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Reviews

Developing Processes for Crystallization-Induced Asymmetric Transformation

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Abstract:

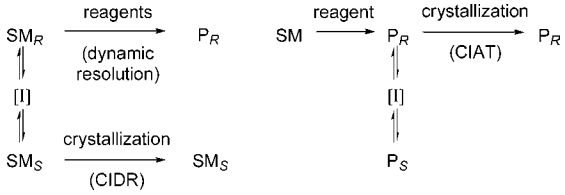
Crystallization-induced dynamic resolution (CIDR) is an adaptation of dynamic resolution, a process that can afford in principle a quantitative yield of chiral product from a racemic starting material through in situ resolution. Crystallization-induced asymmetric transformation (CIAT) includes CIDR and the preparation of diastereomers and olefins that are driven by crystallization. The history of CIAT and CIDR processes is reviewed, along with key observations made by researchers. Recommendations are made for identifying opportunities for and developing CIAT processes.

Introduction

Crystallization is an effective means to develop highly stereoselective processes,[1] and processes centered on crystallization may be the most economical for resolutions.[2] Direct isolation processes, where the product is crystallized directly from the reaction mixture,[3] can be cost-effective even when the yield of isolated product is less than the yield from a conventional workup that uses extraction before crystallization.[4] In addition to compounds that are chiral at carbon, stereoselective processes may be used to generate olefins (*E*- and *Z*-geometries) and compounds that are chiral at phosphorus, boron, sulfur, and other heteroatoms. When one chiral center is present, compounds may be enantiomeric; when more than one chiral center is present, compounds may be enantiomeric or diastereomeric.[5]

Asymmetric synthesis is frequently used in preparing drugs and drug candidates, and the preparation of a desired enantiomer demands special attention. Under classic resolution conditions, such as crystallization of the desired amine enantiomer from a racemic mixture using a chiral acid,[6] the maximum yield of the desired enantiomer is only 50%. More recently kinetic resolutions have been developed as practical approaches to obtaining one enantiomer by exploiting different reactivities of enantiomeric intermediates to enzymes[7] or chiral reagents; to obtain products with high enantiomeric purities, processes may be stopped before 50% conversion, thus reducing the yield of the desired enantiomer to less than 50% of the moles of the initial carbon framework.[8] To recover more of the resources invested in preparing the racemate, some researchers have isolated and racemized the undesired enantiomer and recycled it by subjecting the racemic mixture to the resolution conditions.[9] Although this racemizing−recycling approach requires additional time and materials, the theoretical yield can be raised above 50%.

Scheme 1. **General dynamic resolution approaches**



Dynamic resolution allows each enantiomer to be converted to the desired, chiral product in one operation, through in situ racemization. The principles behind such nonstatic processes have been thoroughly discussed by Faber.[10] The approaches most commonly used are generalized in Scheme 1, where SM_R, SM_S, P_R, and I refer to the *R*-enantiomer of starting material, the *S*-enantiomer of starting material, the *R*-enantiomer of product, and an achiral intermediate, respectively. (For the purpose of this introduction, the chirality of each compound could be reversed.) Elegant examples of the top approach can be found in the work of Noyori,[11] Bäckvall,[12] Trost,[13] and Deng,[14] among others. In situ racemization and selective crystallization can lead to a

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(1) Spargo, P. Low-tech or high-tech? *Chem. Ind.* **2004**, *May 3*, 20.
(2) Hawkins, J. M.; Watkins, T. J. N. Asymmetric Catalysis in the Pharmaceutical Industry. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224.
(3) Chen, C.-K.; Singh, A. K. A Bottom-Up Approach to Process Development: Application of Physicochemical Properties of Reaction Products toward the Development of Direct-Drop Processes. *Org. Process Res. Dev.* **2001**, *5*, 508.
(4) Anderson, N. G. Assessing the Benefits of Direct Isolation Processes. *Org. Process Res. Dev.* **2004**, *8*, 260.
(5) Testa, B. *Principles of Organic Stereochemistry;* Marcel Dekker: Basel; 1979.
(6) Wilen, S. H.; Collet, A.; Jacques, J. Strategies in Optical Resolutions. *Tetrahedron* **1977**, *33*, 2725.
(7) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. Enantioselective Enzymatic Desymmetrizations in Organic Synthesis. *Chem. Rev.* **2005**, *105*, 313.
(8) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. Practical Considerations in Kinetic Resolution Reactions. *Adv. Synth. Catal.* **2001**, *343*, 5.
(9) (a) Racemization of ribose: Schmidt, R. R.; Lieberknecht, A. Functional Derivatives of D- and L-Ribose by Optical Resolution with Recycling. *Angew. Chem., Int. Ed. Eng.* **1978**, *17*, 769. (b) Racemization and recycling of α-methyl DOPA intermediates: Reinhold, D. F.; Firestone, R. A.; Gaines, W. A.; Chemerda, J. M.; Sletzinger, M. Synthesis of L-α-Methyldopa from Asymmetric Intermediates. *J. Org. Chem.* **1968**, *33*, 1209.
(10) Faber, K. Non-Sequential Processes for the Transformation of a Racemate into a Single Stereoisomeric Product: Proposal for Stereochemical Classification. *Chem.—Eur. J.* **2001**, *7*, 5005.

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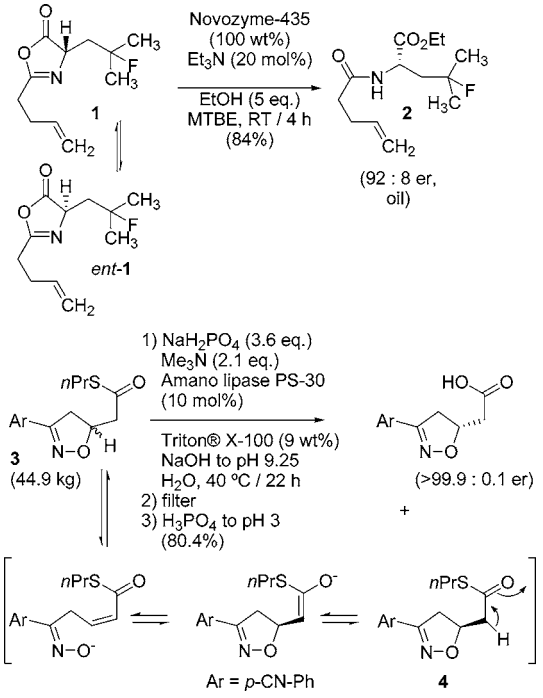
Scheme 2. **Examples of dynamic resolution under basic conditions**



crystallization-induced dynamic resolution (CIDR). In situ racemization (or epimerization) and selective crystallization of a reaction product can lead to a crystallization-induced asymmetric transformation (CIAT). Dynamic resolution has been reviewed by Bull,[15] Vedejs,[16] Beak,[17] Caddick,[18] and Pellissier,[19] and a mathematical approach to optimization has been developed recently by Andraos.[20]

Two recent examples in Scheme 2 illustrate some points of dynamic resolution, the concepts of which can be applied to crystallization-induced dynamic resolutions. Merck researchers converted a mixture of **1** and ent-**1** to the ester **2** in 84% yield, based on the input of racemic starting material.[21] Moderately basic conditions (20 mol % Et_3N) promoted the racemization (pK_a 8.8−9 for the azlactone methine[22]), and in MTBE organic bases accelerated this reaction. An immobilized enzyme provided the chiral framework for the enantioselective opening of the azlactone. In developing this process the Merck researchers screened six solvents, four amines, three alcohols, and various levels of water. Researchers from DuPont-Merck developed a dynamic resolution using a retro-Michael−Michael addition sequence to racemize the undesired enantiomer **4** in the enzyme-catalyzed hydrolysis of the racemic thioester **3**.[23] Optimal conditions included hydrolysis in an aqueous system buffered to pH 9.25 in the presence of a water-soluble organic base and a surfactant. In optimizing the dynamic resolution the researchers examined 8 thioesters, 21 enzymes, 3 organic bases, at least 2 organic solvents, surfactants, and other parameters. The processes described in Scheme 2, with racemization being effected with soluble bases[24] under moderately basic conditions, indicate that a number of parameters may need to be optimized to develop a successful dynamic resolution. Other interesting examples may be found in the hydrolysis of the hydantoin of racemic *tert*-leucine by hydantoinase,[25] asymmetric conjugate reduction of cyclopentenones (introduction of two chiral centers),[26] reduction of β-keto-nitriles by whole cells (introduction of two chiral centers),[27] reduction of racemic α-methoxycyclohexanone (introduction of two chiral centers),[28] and the synthesis of substituted piperidines (induction of three chiral centers).[29]

Dynamic resolution is often called a second-order asymmetric transformation (or, more appropriately, an "asymmetric transformation of the second kind").[10] In addition to

(11) (a) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Noyori, R.; Tokunaga, M.; Kitamura, M. Stereoselective Organic Synthesis via Dynamic Kinetic Resolution. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(12) (a) Pàmies, O.; Bäckvall, J.-E. Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis. *Chem. Rev.* **2003**, *103*, 3247. (b) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis. *Chem. Soc. Rev.* **2001**, *30*, 321. (c) Martín-Malute, B.; Bäckvall, J.-E. Ruthenium- and Enzyme-Catalyzed Dynamic Kinetic Asymmetric Transformation of 1,4-Diols: Synthesis of γ-Hydroxy Ketones. *J. Org. Chem.* **2004**, *69*, 9191.

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(14) Hang, J.; Li, H.; Deng, L. Development of a Rapid, Room-Temperature Dynamic Kinetic Resolution for Efficient Asymmetric Synthesis of α-Aryl Amino Acids. *Org. Lett.* **2002**, *4*, 3321.

(15) Robinson, D. E. J. E.; Bull, S. D. Kinetic resolution strategies using nonenzymatic catalysts. *Tetrahedron: Asymmetry* **2003**, *14*, 1407.

(16) Vedejs, E.; Chapman, R. W.; Lin, S.; Müller, M., Powell, D. R. Crystallization-Induced Asymmetric Transformation vs Quasi-Racemate Formation in Tetravalent Boron Complexes. *J. Am. Chem. Soc.* **2000**, *122*, 3047.

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(18) Caddick, S. J.; Jenkins, K. Dynamic Resolutions in Asymmetric Synthesis. *Chem. Soc. Rev.* **1996**, *25*, 447.

(19) Pellissier, H. Dynamic Kinetic Resolution. *Tetrahedron* **2003**, *59*, 8291.

(20) Andraos, J. Quantification and Optimization of Dynamic Kinetic Resolution. *J. Phys. Chem. A* **2003**, *107*, 2374.

(21) Limanto, J.; Shafiee, A.; Devine, P. N.; Upadhyay, V.; Desmond, R. A.; Foster, B. R.; Gauthier, D. R., Jr.; Reamer, R. A.; Volante, R. P. An Efficient Chemoenzymatic Approach to (*S*)-γ-Fluoroleucine Ethyl Ester. *J. Org. Chem.* **2005**, *70*, 2372.

(22) McCague, R.; Taylor, S. J. C. Four Case Studies in the Development of Biotransformation-based Processes. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York; 1997; p 201.

(23) (a) Pesti, J. A.; Yin, J.; Zhang, L.; Anzalone, L. Reversible Michael Reaction-Enzymatic Hydrolysis: A New Variant of Dynamic Resolution. *J. Am. Chem. Soc.* **2001**, *123*, 11075. (b) Pesti, J. A.; Yin, J.; Zhang, L.; Anzalone, L.; Waltermire, R. E.; Ma, P.; Gorko, E.; Confalone, P. A.; Fortunak, J.; Silverman, C.; Blackwell, J.; Chung, J. C.; Hrytsak, M. D.; Cooke, M.; Powell, L.; Ray, C. Efficient Preparation of a Key Intermediate in the Syntheis of Roxifiban by Enzymatic Dynamic Kinetic Resolution on Large Scale. *Org. Process Res. Dev.* **2004**, *8*, 22. (c) Pesti, J. A.; Anzalone, L. Multi-Kilo Resolution of XU305, a Key Intermediate in the Platelet Glycoprotein IIb/IIIa Receptor Antagonist Roxifiban via Kinetic and Dynamic Enzymatic Resolution. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004; pp 365−84.

(24) For these dynamic resolutions soluble bases were used. For an interesting example of using hydroxide immobilized on an ion-exchange resin, see: Studer, M.; Blaser, H.-U.; Burkhardt, S. Hydrogenation of α-Keto Ethers: Dynamic Kinetic Resolution with a Heterogeneous Modified Catalyst and a Heterogeneous Base. *Adv. Synth. Catal.* **2002**, *344*, 511.

(25) See: Bomarius, A. S.; Schwarm, M.; Stingl, K.; Kottenhahn, K.; Drauz, K. Synthesis and Use of Enantiomerically Pure *tert*-Leucine. *Tetrahedron: Asymmetry* **1995**, *6*, 2581.

(26) Jurkauskas, V.; Buchwald, S. L. Dynamic Kinetic Resolution via Asymmetric Conjugate Reduction: Enantio- and Diastereoselective Synthesis of 2,4-Dialkyl Cyclopentanones. *J. Am. Chem. Soc.* **2002**, *124*, 2892.

(27) Dehli, J. R.; Gotor, V. Dynamic Kinetic Resolution of 2-Oxocycloalkanecarbonitriles: Chemoenzymatic Syntheses of Optically Active Cyclic β-and γ-Aminoalcohols. *J. Org. Chem.* **2002**, *67*, 6816.

these terms, various key phrases have been used in the literature, including dynamic stereoselective processes, dynamic resolution, dynamic kinetic resolution (DKR), dynamic transformation, diastereoselective resolution, diastereoselective transformation, dynamic diastereomeric processes, deracemization, and asymmetric disequilibrating transformations. Sometimes "dynamic resolution" is applied to the preparation of both diastereomeric salts and covalent modifications of the target enantiomer that create diastereomeric centers within the molecule. Use of these terms has created a lack of cohesiveness within the literature.

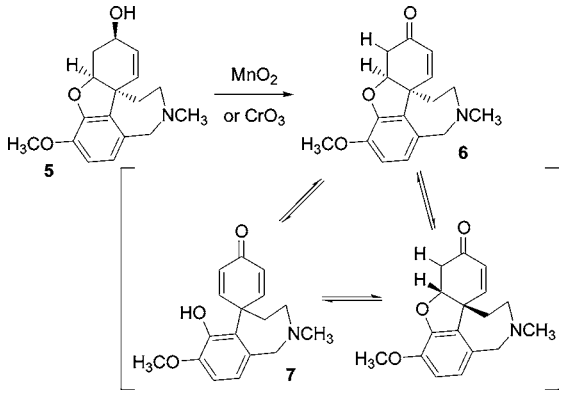
This contribution reviews CIDR and CIAT processes. In this review CIDR refers to the crystallization of one enantiomer either as the free compound or as a diastereomeric salt with a chiral gegenion, and CIAT includes CIDR and other processes, which may include compounds with two or more diastereomeric centers and olefins. Developing a successful CIDR or CIAT process reduces to (1) finding conditions for facile racemization; (2) finding a suitable resolving agent that is effective and stable under the racemization conditions;[30] and (3) isolating and handling the product under conditions that do not lead to degradation. Often the most difficult aspect is the second. This review will address these three issues. Examples have been selected to illustrate considerations key to the successful development of CIDR or CIAT processes.

Examples of CIDR and CIAT. In the following sections, examples of CIDR and CIAT are discussed, grouped together by the types of racemization involved.

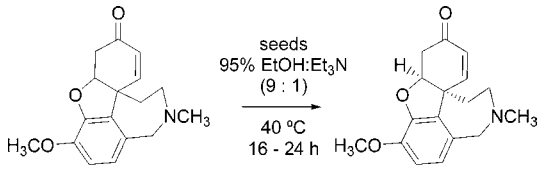
1. Racemization through Phenolic Ring-Opening−Cyclization. One of the earliest examples of CIDR was the "spontaneous" resolution of narwedine, reported by Barton and Kirby in 1962.[31] As (−)-galanthamine (**5**, a structural isomer of codeine) was being oxidized to (−)-narwedine (**6**), the specific rotation became more negative, and the product had a greater (more negative) rotation than the starting material (Scheme 3). Crystallizing **6** from acetone gave a product with a negative rotation, while crystallization from EtOH gave a product with a positive rotation. These researchers found that small amounts of residual **5** led to the crystallization of (+)-narwedine (*ent*-**6**) and that **6** was racemized by heating in EtOH or by chromatography over Al_2O_3. They proposed that racemization proceeded through the achiral dienone **7**.

Shieh and Carlson demonstrated by NMR that under basic conditions (Et_3N/D_2O) deuterium was exchanged for the three hydrogens at the carbons adjacent to the carbonyl (Scheme 4), further supporting racemization of **6** through the achiral

Scheme 3. **Initial investigations into the chemistry of narwedine**

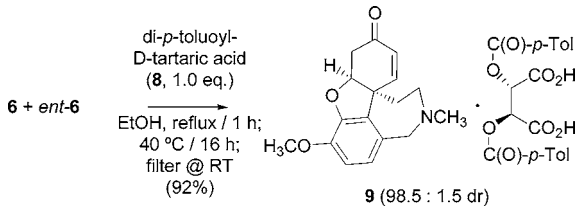


Scheme 4. **CIDR of narwedine by entrainment**



seeds	product	yield	scale
6	**6**	84%	0.20 g
ent-**5**	**6**	92%	10.0 g

Scheme 5. **CIDR of narwedine by salt formation**



dienone **7**.[32] They established that a mixture of **6** and *ent*-**6** exists as a racemic conglomerate and that seeding with either (−)-**6** or (+)-**5** under basic conditions led to the formation of (−)-**6**. Thus resolution by entrainment led to the selective crystallization of one enantiomer.

Researchers at Chiroscience found that a mixture of **6** and *ent*-**6** could be effectively resolved using di-*p*-toluoyl-D-tartaric acid, **8**, forming either a 1:1 or 2:1 salt[33] (Scheme 5). Under the conditions that led to crystallization (EtOH, 40 °C/16 h) the basic nitrogen of free **6** encouraged racemization to afford a high yield of the salt **9**. These researchers stated that the thermodynamic process of diastereomeric salt formation was more rugged on scale than isolating one enantiomer by entrainment, which is a kinetic process. They also noted that narwedine could be selectively crystallized by seeding with other compounds: thus seeding with (*S*)-pyrrolidinone carboxylic acid produced (−)-narwedine free base (**6**, >98:2 er), and seeding with (*R*)-pyrrolidinone carboxylic acid gave (+)-narwedine free base

(28) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. Diastereoselective Synthesis of a Key Intermediate for the Preparation of Tricyclic β-Lactam Antibiotics. *Tetrahedron Lett.* **1999**, *40*, 5043.

(29) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. Dynamic Kinetic Resolution and Desymmetrization of Enantiotopic Groups by Cyclodehydration of Racemic or Prochiral δ-Oxoesters with (*R*)-Phenylglycinol: Enantioselective Synthesis of Piperidines. *Angew. Chem., Int. Ed.* **2002**, *41*, 335.

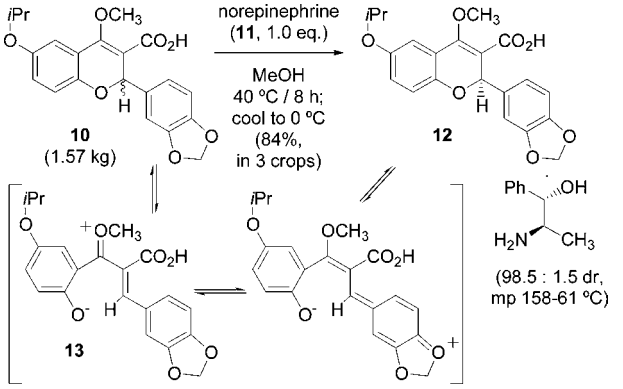
(30) Bruggink, A. Rational Design in Resolutions. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York, 1997; pp 92−4.

(31) Barton, D. H. R.; Kirby, G. W. Phenol Oxidation and Biosynthesis. Part V. The Synthesis of Galanthamine. *J. Chem. Soc.* **1962**, *70*, 806.

(32) Shieh, W.-C.; Carlson, J. A. Asymmetric Transformation of Either Enantiomer of Narwedine via Total Spontaneous Resolution Process, a Concise Solution to the Synthesis of (−)-Galanthamine. *J. Org. Chem.* **1994**, *59*, 5463.

(33) Chaplin, D. A.; Johnson, N. B.; Paul, J. M.; Potter, G. A. Dynamic Diastereomeric Salt Resolution of Narwedine and its Transformation to (−)-Galanthamine. *Tetrahedron Lett.* **1998**, *39*, 6777.

Scheme 6. **CIDR of a benzpyran by phenolic ring-opening − cyclization**

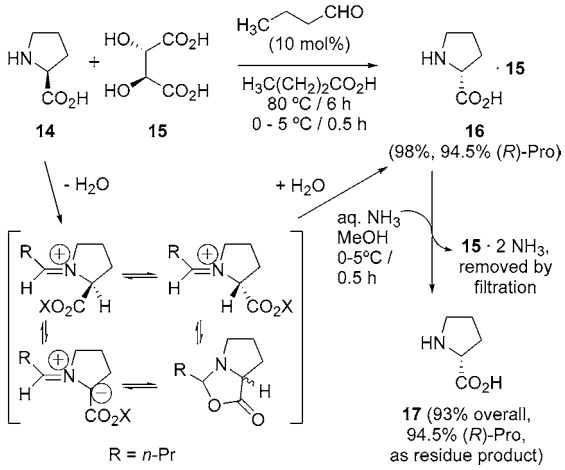


(*ent*-**6**, >98:2 er). Once the salts were split the solutions of free base tended to racemize, so acetic acid (AcOH) was added to the HPLC eluent to prevent samples of the free bases from racemizing during assay. To minimize racemization, the salt **9**, not the free base, was reduced directly to the desired chiral galanthamine.

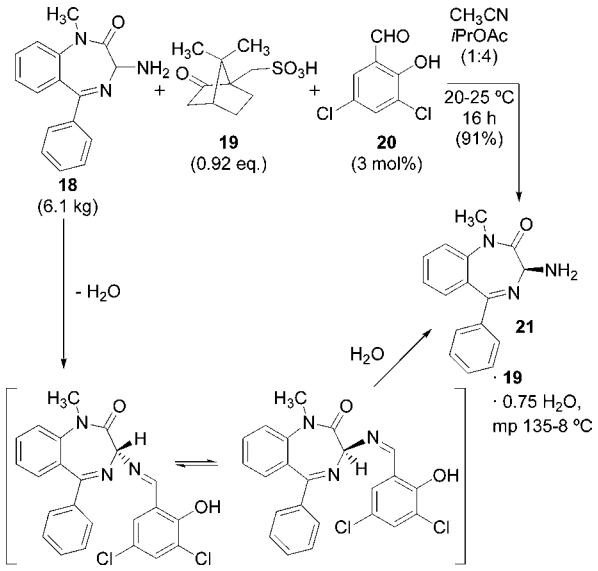
The benzpyran carboxylic acid **10** was resolved dynamically by Shionogi researchers,[34] as shown in Scheme 6. Aging with norepinephrine (**11**) for 8 h in MeOH at 40 °C led to the formation of salt **12** in 84% yield (98.5:1.5 dr). The key observation for developing this process was the observation that heating the mother liquor racemized the undesired salt. The rate of racemization was increased by adding H_2SO_4, aq. NaOH, or Et_3N. The authors proposed that racemization proceeded through the phenolic intermediate **13** and similar intermediates with delocalized charge, as there was no methine H− to D− exchange when **10** was refluxed in CD_3-OD. Conditions for the CIDR of analogues of **10** were rather narrow: when the methyl ether in **10** was exchanged for *p*-CH_3O−Ph (which would have directly afforded the API), no CIDR was found. Similarly, five other amines were examined for CIDR, and only one (cinchonine) was successful in this regard. To minimize racemization of the free base of **12** as the salt was being split, the mixture was buffered at pH 4.0.

2. Racemization through Imine Formation. One of the earliest examples of a CIDR process for amino acid derivatives was described by Glaxo workers in 1976, with the resolution of esters of substituted phenylglycines.[35] In 1989 workers at Kansai University described a CIDR process for the formation of (*R*)-proline[36] (**17**, Scheme 7). (*S*)-Proline, **14**, was racemized in butyric acid at 80 °C by heating in the presence of butyraldehyde, and salt formation with unnatural (*S*,*S*)-tartaric acid, **15**, produced **16**. Imine formation activated the methine proton in **14** and facilitated racemization, as had been demonstrated in 1983 by workers from Tanabe Seiyaku Co.[37] Butyric acid was chosen over AcOH to crystallize **16**, as the salts demonstrated high solubility in AcOH.

Scheme 7. **CIDR of (*R*)-proline using catalytic butyraldehyde**



Scheme 8. **Merck's CIDR with dichlorosalicylaldehyde**



In what is perhaps the best-known example of dynamic resolution, Merck researchers converted the racemic aminodiazepinone **18** to the chiral amine salt **21** (Scheme 8).[38] A deficit of (*S*)-(+)-10-camphorsulfonic acid (**19**, 0.92 equiv) was charged, thus keeping the reaction mixture slightly basic. Racemization with a catalytic amount of 3,5-dichlorosalicylaldehyde, **20**, was carried out at room temperature, and racemization was probably facilitated by the electron-poor nature of both the aldehyde **20** and the amine **18**. Excess amine **18** probably deprotonated the imine methines, leading to racemization. The salt **21** crystallized with 0.75 equiv of H_2O. This elegantly simple CIDR was reported at a scale of 6.1 kg.

(34) Konoike, T.; Matsumura, K.; Yorifuji, T.; Shiomoto, S.; Ide, Y.; Ohya, T. Practical Enantioselective Synthesis of Endothelein Antagonist S-1255 by Dynamic Resolution of 4-Methoxychromene-3-carboxylic Acid Intermediate. *J. Org. Chem.* **2002**, *67*, 7741.

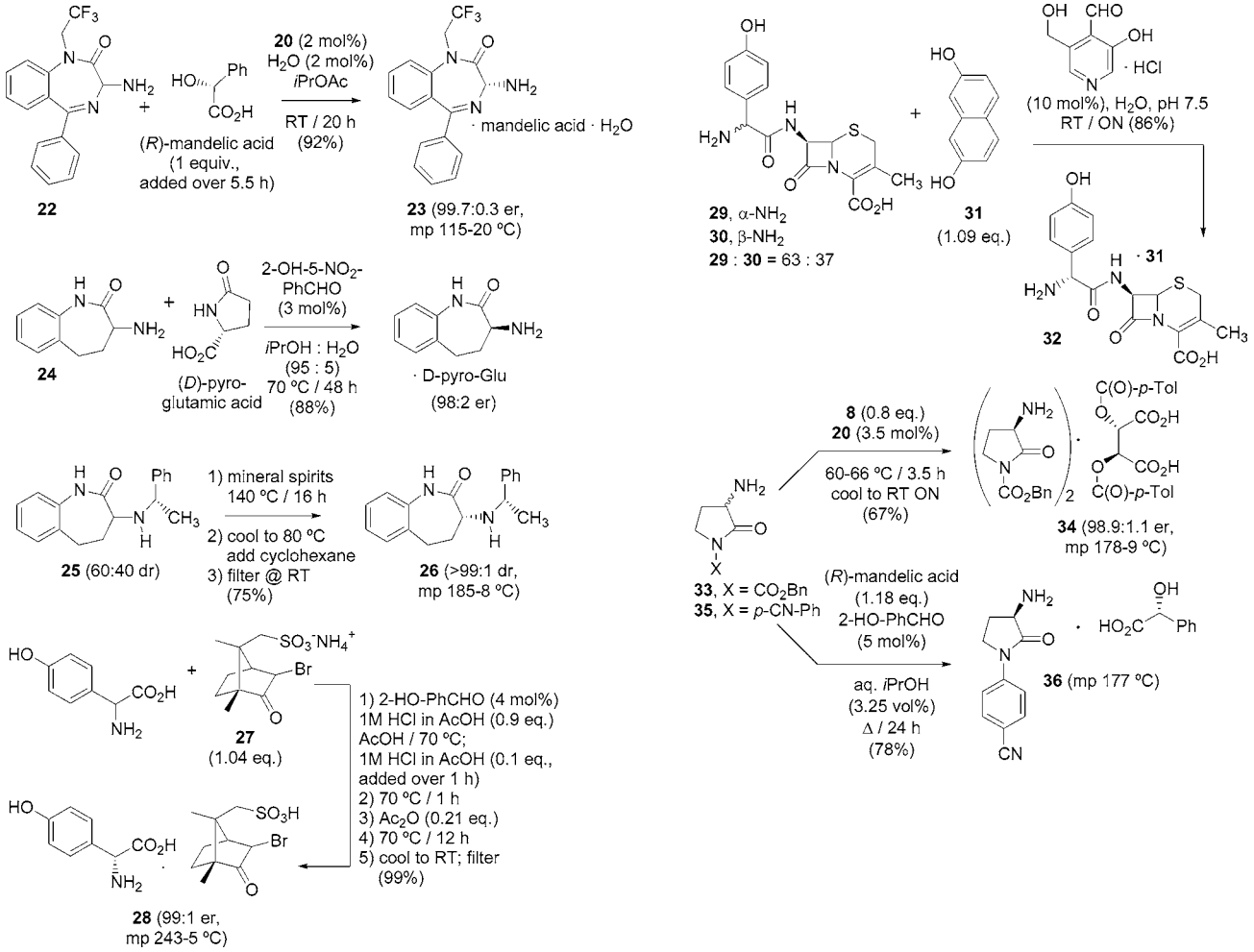
(35) Clark, J. C.; Phillipps, G. H.; Steer, M. R. A New Asymmetric Transformation of α-Amino-acid Esters with (+)-Tartaric Acid. *J. Chem. Soc., Perkins Trans. 1* **1976**, 475.

(36) Shiraiwa, T.; Shinjo, K.; Kurokawa, H. Facile Production of (*R*)-Proline by Asymmetric Transformation of (*S*)-Proline. *Chem. Lett.* **1989**, 1413.

(37) Yamada, S.; Hongo, C.; Yoshioka, R.; Chibata, I. Method for the Racemization of Optically Active Amino Acids. *J. Org. Chem.* **1983**, *48*, 843. These workers noted that the rate of racemization decreased as the amount of H_2O in the solvent (acetic acid) increased but did not identify how H_2O influenced the rate of racemization.

(38) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of a Potent Peripheral CCK Antagonist. *J. Org. Chem.* **1987**, *52*, 955.

Scheme 9. **CIDR of amino acid derivatives using catalytic aryl aldehydes**



Other examples of CIDR using aromatic aldehydes are shown in Scheme 9. Shi and co-workers used 3,5-dichlorosalicylaldehyde (**20**) to racemize the aminodiazepinone **22** at room temperature, and selective crystallization of one enantiomer from aq. *i*PrOH was carried out with (*R*)-mandelic acid to afford the salt **23** as a hydrate.[39] For the α-amino lactam **24**, racemization was carried out using 5-nitrosalicylaldehyde over 48 h, since racemization with **20** required 70 h; the product crystallized from aq. *i*PrOH.[40] In contrast, without any catalyst a temperature of 140 °C was needed to convert the mixture of N_α-methylbenzyl amides **25** to the diastereomer **26**; thermal interconversion probably proceeded through the enol.[41,42] Bristol-Myers Squibb (BMS) researchers also developed a CIDR process for an α-amino azepinone using 5-nitrobenzaldehyde with a 48-h crystallization.[43] Workers at Hoechst-Celanese investigated in detail a CIDR process to produce in excellent yield D-phenylglycine, a precursor for many semisynthetic antibiotics.[44] In the presence of catalytic salicylaldehyde, D-phenylglycine crystallized as the salt **28** with D-3-bromo-camphorsulfonic acid (**27**); Ac_2O (0.21 equiv) was added to raise the yield by consuming the water present in the solvent (glacial AcOH). Researchers at the University of Nijmegen found that a mixture of cefadroxil (**29**) and *epi*-cefadroxil (**30**) (63:37) could be converted in the presence of pyridoxal hydrochloride and 2,7-dihydroxynaphthalene (**31**) to the clathrate **32** in 86% yield; the undesired diastereomer **30** remained

(39) Shi, Y.-J.; Wells, K. M.; Pye, P. J.; Choi, W.-B.; Churchill, H. R. O.; Lynch, J. E.; Maliakal, A.; Sager, J. W.; Rossen, K.; Volante, R. P.; Reider, P. J. Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of L-768,673. *Tetrahedron* **1999**, *55*, 909.

(40) Armstrong, J. D.; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W., Jr.; Choi, W.-B.; Askin, D.; Volante, R. P. An Efficient Asymmetric Synthesis of (*R*)-3-Amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepine-2-one. *Tetrahedron Lett.* **1999**, *35*, 3239.

(41) (a) Shieh, W.-C.; Carlson, J. A.; Zaunius, G. M. Asymmetric Synthesis of *N*-Substituted α-Aminobenzlactam via Crystallization-Induced Asymmetric Transformation of Covalent Diastereomer. *J. Org. Chem.* **1997**, *62*, 8271. (b) In the example in Scheme 9 the CIAT process was carried out in mineral spirits (ligroine), and cyclohexane was added to ease handling of the crystalline suspension. When **25** was heated in solution in refluxing xylene (138 °C/16 h), the diastereomers were formed in the ratio of 60:40.

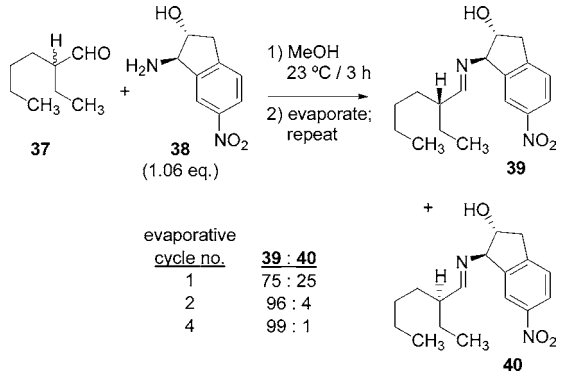
(42) Another benazepril precursor has been epimerized thermally in what may be a CIAT process: Tseng, W.-H.; Schloemer, G. Asymmetric Synthesis of a Key Intermediate for Making Benazepril and Analogues Thereof. U.S. Patent 6,548,665, 2003 (to Scinopharm, Tawain, Ltd.). A mixture of diastereomeric amino amides, (1′*S*,3*RS*)-3-[(1′-carboxy-3′-phenylpropyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepines, was heated in refluxing xylenes or aqueous ethylene glycol to afford the (*S*,*S*)-acid (98:2 dr), mp 287−290 °C.

(43) Singh, J.; Kronenthal, D. R.; Schwinden, M.; Godfrey, J. D.; Fox, R.; Vawter, E. J.; Zhang, B.; Kissick, T. P.; Patel, B.; Mneimne, O.; Humora, M.; Papaioannou, C. G.; Szymanski, W.; Wong, M. K. Y.; Chen, C. K.; Heikes, J. E.; DiMarco, J. D.; Qiu, J.; Deshpande, R. P.; Gougoutas, J. Z.; Mueller, R. H. Efficient Asymmetric Synthesis of the Vasopeptidase Inhibitor BMS-189921. *Org. Lett.* **2003**, *5*, 3155.

(44) Bhattacharya, A.; Araullo-McAdams, C.; Meier, M. B. Crystallization Induced Asymmetric Transformation: Synthesis of D-*p*-Hydroxyphenylglycine. *Synth. Commun.* **1994**, *24*, 2449.

dissolved in the mother liquor.[45] For successful CIAT processing, racemization was carried out at pH 7.5 due to the sensitivity of **29** and **30** to more basic conditions, and **31** was employed to increase the solubility differences between **29** and **30** through clathrate formation. GSK researchers used a catalytic amount of 3,5-dichlorosalicylaldehyde and a deficit of di-*p*-toluoyl-D-tartaric acid to prepare the chiral salt **34**.[46] Searle researchers developed a CIDR process to resolve **35** using catalytic salicylaldehyde and (*R*)-mandelic acid; a small amount of H_2O was necessary for dynamic resolution.[47] Villani described CIDR of *p*-chlorophenylalanine methyl ester using salicylaldehyde, and the (*R*)-ester crystallized as the 2:1 salt with unnatural tartaric acid.[48] DSM has reported a CIDR process to resolve methionine amide using benzaldehyde and either L- or D-mandelic acid,[49] and Ciba-Geigy researchers developed a CIDR process for an aminobenzazepinone (the amide nitrogen of **24** was derivatized with a *tert*-butyl acetate group) using benzaldehyde.[50] Yoshioka et al. resolved racemic *p*-hydroxyphenyl glycine with catalytic salicylaldehyde and (+)-1-phenylethanesulfonic acid in AcOH at 100 °C.[51] Shiraiwa et al. (Kansai University) reported the CIDR of cysteine through the formation of the thiazolidine salts with (+)- or (−)-tartaric acid, with or without salicylaldehyde.[52] A substituted α-pyridylethylamine was resolved using (−)-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid and catalytic 3,5-dichlorosalicylaldehylde.[53] As of 1997, over 100 patents (not including equivalents) were issued for CIAT processes involving Schiff base intermediates.[54] Hence a variety of aldehydes can be used to racemize amines, and racemization is generally more facile when electron-poor aldehydes are used.

Scheme 10. **CIDR through epimerization α- to imines**



Two points on the preparation of the salt **34** merit discussion.[46] First of all, the free amine resulting from splitting the salt **34** was relatively reactive, dimerizing to the diketopiperazines upon concentration or heating. Second, the chiral acid employed for resolution was chosen by screening not for solubility but for melting points. The individual enantiomers of **33**, prepared from the separate enantiomers of methionine, were subjected to crystallization conditions with chiral acids, and the melting points of each enantiomer with a given chiral acid were compared. The researchers anticipated that a higher melting point of one salt indicated both a higher crystalline lattice energy and lower solubility relative to the other salt of the pair. For the pair of salts formed from **8** and either the (*R*)- or (*S*)-amine of **33**, **34** displayed a melting point 44 °C higher, and so di-*p*-toluoyl-D-tartaric acid was selected for the CIDR process.

Imines of aldehydes and ketones have also been resolved by a CIAT process. Weigel et al. demonstrated that the racemic aldehyde **37** could be converted to the diastereomeric imines **39** and **40** by condensation with a slight excess of the chiral *trans*-amino alcohol **38** (Scheme 10).[55] Evaporation of the solvent from the slurries over several hours provided the crystallization pressure. In developing this process, seven other amines were examined, and only **38** provided crystalline imines. The researchers noted that the dr of the imines eroded in solution, so the imines were hydrolyzed (aq. $CuCl_2$ or NaOAc) prior to analyses. Thus this CIAT process afforded resolution of aldehydes and ketones.

3. Racemization through Enolization α- to Carbonyls. Merck researchers have discussed four CIAT approaches (Schemes 11−13) to aprepitant.[56] In the first, the racemic aminolactone **41** was heated in the presence of an excess of [(1*S*)-(endo,anti)]-(−)-3-bromocamphor-8-sulfonic acid(BCSA) to afford the salt **42**; they noted that while **41** readily racemized under acidic conditions, finding conditions for both racemization and salt formation was more difficult.[57] Racemization probably proceeded through the protonated enol. In the second approach, under AcOH-catalyzed condi-

(45) Kemperman, G. J.; Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. Clathration-Induced Asymmetric Transformation of Cefadroxil. *Org. Lett.* **2000**, *2*, 2829.

(46) Barrett, R.; Caine, D. M.; Cardwell, K. S.; Cooke, J. W. B.; Lawrence, R. M.; Scott, P.; Sjolin, A. A practical, two-stage preparation of benzyl (3*R*)-3-amino-2-oxo-1-pyrrolidinecarboxylate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)-oxy]butanedioate (2:1). *Tetrahedron: Asymmetry* **2003**, *14*, 3267.

(47) Colson, P.-J.; Przybyla, C. A.; Wise, B. E.; Babiak, K. A.; Seaney, L. M.; Korte, D. E. An efficient asymmetric synthesis of (3*S*)-3-amino-1-(4-cyanophenyl)-2-oxopyrrolidine hydrochloride salt. *Tetrahedron: Asymmetry* **1998**, *9*, 2587.

(48) Maryanoff, C. A.; Scott, L. A.; Shah, R. D.; Villani, F. J., Jr. A crystallization-induced asymmetric transformation to prepare (*R*)-4-chlorophenylalanine methyl ester. *Tetrahedron: Asymmetry* **1998**, *9*, 3247.

(49) Boesten, W. H. J.; Broxterman, Q. B. Process for the Preparation of Optically Active Methionine Amide. U.S. Patent 5,468,901, 1995 (to DSM N.V.).

(50) Boyer, S. K.; Pfund, R. A.; Portmann, R. E.; Sedelmeier, G. H.; Wetter, H. F. 36. Notiz zur Syntheses eines optisch aktiven ACE-Hemmers mit Amino-oxo-benzazepin-1-alkanesäure-Struktur mittels enantiokonvergierender, kristallisationinduzierter Racemat-Trennung. *Helv. Chim. Acta* **1988**, *71*, 337.

(51) Yoshioka, R.; Tohyama, M.; Ohtsuki, S.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 649.

(52) Shiraiwa, T.; Kataoka, K.; Sakata, S.; Kurokawa, H. Asymmetric Transformation of (*RS*)-Cysteine via Formation of (*RS*)-Thiazolidine Carboxylic Acids. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 109.

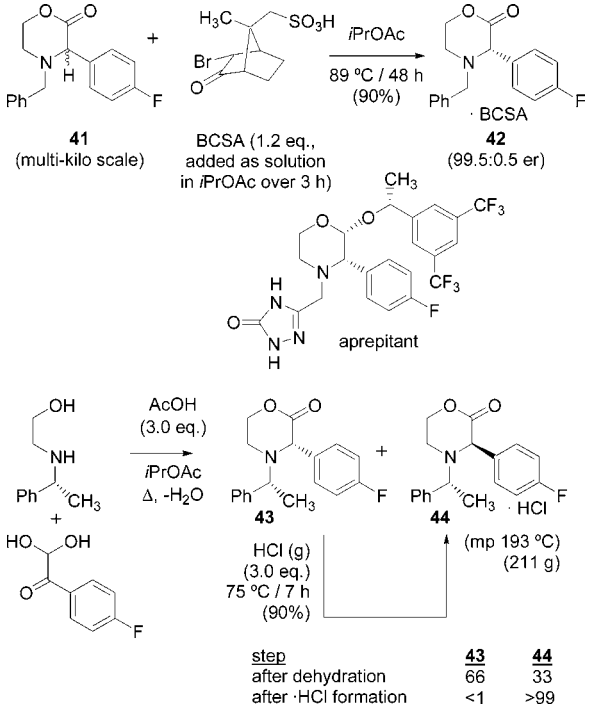
(53) Negi, S.; Matsukura, M.; Mizuno, M.; Miyake, K.; Minami, N. Synthesis of (2*R*)-1-(4-Chloro-2-pyridyl)-2-(2-pyridyl)ethylamine: A Selective Oxime Reduction and Crystallization-Induced Asymmetric Transformation. *Synthesis* **1996**, 991.

(54) Ebbers, E. J.; Ariaans, G. J. J.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. Controlled Racemization of Optically Active Organic Compounds: Prospects for Asymmetric Transformation. *Tetrahedron* **1997**, *53*, 9417.

(55) Kosmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. Unfunctionalized, α-Epimerizable Nonracemic Ketones and Aldehydes Can be Accessed by Crystallization-Induced Dynamic Resolution of Imines. *J. Am. Chem. Soc.* **2003**, *125*, 3208.

(56) For an overview of Merck's processes to aprepitant, see: Nelson, T. D. Synthesis of Aprepitant. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: San Diego; 2005; pp 321−51.

Scheme 11. **Acid-catalyzed CIDR and CIAT of α-amino lactones**

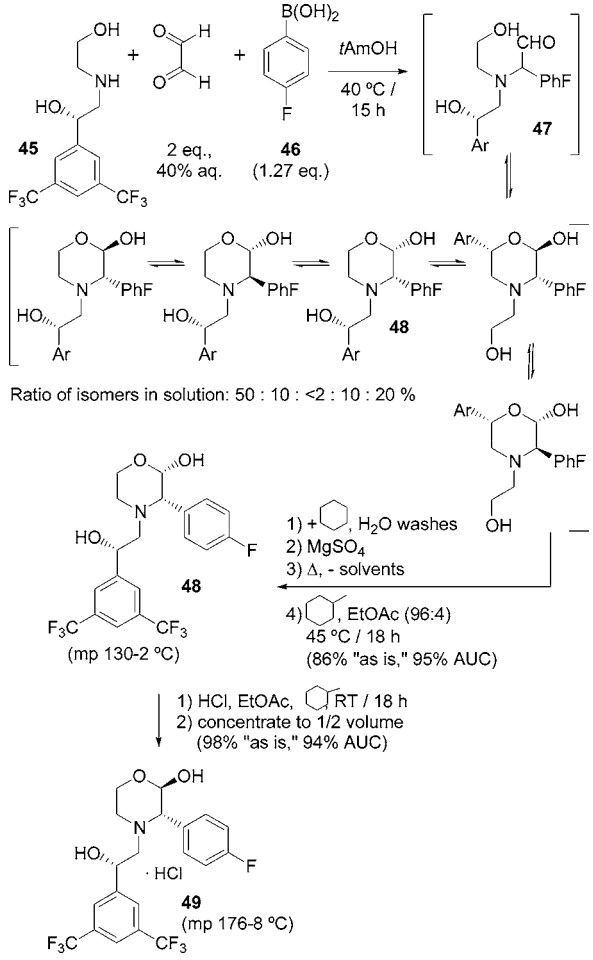


tions with azeotropic removal of H_2O the diastereomeric aminolactones **43** and **44** were formed in a ratio of 66:33, respectively, and after addition of HCl and crystallization the ratio of **43** and **44** (as the HCl salts) was 1:99, respectively.[58] No salts were formed when TsOH, methanesulfonic acid, or trifluoroacetic acid was substituted for HCl. Since the HCl salt of **44** readily epimerized in solution, the salt was split for spectral analyses, optical rotation, and the next synthetic step (DIBAL-H reduction).

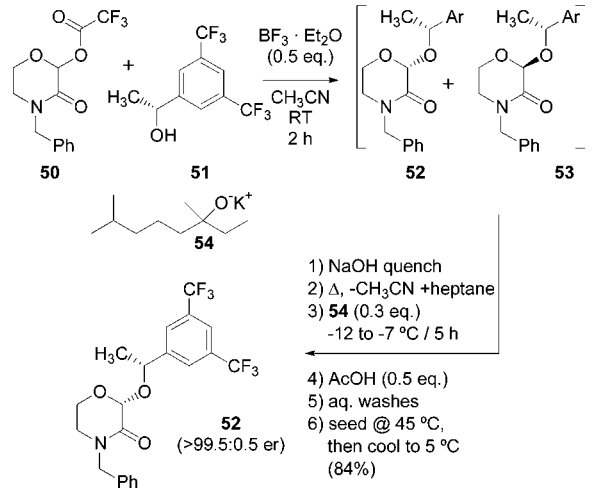
In another acid-catalyzed approach to aprepitant (Scheme 12), the condensation of the chiral diol **45**, glyoxal, and the aryl boronic acid **46** led to a mixture of products in solution, in a ratio of 50:10:<2:10:20 [HPLC area under the curve (AUC)], but crystallization with extended aging produced the free base **48** that was present in the smallest amount in solution.[59] In the presence of HCl the free base was converted by a CIAT process to the salt **49**, with the desired stereochemistry. Epimerization leading to the crystallizations of **48** and **49** probably proceeded through the aldehyde **47**. The researchers noted that the free base of **49** was stable.

In the base-catalyzed approach to aprepitant (Scheme 13), BF_3-catalyzed condensation of the trifluoroacetate **50** with the chiral alcohol **51** led to a 55:45 mixture of the diastereomers **52** and **53**.[60] No interconversion to **52** was found with Lewis acids or Brönsted acids, but basic conditions led to epimerization. Epimerization with KO*t*Bu led to reduced

Scheme 12. **Acid-catalyzed CIAT of an advanced aprepitant intermediate**



Scheme 13. **Base-catalyzed CIAT of an amide−acetal**



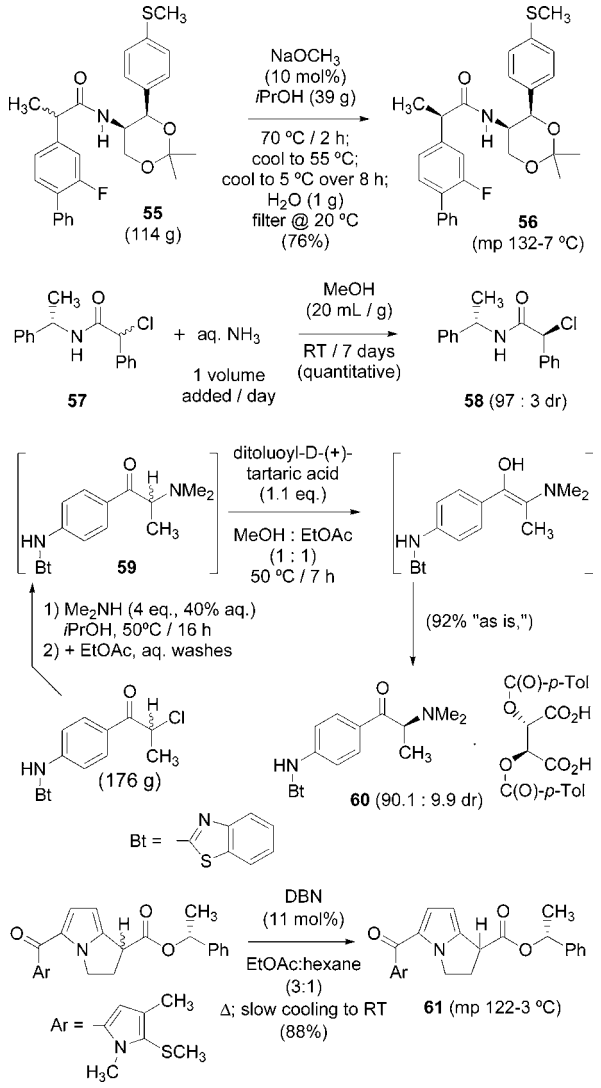
(57) Alabaster, R. J.; Gibson, A. W.; Johnson, S. A.; Edwards, J. S.; Cottrell, I. F. Synthesis of *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one via a crystallization-induced asymmetric transformation. *Tetrahedron: Asymmetry* **1997**, *8*, 447.

(58) Zhao, M. M.; McNamara, J. M.; Ho, G.-J.; Emerson, K. M.; Song, Z. J.; Tschaen, D. M.; Brands, K. M. J.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. M.; Cottrell, I. F.; Ashwood, M. S.; Bishop, B. C. Practical Synthesis of Aprepitant, a Potent Human NK-1 Receptor Antagonist, via a Stereospecific Lewis Acid-Catalyzed Trans Acetalization Reaction. *J. Org. Chem*. **2002**, *67*, 6743.

(59) Pye, P. J.; Rossen, K.; Weissman, S. A.; Malialkal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. Crystallzation-Induced Diastereoselection: Asymmetric Synthesis of Substance P Inhibitors. *Chem. Eur.—J.* **2002**, *8*, 1372.

(60) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. Efficient Synthesis of NK_1 Receptor Antagonist Aprepitant Using a Crystallization-Induced Diastereoselective Transformation. *J. Am. Chem. Soc.* **2003**, *125*, 2129.

Scheme 14. **CIDR and CIAT through base-catalyzed racemization α- to amides, a ketone, and an ester**



yields upon workup because the byproduct *t*BuOH partially solubilized **52**. The potassium salt of tetrahydrolinalool (**54**) had no such negative impact with isolation of **52** and also afforded more rapid equilibration. After aging the slurry at −12 to −7 °C for 5 h in the presence of a catalytic amount of **54**, the ratio of **52**:**53** was 96:4, and this rose to >99.5:<0.5 after isolation. The authors noted that higher solubility of the undesired diastereomer **53** (51 mg/mL vs 25 mg/mL for **52**) was consistent with its lower mp (43 °C vs 93 °C).

Dynamic crystallization processes involving epimerization or racemization α- to the carbonyls of amides, a ketone, and an ester have been described. Racemic flurbiprofen was coupled with thiomicamine and ketalized with acetone to afford the amide **55** as a mixture of diasteromers, and epimerization was carried out with catalytic $NaOCH_3$ in warm *i*PrOH; gradual cooling led to the desired diastereomer **56** in good yield (Scheme 14).[61] A mixture of diastereomeric α-chloramides **57** was converted to the product **58** with a dr of 97:3.[62] The researchers noted that for good conversion it was necessary to add a portion of aq. NH_4OH daily for 1 week, and that shorter reaction times gave products with a decreased dr.[63] When the α-bromo analogue of **57** was subjected to the reaction conditions, a mixture of the α-amino amides was produced with 1:1 dr. A group from Janssen reported a CIDR process for the resolution of the α-dimethylaminoketone **59**.[64] Aging **59** at 50 °C in the presence of an excess of di-*p*-toluoyl-D-tartaric acid led to the 1:1 salt **60**. Racemization probably proceeded through the intermediate enol. CIAT of an ester from (*S*)-α-methyl benzyl alcohol was noted using DBN for epimerization; slow cooling from EtOAc−hexane led to crystallization of the desired (−)-diastereomer, **61**.[65] The lipophilic base DBN probably participated in the formation and solubilization of the achiral enolate intermediate in the nonpolar solvent mixture.

3. Racemization through retro-Michael−Michael Additions and Ring-Opening−Closing. In Scheme 15 are four examples where epimerization in CIAT processes has been shown to occur through Michael−retro-Michael additions and ring formation−ring opening. Tanabe researchers prepared the amino acids **63** and **64** by equilibrating the enone **62** and a slight excess of the chiral α-methylbenzylamine; the basic amine was responsible for racemization.[66] This approach can be generalized to other amino acids by adjusting solvents.[66b] Kolarovic and Berkeš demonstrated that chiral amino alcohols such as **66** can be condensed with enones such as **65** to produce Michael adducts (**67**).[67] More recently the latter authors have expanded their work to the enones **68**.[68] The thiazolidines **71** have also been prepared by CIAT processes.[69] Excess NaOAc used in the condensation promoted racemization, and equilibrium probably proceeded through the imine **72** (not detected).

4. Racemization through Anomerization. Researchers at BMS described two CIAT approaches to etoposide phosphate, as shown in Scheme 16. In the first, the sugar **73** was condensed with the phenolic alcohol **74** in the presence

(61) Pozzoli, C.; Castaldi, G. Process for the Preparation of the Enantiomers of 2-(2-Fluoro-4-biphenyl)propionic Acid. U.S. Patent 5,840,964 (1998, to Zambon Group S.P.A.). The product was hydrolyzed with HCl in AcOH to produce chiral flurbiprofen.

(62) Lee, S.-K.; Lee, S. Y.; Park, Y. S. Crystallization-Induced Dynamic Resolution of α-Chloro Acetamide. *Synlett* **2001**, *12*, 1941.

(63) For successful scale-up of this crystallization it probably would be necessary to monitor both the addition of the antisolvent (water) and the loss of the volatile base.

(64) Aelterman, W.; Lang, Y.; Willemsens, B.; Vervest, I.; Leurs, S.; DeKnaep, F. Conversion of the Laboratory Synthetic Route of the *N*-Aryl-2-benzothiazolamine R116010 to a Manufacturing Method. *Org. Process Res. Dev.* **2001**, *5*, 467.

(65) Hagmann, W. K. The Asymmetric Transformation of a 1,2-Dihydro-3*H*-pyrrolo[1,2-a]pyrrole-1-carboxylate Ester. *Synth. Commun.* **1986**, *16*, 437. The stereochemistry of the product was not defined.

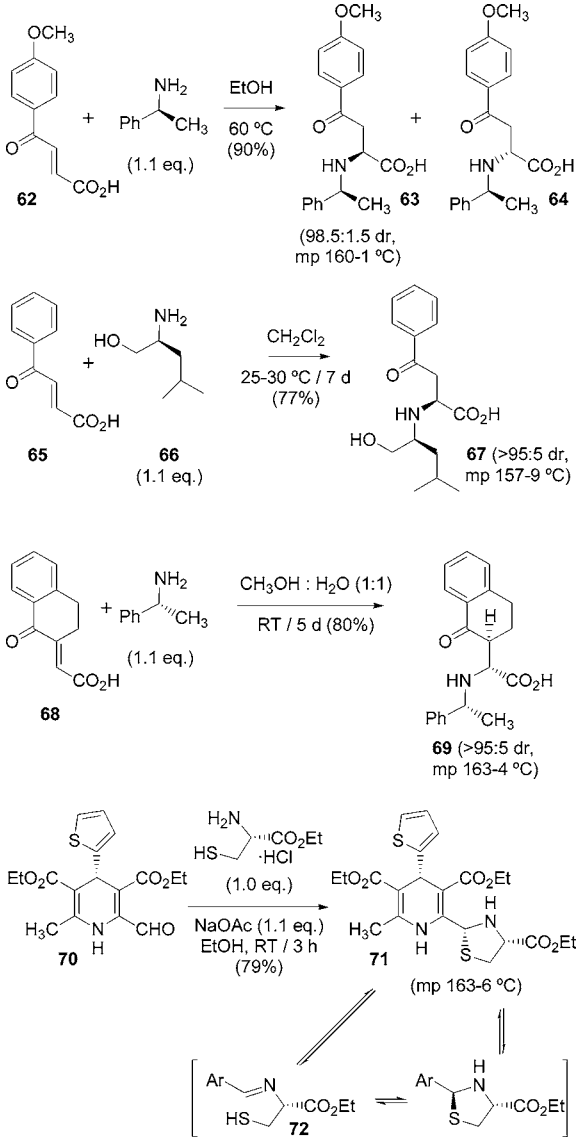
(66) (a) Yamada, M.; Nagashima, N.; Hasegawa, J.; Takahashi, S. A Highly Efficient Asymmetric Synthesis of Methoxyhomophenylalanine Using Michael Addition of Phenyethylamine. *Tetrahedron Lett.* **1998**, *39*, 9019. (b) Stinson, S. Custom Chemicals. *Chem. Eng. News* **1999**, *77*(3), 69.

(67) Kolarovic, A.; Berkeš, D.; Baran, P.; Povazanec, F. Crystallization-induced dynamic resolution (CIDR) and its application to the synthesis of unnatural *N*-substituted amino acids derived from aroylacrylic acids. *Tetrahedron Lett.* **2001**, *42*, 2579.

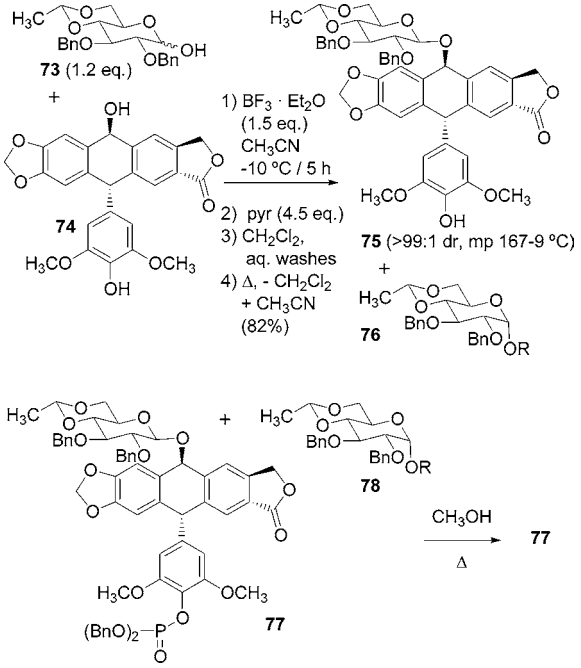
(68) Kolarovic, A.; Berkeš, D.; Baran, P.; Povazanec, F. Crystallization-induced asymmetric transformation (CIAT) with simultaneous epimerization at two stereocenters. A short synthesis of conformationally constrained homophenylalanines. *Tetrahedron Lett.* **2005**, *46*, 975.

(69) Marchalin, S.; Cvopova, K.; Kriz, M.; Baran, P.; Oulyadi, H.; Daich, A. New Resolution of 2-Formyl-1,4-DHP Derivatives Using CIDR Methodology. Facile Access to New Chiral Tricyclic Thiolactam. *J. Org. Chem.* **2004**, *69*, 4227.

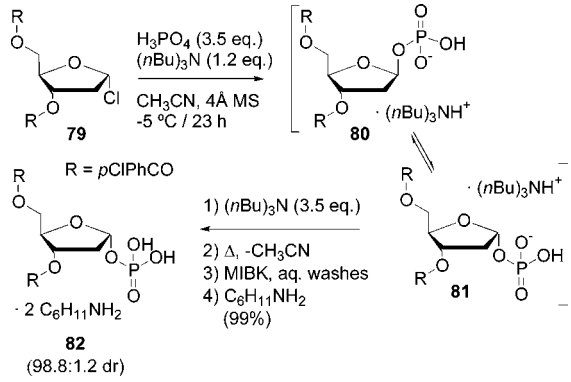
Scheme 15. **CIAT through retro-Michael−Michael additions and ring opening−closing**



Scheme 16. **CIAT processes for anomers of etoposide phosphate precursors**



Scheme 17. **CIAT through anomerization of deoxyribose derivatives**



of an excess of $BF_3{\cdot}Et_2O$.[70] Crystals began to form 10 min after the addition of the Lewis acid, and 20 min after the addition the ratio of the β-anomer **75** to the α-anomer **76** was 71:29. After 5 h the ratio of **75** to **76** was 95:5, and the reaction was quenched with pyridine. This BF_3-mediated anomerization is driven by the low solubility of **75** in acetonitrile. After an extractive workup and crystallization, **75** was isolated in 82% yield. The product was less stable when it was directly isolated without an extractive workup, perhaps due to traces of $BF_3{\cdot}Et_2O$ in the crystals. In another approach to etoposide phosphate it was found that recrystallization of a mixture of phosphate anomers **77** and **78** from MeOH afforded exclusively the β-anomer **77**.[71] This facile interconversion was dependent on the protecting groups on both the sugar and the phosphate (nine analogues of **77** and **78** with different substituted benzyl groups on the sugar crystallized with less selectivity).

α-Deoxyribosyl phosphate has also been prepared using CIAT by researchers from Mitsui Chemicals (Scheme 17). The α-chlorosugar **79** was condensed with excess H_3PO_4 under anhydrous conditions in CH_3CN.[72] Acid-catalyzed anomerization occurred, and the product **81** crystallized selectively as the salt with $(n\text{Bu})_3\text{N}$. No CIAT was observed using Et_3N or pyridine. The reaction was quenched with excess $(n\text{Bu})_3\text{N}$, as **81** was unstable below pH 8, and the product was isolated as the bis-cyclohexylamine salt **82**.

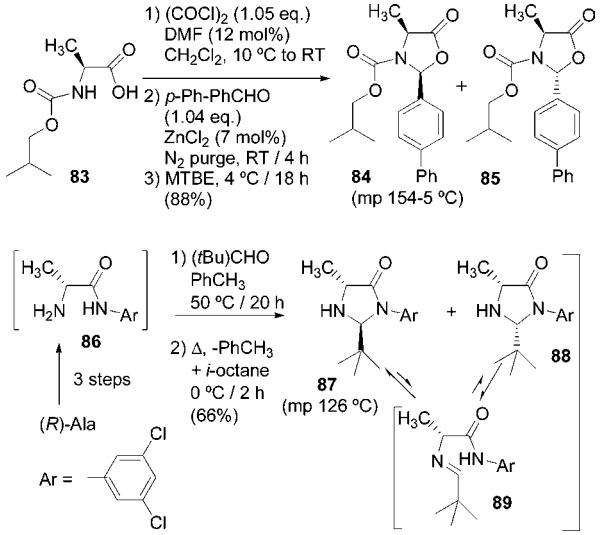
Researchers at Boehringer-Ingelheim have developed CIAT processes for the self-regeneration of stereocenters (SROSC) in five-membered rings (Scheme 18). The (*S*)-alanine derivative **83** was converted to the acid chloride and condensed with *p*-phenylbenzaldehyde in the presence of

(70) Silverberg, L. J.; Kelly, S.; Vemishetti, P.; Vipond, D. H.; Gibson, F. S.; Harrison, B.; Spector, R.; Dillon, J. L. A Crystallization-Induced Stereoselective Glycosidation Reaction in the Synthesis of the Anticancer Drug Etoposide. *Org. Lett.* **2000**, *2*, 3281.

(71) Silverberg, L. J.; Dillon, J. L.; Vemishetti, P.; Sleezer, P. D.; Discordia, R. P.; Hartung, K. B. Efficient Synthesis of the Anticancer Drug Etoposide 4′-Phosphate: Use of Benzylic Ether-Protecting Groups on the Carbohydrate Segment. *Org. Process Res. Dev.* **2000**, *4*, 34.

(72) Komatsu, H.; Awano, H. First Stereoselective Synthesis of 2-Deoxy-α-D-ribosyl-1-phosphate: Novel Application of Crystallization-Induced Asymmetric Transformation. *J. Org. Chem.* **2002**, *67*, 5419.

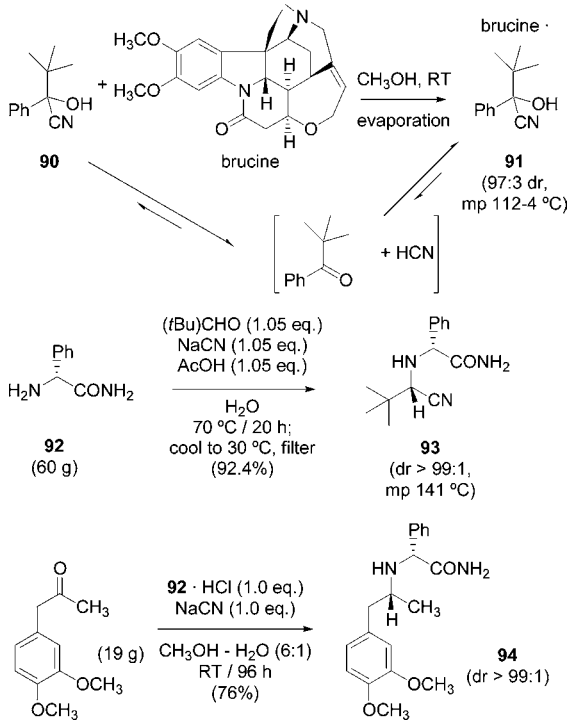
Scheme 18. **SROSC processes driven by CIAT**



$ZnCl_2$; after the addition of MTBE and subsequent aging, the oxazolidinone *cis*-diastereomer **84** was isolated, with the *trans*-diastereomer dissolved in the mother liquor.[73] $ZnCl_2$ mediates the epimerization of **85** to **84**, and when a series of aryl aldehydes including *p*-phenylbenzaldehyde was studied it was found that in general the increased size of protecting groups led to increased amounts of the corresponding *cis*-diastereomer upon equilibration. CIAT processes were also studied for a series of imidazolidinones, such as **87**.[74] Condensation of **86**, the amide from (*R*)-alanine, with pivaldehyde and crystallization from *i*-octane led to the complete conversion of the mixture to the *trans*-diastereomer **87**. In solution the equilibrium ratios of **87** to the cis-diastereomer **88** ranged from 91:9 (DMSO) to 77:23 (benzene), and the authors concluded that the crystallization of **87** from nonpolar solvents must be due to the lesser solubility of **87** as compared to **88** and the intermediate imine **89**.

5. Racemization through Addition−Elimination of Cyanide to sp² Carbons. Cyanohydrins and cyanoamines (intermediates of amino acids by Strecker synthesis) have been converted to chiral products by CIDR processes (Scheme 19). Researchers at Ehime University found that when a solution of the racemic cyanohydrin **90** and brucine in methanol was allowed to evaporate to about one-third of the original charge of solvent over 24 h, a chiral complex **91** was formed in quantitative yield.[75] More recently DSM researchers discussed the Strecker condensation of (*R*)-phenylglycine amide (**92**, commercially available on industrial scale from antibiotic preparation) with pivaldehyde and NaCN, leading to the crystallization of the (*S*)-*tert*-leucine

Scheme 19. **Racemization through addition−elimination of cyanide to sp² carbons**



precursor **93**.[76] Each of these articles showed that with extended stirring the respective crystalline suspensions increased the er or dr of the products. The DSM researchers also applied their CIAT technology to the preparation of a chiral α-methyl DOPA precursor, **94**. A solid-state CIAT process for α-amino nitriles has also been described.[77]

6. Racemization by Bromide Ions. The potential racemization of alkyl bromides by bromide or iodide is not widely recognized,[78] but successful DKR of alkyl bromides has been demonstrated.[79] Successful CIAT approaches have been developed (Scheme 20). Caddick and Jenkins[80] showed that when a solution of the equimolar mixture of diastereomers **95** and a catalytic amount of $(n\text{Bu})_4\text{NBr}$ was allowed to evaporate the diastereomer **96** was isolated in excellent

(73) Napolitano, E.; Farina, V. Crystallization-induced asymmetric transformations and self-regeneration of stereocenters (SROSC): enantiospecific synthesis of α-benzylalanine and hydantoin BIRT-377. *Tetrahedron Lett.* **2001**, *42*, 3231.

(74) Yee, N. K.; Nummy, L. J.; Frutos, R. P.; Song, J. J.; Napolitano, E.; Byrne, D. P.; Jones, P.-J.; Farina, V. Practical synthesis of a cell adhesion inhibitor by self-regeneration of stereocenters. *Tetrahedron: Asymmetry* **2003**, *14*, 3495.

(75) Toda, F.; Tanaka, K. Conversion of Racemic Cyanohydrin into One Optically Active Isomer in the Presence of Brucine. *Chem. Lett.* **1983**, 661. The chirality of the cyanohydrin was not established.

(76) Boesten, W. H. J.; Seerden, J.-P.; de Lange, B.; Dielemans, H. J. A.; Eisenberg, H. L.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. Asymmetric Strecker Synthesis of α-Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (*R*)-Phenylglycine Amide as Chiral Auxiliary. *Org. Lett.* **2001**, *3*, 1121.

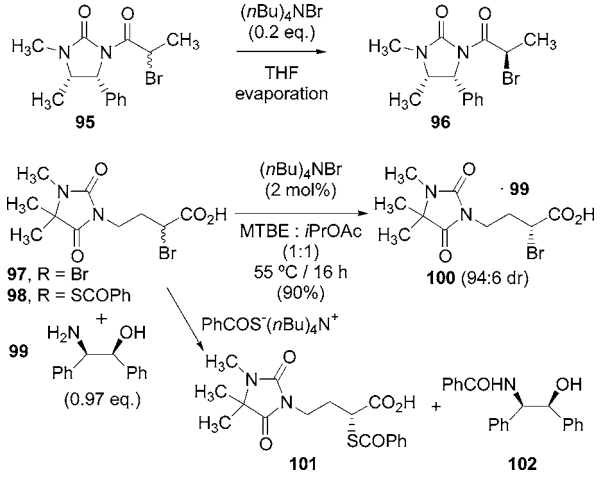
(77) Sakurai, R.; Suzuki, S.; Hashimoto, J.; Baba, M.; Itoh, O.; Uchida, A.; Hattori, T.; Miyano, S.; Yamamura, M. Epimerization of Diastereomeric α-Amino Nitriles to Single Stereoisomers in the Solid State. *Org. Lett.* **2004**, *6*, 2241.

(78) For interesting examples, see: (a) Koh, K.; Ben, R. N.; Durst, T. A Facile Synthesis of Optically Active C_2-Symmetric 2,5-Disubstituted Pyrrolidines and other *β*,*β*′-Dihydroxyamines. *Tetrahedron Lett.* **1994**, *35*, 375. (b) Seki, M.; Yamanaka, T.; Kondo, K. Practical Synthesis of (*R*)-4-Mercaptopyrrolidine-2-one from L-Aspartic Acid. Preparation of a Novel Orally Active 1-*β*-Methylcarbapenem, TA-949. *J. Org. Chem.* **2000**, *65*, 517.

(79) (a) Lee, S.; Nam, J.; Park, Y. S. Dynamic Resolution of α-Bromo- α-Alkyl Esters Using *N*-Methyl Pseudoephedrine as a Chiral Auxiliary: Asymmetric Syntheses of α-Amino Acid Derivatives. *Synlett* **2002**, *5*, 790. (b) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. Synthesis of α-amino esters by dynamic kinetic resolution of α-haloacyl imidazolildinones. *Tetrahedron* **2001**, *57*, 6589. (c) Ben, R. N.; Durst, T. Synthesis of Optically Active α-Amino Esters via Dynamic Kinetic Resolution: A Mechanistic Study. *Tetrahedron Lett.* **1994**, *35*, 375.

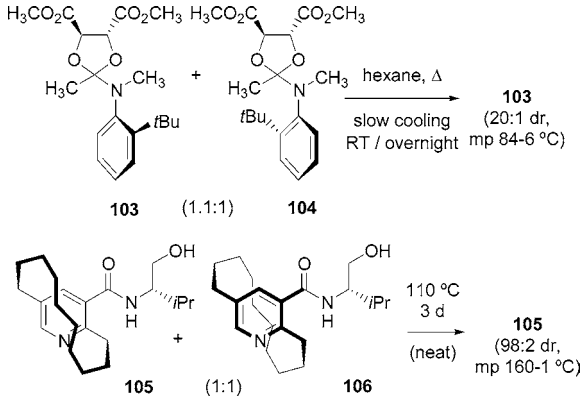
(80) Caddick, S.; Jenkins, K. A New Dynamic Resolution Strategy for Asymmetric Synthesis. *Tetrahedron Lett.* **1996**, *37*, 1301.

Scheme 20. **CIDR and CIAT processes through racemization by bromide**

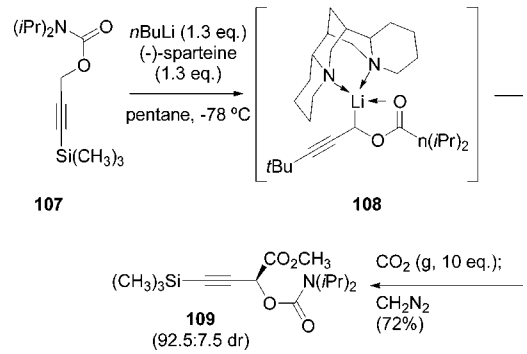


yield. This approach for *N*-(α-bromopropionyl)-imidazolidinones has recently been extended by Santos et al.[81] BMS researchers extensively studied the CIDR of an α-bromo carboxylic acid, also through racemization by $(n\text{Bu})_4\text{NBr}$.[82] Madding recognized the potential for bromide to racemize the undesired enantiomer of **97** and theorized that a suitable chiral amine might be found for a CIDR process.[83] In parallel experiments 47 chiral amines were screened with a total of 341 amine−solvent combinations in order to find crystalline salts, and five chiral amines were identified. To select an amine for CIDR, suspensions of the salts and KBr or $(n\text{Bu})_4\text{NBr}$ were screened at 55 °C for salts enriched in chirality. Through this screening the enantiomer of 1*R*,2*S*-2-amino-1,2-diphenylethanol (**99**) led to a salt enriched in the enantiomer of **100**, and hence **99** was chosen to generate **100**. (Under similar conditions, the racemic α-thiobenzoyl carboxylic acid **98** could also be resolved using the tetrabutylammonium salt of thiobenzoic acid; unfortunately a portion of **99** was benzoylated under the reaction conditions, and this approach was abandoned.) Optimal conditions were found by screening temperature, equivalents of $(n\text{Bu})_4\text{NBr}$ and **99**, reaction concentration, and solvent composition. The yield was optimized at 90% with a 94:6 dr, as the best compromise between yield and cycle time.[84] BMS also described the CIDR of (*R*)-2-bromo-3-phenylpropanoic acid using (*R*)-bornylamine and Et_4NBr.[85] The authors commented that about 48 h of stirring at 55 °C was necessary to reach 98:2 er, due to the low solubility of each salt under these conditions.

Scheme 21. **CIAT processes for an atropisomer and a cyclophane**



Scheme 22. **CIDR using sparteine**



7. Racemization through Thermal Methods. In a recent review Beak has discussed the importance of temperature control in dynamic thermodynamic resolution.[17] Curran and Ates described how atropisomer **103** crystallized with slow cooling from a mixture of **103** and its isomer **104**[86] (Scheme 21). Crystals of **103** were stable for weeks, but equilibration to the 1.1:1 ratio occurred within hours in solution. Dynamic resolution of aminal atropisomers of hindered naphthamides was reported by Layden.[87] Through a "jump-rope" rotation of the carbon framework the planar-chiral cyclophane **105** was resolved from its diastereomer **106** by heating without solvent at 110 °C.[88]

Deprotonation of the alkynyl urethane **107** with *n*BuLi and (−)-sparteine in pentane under cold conditions led to crystallization of the organolithium-sparteine complex **108**, which reacted in the presence of excess CO_2 and diazomethane to afford the chiral ester **109**[89] (Scheme 22). When $PhCH_3$ was used in place of pentane, crystallization of intermediate **108** did not occur, and **109** was generated with

(81) Santos, A. G.; Pereira, J.; Afonso, C. A. M.; Frenking, G. New Chiral Auxiliaries for Dynamic Kinetic Resolution: From Theory to Experiment. *Chem.—Eur. J.* **2005**, *11*, 330.

(82) Kiau, S.; Discordia, R. P.; Madding, G.; Okuniewicz, F. J.; Rosso, V.; Venit, J. J. Efficient Crystallization-Induced Dynamic Resolution of α-Substituted Carboxylic Acids. *J. Org. Chem.* **2004**, *69*, 4256.

(83) Madding, G. D. Personal communication.

(84) This CIAT provides another example of how an ee of >99.9% may be economical. Extra-high optical purities may not be necessary, as materials can often be upgraded by routine crystallization. For an interesting discussion, see: Hudlicky, T. Design Constraints in Practical Synthesis of Complex Molecules: Current Status, Case Studies with Carbohydrates and Alkaloids, and Future Perspectives. *Chem. Rev.* **1996**, *96*, 3.

(85) Chen, J. G.; Zhu, J.; Skonezny, P. M.; Rosso, V.; Venit, J. J."Crystallization-Induced Chiral Inversion As the Key Step for Synthesis of (*S*)-2-Acetylthio-3-phenylpropanoic Acid," *Org. Lett.* **2004**, *6*, 3233.

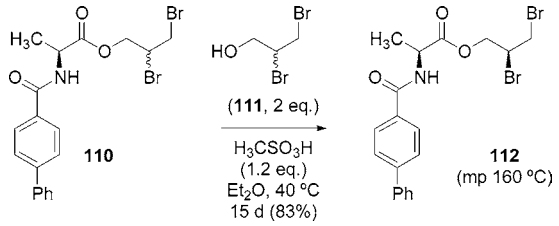
(86) Ates, A.; Curran, D. P. "Synthesis of Enantioenriched Axially Chiral Anilides from Atropisomerically Enriched Tartrate Ortho-Anilides," *J. Am. Chem. Soc.* **2001**, *123*, 5130.

(87) Clayden, J.; Lai, L. W. Enantioselective Synthesis of Atropisomeric Amides by Dynamic Resolution: Thermodynamic Control with a Proline-Derived Resolving Agent. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2556.

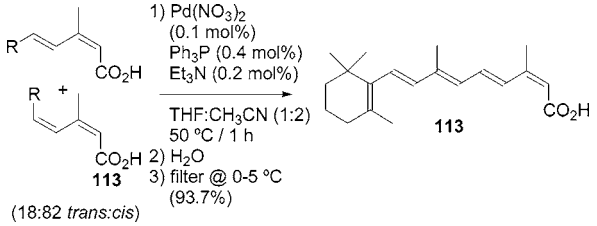
(88) (a) Kanomata, N.; Ochiai, Y. Stereocontrol of molecular jump-rope: crystallization-induced asymmetric transformation of planar-chiral cyclophanes. *Tetrahedron Lett.* **2001**, *42*, 1045. (b) Ueda, T.; Kanomata, N.; Machida, H. Synthesis of Planar-Chiral Paracyclophanes via Samarium(II)-Catalyzed Intramolecular Pinacol Coupling. *Org. Lett.* **2005**, *7*, 2365.

(89) Schultz-Fademrecht, C.; Wibbeling, B.; Frölich, R.; Hoppe, D. Synthesis of Enantiomerically Enriched Allenes by (−)-Sparteine-Mediated Lithiation of Alkynyl Carbamates. *Org. Lett.* **2001**, *3*, 1221.

Scheme 23. **CIAT through transesterification**



Scheme 24. **CIAT in the preparation of olefins**



a 58.5:41.5 dr. (−)-Sparteine led to the deracemization of binaphthol through a CIDR process.[90]

Napolitano has described a CIAT reaction by an acid-mediated transesterification[91] (Scheme 23). A suspension of the diastereomeric alanine esters **110** was treated with 2 equiv of the racemic alcohol **111**, leading to the isolation of **112** in 83% yield (corrected for purity). CIAT of **110** with bromide was not feasible, due to the high solubilities of the diastereomers.

A diastereomeric mixture of oxazolidinones from dipeptides has been converted to primarily one diastereomer by brief refluxing in CH_2Cl_2−light petrol (bp 40−60 °C).[92] The product epimerized in solution, especially under basic conditions; $LiAlH_4$ reduction at −78 °C opened the ring with essentially no epimerization. CIAT was observed by heating a mixture of an *o*-aminomethylnaphthol (from a Mannich reaction) and *p*-tolylaldehyde (neat) at 60 °C; racemization proceeded through an intermediate oxazine.[93]

8. Miscellaneous Examples of CIDR and CIAT. CIAT processes have also been reported for compounds with chiral heteroatoms. Wilen et al. prepared salts of Troger's base using a phosphate of chiral binaphthol.[94] Vedejs et al. have described CIAT processes for phosphines[95] and tetravalent boron complexes.[16] Harman has described the CIAT of arene−Re complexes.[96]

Olefins can also be produced by CIDR and CIAT processes, which can include the preparation of *cis*- and *trans*-olefins. A Hoffmann-La Roche patent has described the Pd-catalyzed isomerization of a 18:82 mixture of 11-*trans*- and 11-*cis*-olefins of 13-*cis*-retinoic acid (the mixture arising from a Wittig reaction) to the 11-*trans*-13-*cis*-retinoic acid ("13-*cis*-retinoic acid," **113**)[97] (Scheme 24). Under these conditions effectively no other olefins were isomerized, probably because the product crystallized from solution. DKR has also been noted for the formation of chiral olefins from racemic phenylalanal and a chiral phosphonate,[98] which presents an intriguing possibility for a CIAT process.

Summary, Perspective and Recommendations

CIDR or CIAT processes require that the products be crystalline and that the products and undesired enantiomers or diastereomers be interconvertable at temperatures below the melting point of the products. In the majority of CIDR and CIAT processes surveyed, researchers made a key observation that indicated the desired product could be racemized or epimerized, and then CIDR or CIAT processes were developed. Most authors found that developing effective conditions for racemization was easier than developing a rugged crystallization, and high-throughput screening was often employed. Many researchers have found that products from CIDR or CIAT processes are unstable in solution, which reflects the labile nature of CIDR and CIAT products.

Many different approaches were taken to racemize or epimerize the undesired enantiomers or diastereomers corresponding to the desired drugs and intermediates. A broad category of racemization[54,99] includes thermal racemization, which can proceed through enolization as the case for **25** (Scheme 9), retro-Diels−Alder−Diels−Alder sequence as the case for lysergic acid,[100] retro-Michael−Michael additions (Scheme 15), and others. The prepared chemist may find that heating a suspension for dissolution or heating a mother liquor leads to racemization or epimerization, and extended aging at the crystallization temperature may change the product composition. An equilibrium may also be established in the addition of a nucleophile to an sp^2-hybridized carbon, such as an imine or carbonyl. Epimerization or racemization may occur α- to carbonyls or masked carbonyls. Acidic and basic conditions, which may be provided by excess reagents during the preparation of the product, have been shown to promote racemization and epimerization; D− for H− exchange under acidic or basic conditions (NMR) may reveal labile functionality. Catalysts, such as aldehydes used in the racemization of amines, may be employed to increase the

(90) Smrčina, M.; Lorenc, M.; Hanuš, V.; Sedmera, P.; Kočovský. Synthesis of Enantiomerically Pure 2,2′-Dihydroxy-1,1′-binaphthyl, 2,2′-Diamino-1,1′-binaphthyl, and 2-Amino-2′-hydroxy-1,1′-binaphthyl. Comparison of Processes Operating as Diastereoselective Crystallization and as Second-Order Asymmetric Transformation. *J. Org. Chem.* **1992**, *57*, 1917.

(91) Brunetto, G.; Gori, S.; Fiaschi, R.; Napolitano, E. Crystallization-Induced Asymmetric Transformations. Enantiomerically pure (−)-(*R*)- and (+)-(*S*)-2,3-Dibromopropan-1-ol and Epibromohydrins. A Study of Dynamic Resolution via the Formation of Diastereoisomeric Esters. *Helv. Chim. Acta* **2002**, *85*, 3785.

(92) Stock, H. T.; Turner, N. J. Crystallisation-Induced Dynamic Resolution of Dipeptide-Derived 5(4*H*)-Oxazolidinones. *Tetrahedron Lett.* **1996**, *36*, 6575.

(93) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. "Solvent-Free Asymmetric Aminoalkylation of Electron-Rich Aromatic Compounds: Stereoselective Synthesis of Aminoalkylnaphthols by Crystallization-Induced Asymmetric Transformation. *J. Org. Chem.* **2001**, *66*, 4759.

(94) Wilen, S. H.; Qi, J. Z. Resolution, Asymmetric Transformation, and Configuration of Tröger's Base. Application of Tröger's Base as a Chiral Solvating Agent. *J. Org. Chem.* **1991**, *56*, 485.

(95) Vedejs, E.; Donde, Y. Crystallization-Induced Asymmetric Transformation of a Tertiary Phosphine. *J. Org. Chem.* **1999**, *65*, 2337.

(96) Keane, J. M.; Ding, F.; Sabat, M.; Harman, W. D. Solid-State Induced Control of Kinetically Unstable Stereoisomers. *J. Am. Chem. Soc.* **2004**, *126*, 785.

(97) Lucci, R. Preparation of 13-Cis Retinoic Acid. U.S. Patent 4,556,518, 1985 (to Hoffmann-La Roche).

(98) Rein, T.; Pedersen, T. M. Asymmetric Wittig Type Reactions. *Synthesis* **2002**, *5*, 579.

(99) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York; 1994; pp 424−40.

(100) See: (a) Armstrong, V. W.; Coulton, S.; Ramage, R. A New Synthetic Route to (±)-Lysergic Acid. *Tetrahedron Lett.* **1978**, *19*, 4311. (b) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. A Concise, Palladium-Catalyzed Approach to (±)-Lysergic Acid. *Tetrahedron Lett.* **1988**, *29*, 3117 and references therein.

reactivity of the system. Polar solvents often provide faster racemization or epimerization when polar intermediates or transition states are involved.

Crystallization pressures have been generated either by controlling the temperature and solvent−antisolvent ratios or by concentrating the crystalline slurry. To develop a rugged process using the latter approach, the rates of solvent removal would have to be thoroughly investigated; fine control may be easier on a large scale. Process times have ranged from hours to days, and lengthy crystallization times decrease process productivity. Extended crystallization times may be due to low solubility of undesired materials in the slurry, and solubility may be increased by operating at higher temperatures or by adjusting the solvent mixtures. For all but one of the detailed examples covered in this review, crystallization was carried out by aging at a constant temperature and then cooling (plateau cooling conditions).

As expected, the products from CIDR or CIAT processes are highly crystalline. For 25 examples in the schemes of this review, the average mp was 155 °C, and crystallizations were conducted on average 115 C° below the mp of the products. Crystallizations at temperatures close to the product mp may extend processing time.

Of the two approaches to resolving compounds, i.e., preparation of diastereomeric derivatives or crystallization of conglomerates by entrainment, the former is much more popular, since no more than 10% of racemic compounds have been found to be conglomerates.[101,102] Entrainment is an effective method to resolve materials, as has been shown on large scales for the preparation of thiamphenicol,[103] monosodium glutamate, binaphthol dimethyl ether,[104] naproxen,[105] and α-methyl-DOPA.[106] Entrainment is a kinetic process, and it is essential to understand the conditions and times when crystallization of the undesired enantiomer or other form is likely to occur. Resolutions have failed on scale when the crystallization was based on the kinetics of crystal growth (for diastereomers),[107] so knowing the kinetics is particularly important for successful scale-up, where a 10× scale-up is likely to at least double the processing times for unit operations.[4] Small molecules[108] and polymers[109] have been used to suppress the crystallization of unwanted forms; the advantages of such additives for a dedicated manufacturing process may outweigh the inconveniences of studying additional parameters and qualifying and using additional materials. Thus the disadvantages of developing resolution by entrainment include understanding and controlling the kinetics of crystallization of the undesired enantiomer; the disadvantages of a diastereomeric resolution include adding a portion of a molecule with an additional chiral center, in what is essentially ballast after the resolution step. If one has the opportunity to choose between resolution by entrainment or resolution by the formation of diastereomers, the benefits and disadvantages of each must be weighed. For rapid scale-up, resolution by diastereomer formation may be more reliable and easier to implement.

Developing a rugged crystallization requires close attention to detail, and excellent reviews have been written.[110,111] Differential scanning calorimetry (DSC) is a powerful tool used to screen salts for resolution,[112] and in general lower solubilities and hence higher yields are associated with higher melting points. Once the appropriate salt has been selected, optimal conditions are developed to crystallize and isolate the product. Very large differences in solubilities of the salts may be found for different solvents,[113,114] and high-throughput screening of solvents and solvent mixtures may be necessary. Controlling the water content has often been found to be important in some CIDR processes, for at least three reasons: (1) to solubilize reaction components and hence promote rapid, reliable reactions; (2) to hydrolyze any imine intermediates; and (3) to optimize isolated yields through crystallization of hydrates[115,116] or by using H_2O as an antisolvent. Controlling impurities such as NaCl and HCl may also be necessary for rugged processing.[117] If any

(101) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981; p 81.
(102) For a concise discussion, see ref 16.
(103) Coppi, L.; Giordano, C.; Longoni, A.; Panossian, S. Thiamphenicol: a Manufacturing Process Involving a Double Inversion of Stereochemistry. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York; 1997; p 358.
(104) Gottarelli, G.; Spada, G. P. Spontaneous Resolution of 2,2′-Dimethoxy-1,1′-binaphthalene. *J. Org. Chem.* **1991**, *56*, 2096.
(105) Crosby, J. Chirality in Industry: An Overview. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York, 1992; pp 25−6.
(106) Bayley, C. R.; Vaidya, N. A. "Resolution of Racemates by Diastereomeric Salt Formation," in *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York; 1992; p 69.
(107) Ref 30, p 83. The goal was to develop a rugged process for the resolution of the S-acetyl acid leading to captopril.
(108) Mohan, R.; Koo, K.-K.; Strege, C.; Myerson, A. Effect of Additives on the Transformation Behavior of L-Phenylalanine in Aqueous Solution. *Ind. Eng. Chem. Res.* **2001**, *40*, 6111.
(109) Zbaida, D.; Lahav, M.; Drauz, K.; Knaup, G.; Kottenhahn, M. A Cyclic Continuous Process for Converting Conglomerates into Optically Pure Enantiomers by Crystallization and Dissolution with the Assistance of "Tailor-made" Polymers. *Tetrahedron* **2000**, *56*, 6645.
(110) Wood, W. M. L. Crystal Science in the Manufacture of Chiral Compounds. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York; 1997; pp 119−56.
(111) Ref 30, pp 81−98.
(112) Ebbers, E.; Ariaans, G. J. A.; Zwanenburg, B.; Bruggink, A. Controlled design of resolutions. Prediction of the efficiency of resolutions based on samples of arbitrary composition. *Tetrahedron: Asymmetry* **1998**, *9*, 2745.
(113) Borates of racemic binaphthol have been shown to form salts with (*R*)-α-methylbenzylamine, and one diastereomeric salt is insoluble in THF, while the other diastereomer is insoluble in CH_3CN: Periasamy, M.; Venkataraman, L.; Sivakumar, S.; Sampathkumar, N.; Ramanathan, C. R. A New, Convenient Method of Resolution of Racemic 1,1′-Bi-2-naphthol Using Boric Acid and (*R*)-α-Methylbenzylamine. *J. Org. Chem.* **1999**, *64*, 7643.
(114) For instance, to increase the solubility of the undesired crystalline diastereomer of a salt formed from di-*p*-toluoyl-D-tartaric acid, 33 vol % of MeOH was added to the crystallization solvent, *i*PrOH: Hoard, D. W.; Moher, E. D.; Turpin, J. A. Synthesis of (*R*)-(−)-1-Piperidino-3,3-dimethylbutan-2-ol: Application in the Molar Scale Asymmetric Ethylation of *trans*-Crotonaldehyde. *Org. Process Res. Dev.* **1999**, *3*, 64.
(115) The solvent that was most often successful for resolution by crystallization is 96% aq. EtOH: see ref 101, pp 381−95.
(116) For a detailed example on how anhydrous conditions were necessary for a classical resolution, see: Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G.-J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F.-R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. A Highly Efficient Synthesis of Fibrinogen Receptor Antagonist L-734,217 via a Novel Chemoselective Silyl-Mediated Conjugate Addition of δ-Lactams to 4-Vinylpyridine. *J. Org. Chem.* **1996**, *61*, 215.
(117) For an interesting example in a classical resolution of phenylglycine with (1*S*)-(+)-camphor-10-sulfonic acid, see: Yoshioka, R.; Hiramatsu, J.; Okamura, K.; Tsujioka, I.; Yamada, S. Crystal structure − solubility relationships in optical resolution by diastereomeric salt formation of DL-phenylglycine with (1*S*)-(+)-camphor-10-sulfonic acid. *J. Chem. Soc., Perkins Trans. 2* **2000**, 2121.

resolving agent used in the CIAT or CIDR process is unstable to the reaction conditions,[118] additional considerations are necessary to develop a process that may already require controlling a number of parameters. Additional compounds may be added to form cocrystals or clathrates,[119] as the case for compound **32** (Scheme 9).[120] These crystalline materials are sometimes discovered during research during formulation studies of a drug product.[121] In principle a useful clathrate can be formed from any nontoxic compound, such as compounds from the GRAS (generally recognized as safe) list.[122,123] Exploring many parameters may be necessary to develop useful CIDR and CIAT processes.

In conclusion, crystallization-induced dynamic resolution (CIDR) and crystallization-induced asymmetric transformation (CIAT) are adaptations of dynamic resolution, a process that can afford in principle a quantitative yield of chiral product through in situ resolution. Highly crystalline materials may be good candidates for CIDR and CIAT processes and may lead to the isolation in good yield of what is the minor product in solution. To efficiently develop rugged CIDR and CIAT processes, it is necessary to optimize parameters for both racemization and crystallization, and development times may be shortened by high-throughput screening and design of experiments. Crystalline products arising from CIDR and CIAT processes often racemize or epimerize if redissolved, which can complicate analyses and downstream processing. It is intriguing to consider that, under the right conditions, an extended crystallization may increase the theoretical yield of a resolution from 50% to 100%. CIDR and CIAT processes will continue to be developed, due to their significant economic advantages.[124,125]

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(118) For developing a rugged process, the stability of resolving agents for splitting the salts and recycle−recovery should also be considered. Researchers from Celltech have noted that di-*p*-toluoyl-tartaric acid can hydrolyze rapidly at ≥pH 9: Evans, G. R.; Henshilwood, J. A.; O'Rourke, J. Highly efficient resolution of (±)-Tramadol with di-*p*-toluoyl-tartaric acid (DTTA). *Tetrahedron: Asymmetry* **2001**, *12*, 1663.

(119) In clathrates, also known as inclusion complexes, any of several molecules may be the guest inside the cavity of the host molecule, and weak hydrogen bonding may or may not be involved. In cocrystals the partner molecules form essential, strong hydrogen bonding within the crystals. See: Bingham, A. L.; Hughes, D. S.; Hursthouse, M. B.; Lancaster, R. W.; Tavener, S.; Threlfall, T. L. Over one hundred solvates of sulfathiazole. *Chem. Commun.* **2001**, 603.

(120) For examples of classical resolution involving cocrystals or clathrates, see: (a) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. Simple and Efficient Resolution of 1,1′-Bi-2-naphthol. *Tetrahedron Lett.* **1995**, *36*, 7991. (b) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsolona, R. Scalable, efficient process for the synthesis of (*R*)-3,5-bistrifluoromethylphenyl ethanol via catalytic asymmetric transfer hydrogenation and isolation as a DABCO inclusion complex. *Tetrahedron: Asymmetry* **2003**, *14*, 3581.

(121) For instance, ethyl *p*-hydroxybenzoate ("ethyl paraben," a preservative in cosmetics) can be used to effectively recover loracarbef from mother liquors: Amos, J. G.; Indelicato, J. M.; Pasini, C. E.; Reutzel, S. M. Complexes of Cephalosporins and Carbacephalosporins with Parabens. U.S. Patent 6,001,996, 1999 (to Eli Lilly).

(122) Reutzel-Edens, S. M. Personal communication.

(123) For the Inactive Ingredients Database, see: *www.accessdata.fda.gov/scripts/cder/iig/index.cfm*.

(124) By using CIAT processing for the manufacture of aprepitant Merck has raised the overall yield to 76% and reduced waste by 85%. In recognition of these achievements Merck received a 2005 Presidential Green Chemistry Challenge Award: Ritter, S. K. Green Success. *Chem. Eng. News* **2005**, *83* (26), 40.

(125) I selected the CIDR and CIAT references included in this review for their relevance in describing the scope of such processes or for their approaches to developing such processes. To access these references I used citation searches and searches for the key words mentioned in the paragraph under Scheme 2. I believe this review is reasonably complete for practical examples, but it is difficult to assess how many examples I have missed. Other examples may be found in the cited references.