditions) resulted in an isomer upgrade to 35:1 **22c**:**23c**. No quasi-racemate fromation was observed, although this system was not explored in detail. Evidently, replacement of the BOC protecting group of **22a** by the relatively polar heteroaromatic sulfonyl protecting groups is sufficient to prevent quasi-racemate formation.[21]

Enolate Generation from *ent*-22b. Several of the substances described above contain potentially enolizable amino acid subunits in a chiral environment defined by stereogenic boron. We therefore considered the possibility that they might serve as substrates for the enantiocontrolled introduction of carbon bonds adjacent to carbonyl. In particular, the enantiomers **22b** or *ent*-**22b** were of interest because they have the potential to

(20) Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796.

(21) The *N*-benzyloxycarbonyl analogue of **22a**/**23a** also crystallizes as a quasi-racemate, as evidenced by the formation of a 1:1 crystalline isomer mixture from the 3:1 ratio of diastereomers in solution. The *N*-tosyl derivative crystallizes to afford a single diastereomer analogous to **22b**.

Scheme 5



serve as chiral glycine equivalents.[22] Early experiments with *ent*-**22b** were promising. Thus, treatment with typical lithium or potassium bases at −78 °C gave the enolate and reaction with iodomethane formed **26a** (structure confirmed by X-ray crystallography) and a minor product tentatively assigned as the diastereomer. The best product ratio (>40:1) was obtained using KHMDS as the base for enolate generation, but the yield was only 50% and it was necessary to deprotonate *ent*-**22b** in the presence of iodomethane to intercept the enolate prior to decomposition. Better yields, but lower isomer ratios were obtained using lithium bases, and the best compromise was to use mesityllithium or LDA in THF/TMEDA for generation of the enolate **25**. This afforded **26a** in 86−90% yield (17:1 isomer ratio) after methylation over 2 h at −78 °C. The corresponding reaction of **25** with benzyl bromide was not successful, and produced a 3:1 mixture of isomers in only 7% yield, assumed to favor the diastereomer **26b** by analogy. The reaction was slow compared to the methylation, but attempts to achieve greater conversion at higher temperatures were thwarted by decomposition of the enolate. In a control experiment, a solution of **25** was kept for 1 h at −60 °C, and was then quenched with water. Only 20% of **22b** was recovered, along with a complex mixture of decomposition products, so the enolate alkylations were not pursued.

The reaction of the lithium enolate **25** with aldehydes was also explored briefly. Reactivity was sufficient at −78 °C for efficient conversion into adducts, and the reaction with isobutyraldehyde gave a single dominant product **27a** (85%) according to X-ray evidence. This result was unexpected because the sense of carbon bond formation at enolate C-α is opposite compared to the methylation result. The corresponding reaction with pivaldehyde was less selective, and gave an 8:1 ratio of isomeric products. On the basis of similarities in the NMR spectra compared to **27a**, the major isomer (66%) is believed to have the configuration shown in **27b**, but the stereochemistry of the minor isomer is not known. An attempt to use propionaldehyde as the carbonyl reactant gave a complex mixture of four diastereomers that was not investigated further.

The reaction of **25** with aromatic aldehydes proceeded well, but diastereoselectivity was low. In a representative example, *p*-nitrobenzaldehyde gave a mixture of isomers (1.3:1) in 64% yield. Suitable crystals of the major product were obtained for X-ray crystallography, and the structure proved to be that shown in **28**. The carbon configuration at enolate C-α is the same as in the highly selective isobutyraldehyde reaction, but the hydroxyl group is in the alternative orientation. In view of the inconsistent selectivity patterns, these reactions were not explored in detail, and the origins of the diastereoselectivity remain unclear.

One final experiment was performed with **26a** to demonstrate that the boron complex can be cleaved to release the amino acid. Thus, **26a** was treated with Zn/HOAc at room temperature, conditions that are known to cleave the Bts group.[20] The intermediate **29** did not survive, presumably because removal of the electron-withdrawing Bts group destabilizes tetravalent, anionic boron. After ion exchange chromatography, *(S)*-alanine was obtained in 90% yield and with 97% ee. This experiment shows that **25** must retain boron configuration over the sequence of enolate formation and alkylation. Furthermore, use of **25** as a chiral glycine enolate equivalent is confirmed, but the scope of the method is restricted due to limitations in enolate stability and diastereoselectivity.

Summary

Crystallization-induced asymmetric transformation (AT) has been achieved with the salicaldimine complexes **8**/**9**, **11**/**12**, and **14a**/**15a** and with the oxazaborolidinone complexes **22b**/**23b** and **22c**/**23c**. A more subtle situation was encountered with **22a** and **23a**. Technically, these diastereomers also undergo AT because the equilibrium ratio in solution (3:1) is different compared to the ratio of isomers in the solid (1:1). However, the **a** series affords a quasi-racemate **24** with both diastereomers present in the crystal lattice. In the **b** series, the starting diastereomer ratio is so high (20:1 **22b**:**23b**) that AT is not necessary for practical recovery of the favored isomer, but the AT phenomenon does take place as evidenced by the increase in the diastereomer ratio to 40:1. The crystallization to afford a dominant diastereomer appears to be under thermodynamic control.

The new findings with interconvertible boron diastereomers resemble the earlier study of equilibrating acylphosphine invertomers **1**[6] in that quasi-racemate formation is a significant risk in the AT-based approach to stereogenic heteroatoms. However, in both of the examples of quasi-racemate formation (**1a**; **22a**/**23a**), it was possible to change the favored mode of crystallization by increasing the polarity of substituents. We do not know which specific crystal lattice properties of the Bts or Ths groups are responsible for promoting the formation of crystals containing a single diastereomer in the unit cell in the case of **22b** or **22c**. However, we can tentatively conclude that quasi-centrosymmetric arrangements similar to that present in the quasi-racemate **24** are more likely if the appendages (protecting groups; side chains; chiral auxiliaries; etc.) make few specific demands, inter- as well as intramolecular, for packing in the crystal lattice. Substituents that interact more strongly with neighboring molecules due to demanding geometry, bulk, electrostatic interactions, π-stacking, H-bonding, etc. are more likely to promote crystallization with a single diastereomer in the unit cell starting from an equilibrating mixture of diastereomers. If suitable precautions are taken in designing the structural features of substrates intended to exploit AT, then

(22) Ikegami, S.; Uchiyama, H.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009. O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(23) Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chim. Acta* **1981**, *64*, 716.

(24) Brückner, H.; Wittner, R. *J. Chromatogr.* **1989**, *476*, 73.

crystallization under equilibrating conditions should provide a reliable means for controlling heteroelement configuration.

Acknowledgment. This work was supported by the National Institutes of Health (GM 44724).

Supporting Information Available: Experimental procedures and X-ray data tables (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA994023T