Crystallization-Induced Diastereomer Transformations†

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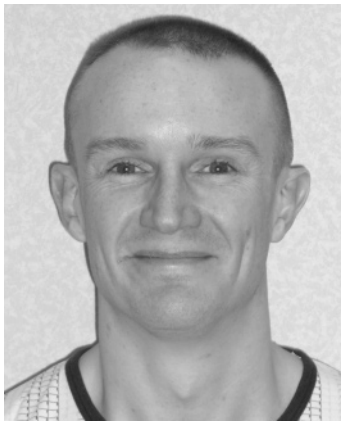

Tony J. Davies was born in 1967 in Nelson, U.K. He studied chemistry at the University of Anglia, receiving his B.Sc. (Hons) degree in 1988. Remaining at UEA he obtained his Ph.D. degree in 1992 under the supervision of Professor Richard Taylor. In 1992 he joined Merck, Sharp & Dohme as a process chemist. In 2000 he graduated from City University Business School with his M.B.A. degree, where his dissertation was concerned with parallel trade within the pharmaceutical industry. Today is he a Senior Research Fellow within the department of Process Research at MSD.

1. Introduction and Scope

In modern organic synthesis chromatographic separation of crude reaction products has largely supplanted the more time-consuming development of an efficient crystallization.[1] As such it has greatly contributed to the accelerated progress in this science. However, while chromatography is rapid and can be readily automated, crystallizations can offer opportunities which are far beyond a simple isolation. Crystallization or precipitation of products directly from a crude reaction mixture invariably simplifies a process while concomitantly increasing productivity and decreasing the amount of both energy required and waste generated.[2,3] The power of crystallization is particularly exemplified when the thermodynamic driving force of molecules ordering themselves into a lattice structure is used to drive a chemical transformation. Many examples of the crystallization of enantiomerically or diastereomerically pure products from a solution containing several equilibrating isomers in a yield exceeding that given by its solution concentration have been reported since the earliest days of organic chemistry. Crystallization-induced stereoisomer transformations (CIST) can in principle be divided into two main categories: crystallization-induced enantiomer transformations (CIET) and the much more common crystallization-induced diastereomer transformations (CIDT). The discovery of CIST has mostly been based on serendipity. It took until late in the 20th century before CIST started being used as a design element in practical asymmetric synthesis.

This review will cover the use of CIDT from the first recorded case in 1846 through to the middle of 2005, with particular emphasis on progress in the last 25 years. The related CIET (often called *total spontaneous* resolutions) can only occur under very special conditions (vide infra) and are therefore not included in this review. CIDT has been reviewed on several occasions with varying degrees of comprehensiveness.[4−11] We decided to focus this review on examples of CIDT in the field of organic chemistry with a

† Dedicated to the memory of Dr. Ramon J. Alabaster (1941−2005).

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few striking examples from organometallic chemistry. Examples of CIDT from the inorganic arena are not included. Iterative processes in which mother liquors are equilibrated and subjected again to crystallization conditions in order to achieve a high overall efficiency with respect to pure isolated diastereomer are closely related to CIDT and much practiced, but they are not considered for this review.[12]

2. Physical Basis and Nomenclature

Before describing the physical basis of CIDT, it is important to briefly review the different crystallization behaviors which can be displayed by mixtures of enantiomers and diastereomers. Mixtures of mirror-image stereoisomers can crystallize as *conglomerates* (mechanical mixture of crystals of pure enantiomers with each unit cell containing only a single enantiomer), *racemic compounds* (both enantiomers are present in a 1:1 ratio in the unit cell), and *solid solutions* (sometimes also called *pseudo-racemates*; both enantiomers are present in the condensed phase in a nonordered arrangement).[13] The fundamental difference in these crystallization behaviors is reflected in the physical properties of the solids (e.g., melting point and solubility) and has a profound impact on the possibility of designing CIET (vide infra). Likewise, mixtures of diastereomers can crystallize in three analogous forms.[14] Most often, diastereomers produce a *eutectic mixture* (the compounds are crystallizing as separate entities, "conglomerate-like" behavior). However, occasionally diastereomers can crystallize as a *quasi-racemate* (a 1:1 pairing of two structurally similar and configurationally quasi-enantiomeric compounds; "racemic compound-like" behavior) or as a *solid solution* (also often called *mixed crystal*; molecules of one diastereomer replacing those of another without significantly impacting the crystal packing). A CIDT can only become viable when the diastereomers crystallize as a *eutectic mixture*.

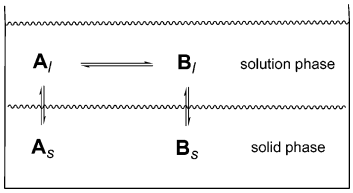


Figure 1. Schematic representation of a crystallization-induced process

The thermodynamic basis of crystallization-induced processes has been outlined rather lucidly by Kuhn and Jochims.[15,16] Figure 1 schematically represents a system in which two solid diastereomers $\mathbf{A}_s$ and $\mathbf{B}_s$ can equilibrate with each other (at a temperature below their melting points) via their dissolved counterparts $\mathbf{A}_l$ and $\mathbf{B}_l$.[17] The solubility products of compounds **A** and **B** are given by $L_A = [\mathbf{A}_l]$ and $L_B = [\mathbf{B}_l]$, and the equilibrium constant for **A** and **B** in solution is given by $K = [\mathbf{B}_l]/[\mathbf{A}_l]$. The interconversion between $\mathbf{A}_l$ and $\mathbf{B}_l$ has historically been called an asymmetric transformation of the first kind. If either $\mathbf{A}_s$ or $\mathbf{B}_s$ selectively crystallizes from a solution of equilibrating isomers in a yield which exceeds its solution concentration, the process is often called an asymmetric transformation of the second kind.[18]

Since the equilibria in Figure 1 are coupled, a simple mathematical treatment allows the following conclusions to be drawn.[19] When $L_AK = L_B$, the system is stationary and there is no net transformation of $\mathbf{A}_s$ into $\mathbf{B}_s$ or vice versa. For $L_AK > L_B$ the mixture of $\mathbf{A}_s$ and $\mathbf{B}_s$ should eventually be transformed into pure $\mathbf{B}_s$. For $L_AK < L_B$ the mixture of $\mathbf{A}_s$ and $\mathbf{B}_s$ should eventually be transformed into pure $\mathbf{A}_s$. When it is assumed that the amount of solvent used in this process is relatively small, the amounts of $\mathbf{A}_l$ and $\mathbf{B}_l$ will be small and it can be seen that such a process can be used to efficiently convert one stereoisomer into the other. Pure product can then be isolated via a straightforward filtration.

Diastereomers **A** and **B** in a CIDT can be chiral or nonchiral (e.g., *E*/*Z* double-bond isomers). The most common situation is when **A** and **B** each consist of two separate moieties which are either electrostatically (i.e., a salt) or covalently held together. In either case, the molecule contains at least one center which can equilibrate and one other which does not (i.e., the directing center). The distance between equilibrating and nonequilibrating centers is not important. The nonequilibrating center only functions as an influence in the intermolecular interactions which determine the crystal packing.

Some investigators have observed that the minor (hence, less stable) diastereomer present in the solution equilibrium crystallizes preferentially in the CIDT and have dubbed this phenomenon the "van't Hoff-Dimroth rule".[8] Others have suggested that a CIDT always produces the least soluble diastereomer.[20] However, the above mathematical treatise clearly shows that neither of these assertions can be accurate because it is the balance between the position of the solution equilibrium and the solubility products which determines which component will selectively crystallize.

In the above-described case compounds **A** and **B** are diastereomers. When **A** and **B** are enantiomers their solubilities are necessarily equal and the driving force for the process is no longer thermodynamic but kinetic. This phenomenon is often called total spontaneous resolution, but we prefer the term crystallization-induced enantiomer transformation (CIET). The process can only work when $\mathbf{A}_s$ and $\mathbf{B}_s$ crystallize as a conglomerate rather than a racemic compound.[21] Unfortunately, the large majority of enantiomers (estimated at >90%) crystallize as a racemic compound and not as a conglomerate.[22] Even though CIET has some practical significance, it is not covered in this review.

The nomenclature related to the version of the above-described process which involves diastereomers can be quite confusing. The following terms have all been used to describe the same process: asymmetric transformation of the second kind (as this term was originally coined in German and later translated into English, where it is often wrongly referred to as a "second-order asymmetric transformation"), asymmetric transformation (AT), crystallization-induced asymmetric disequilibration, crystallization-induced asymmetric transformation (CIAT), and crystallization-induced dynamic resolution (CIDR). The latter term appears to express a relationship with so-called dynamic kinetic resolutions (DKR).[23] These are typically defined as transformations in which two rapidly equilibrating enantiomers react irreversibly at different rates with a chiral catalyst or reactant, thus in principle allowing the conversion of the racemic substrate into a single stereoisomeric product with a theoretical yield of 100%. As this review will show, in many cases the goal of the crystallization-induced process is not to transform a racemate into a single enantiomer via the (temporary) formation of diastereomers (i.e., to achieve a classical resolution with >50% yield).[24] In those cases both the equilibrating and directing center(s) are an integral part of the target structure. Since the physical basis of processes dealing with enanti-

omers is also significantly different from those dealing with diastereomers (vide supra), we think the term crystallization-induced diastereomer transformations (CIDT) provides a more accurate description, and therefore, we will use this term throughout this review.

3. Organization

For this review the many examples of CIDT have been organized, somewhat arbitrarily, into two broad categories. The first category will highlight CIDT in which the equilibrating and nonequilibrating center(s) reside in different counterions of a salt. This category has been further subdivided into non-amino acid compounds and amino acid and related compounds. A second category deals with molecules in which the equilibrating center(s) and nonequilibrating center(s) are part of the same covalent backbone. Transformations involving compounds which are technically salts but in which the counterion is not chiral will be discussed in this section rather than in the salt category. In each section examples of CIDT are loosely grouped according to the mechanism of equilibration.

The margin between success and failure of a CIDT is often quite small, and experimental conditions are of the utmost importance. Some description of the experimental conditions is therefore provided for many of the examples. Often, particularly in the earlier examples, the absolute configuration of chiral compounds is not known, and in those cases an arbitrary decision was made in drawing the absolute structure.

The concluding section will list a number of key considerations to be taken into account when development of a new CIDT is contemplated.

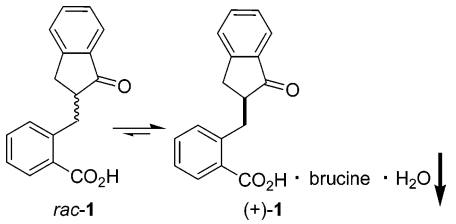
4. Diastereomeric Salts

A large number of CIDT have been described for molecules in which the equilibrating and nonequilibrating centers reside on different counterions of a salt. Often, these were serendipitously discovered during an attempted classical resolution of a racemic mixture of enantiomers. Most of the earliest examples involve non-amino acid compounds. In recent times attention has shifted to the development of CIDT of amino acids and related compounds mostly due to their utility in the pharmaceutical and agrochemical industry.

4.1. Non-Amino Acid Compounds

One of the earliest examples of CIDT was reported by Leuchs in 1913 (Scheme 1).[25] Attempted resolution of

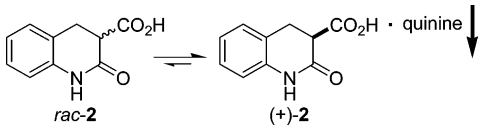
Scheme 1



indanone *rac*-**1** with brucine (1.0 equiv) from hot acetone yielded the diastereomerically pure (+)-**1** as a monohydrate salt in 93% yield. Leuchs found that the corresponding acid, particularly the sodium salt, showed rapid mutarotation in solution. All of these compounds converted back to the racemate within 24 h at room temperature. Interestingly, Leuchs explicitly comments in his paper on the value of CIDT for asymmetric synthesis.

Facile interconversion of the keto and enol forms of the indanone moiety under the reported conditions is undoubtedly key in the success of the above CIDT. A large number of other examples have been reported in which the equilibration is based on epimerization of a relatively acidic carbon−hydrogen bond. Leuchs himself provided another early example which is shown in Scheme 2.[26] When *rac*-**2** and

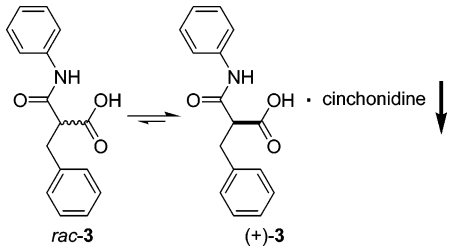
Scheme 2



quinine were dissolved in hot methanol and the solution was allowed to cool, the diastereomerically pure (+)-**2** was obtained in three crops with an overall yield of 95%.

Similar observations were made for another malonic acid derivative (Scheme 3).[27] Treatment of *rac*-**3** with cinchoni-

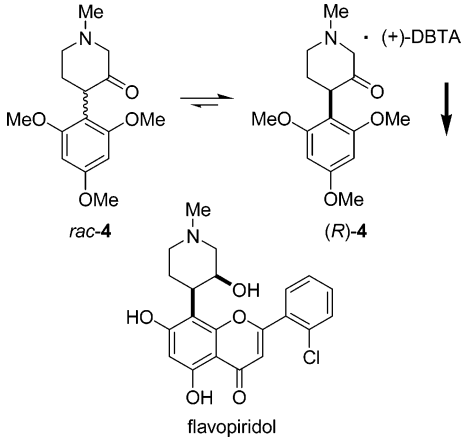
Scheme 3



dine (1 equiv) in hot acetone yielded the diastereomerically pure salt (+)-**3** in 90% yield. Other groups have reported similar CIDT on closely related compounds.[28−30]

A carbon−hydrogen bond flanked by aryl and ketone groups is sufficiently activated for a CIDT, as demonstrated by a recent example from a Bristol-Myers Squibb group who used this process in a synthesis of the cyclin-dependent kinase 1 inhibitor flavopiridol (Scheme 4).[31] When a mixture

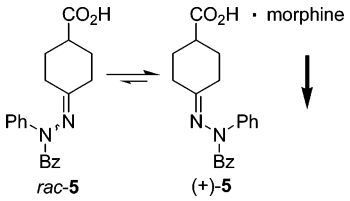
Scheme 4



of *rac*-**4** and dibenzoyl-(+)-tartaric acid ((+)-DBTA) in methanol was heated to reflux and then allowed to cool to room temperature, the desired (*R*)-(+) salt (>99% de) could be isolated in two crops with an overall yield of 76%. Another example was recently described by a Pfizer group.[32]

The following two examples of CIDT have considerable historical significance. During their pioneering studies on the configuration of oximes[33] and hydrazones,[34] Mills and Bain observed in 1914 that the morphine salt of the benzoylphenylhydrazone of cyclohexanone-4-carboxylic acid rapidly racemized in solution (Scheme 5). Even though yields

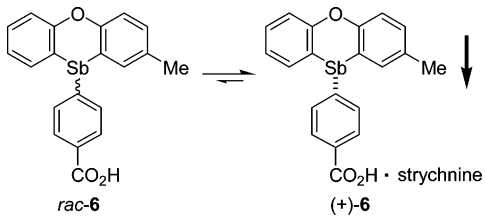
Scheme 5



were not mentioned in their paper, the authors reported that only the dextrotatory salt (+)-**5** was deposited from an aqueous methanol solution of *rac*-**5**. Attempted isolation of the levorotatory salt from the mother liquors only afforded additional solids of the dextrotatory salt.

Scheme 6 provides another interesting early CIDT ex-

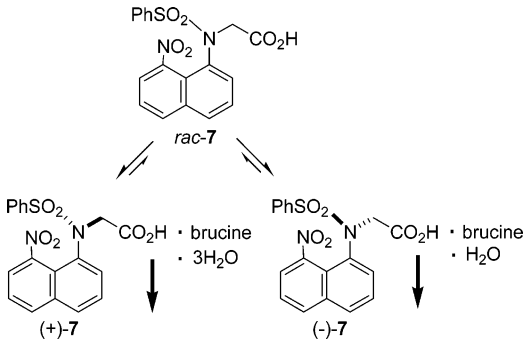
Scheme 6



ample.[35] During an attempted classical resolution of racemic antimony compound *rac*-**6** with strychnine in a 6:1 mixture of ethanol and chloroform, it was noted that near diastereomerically pure (+)-**6** was obtained in greater than the expected yield. In this case, epimerization occurs at the heteroatom under the reaction conditions. A CIDT involving a cobalt complex was reported in the same time frame.[36]

A large number of CIDT examples involve atropisomers. An elegant early example was reported by Mills and Elliott in 1928 as part of their study of fundamental aspects of atropisomerism (Scheme 7).[37] When equimolar quantities of

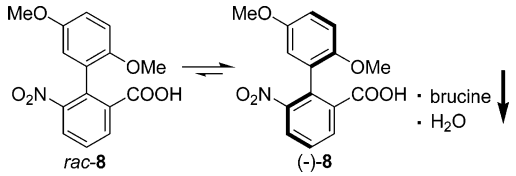
Scheme 7



rac-**7** and brucine were mixed in acetone, the levorotatory salt (−)-**7** precipitated in 98% yield. It was determined that this salt was a monohydrate. Interestingly, when monohydrate (−)-**7** was heated in methanol the dextrorotatory acid (+)-**7** crystallized in 75% yield as a trihydrate. When the latter was dissolved in acetone, (−)-**7** monohydrate crystallized again. Even though this was apparently not examined in detail, the solubility difference between the two diastereomeric salts apparently completely reverses depending on the amount of hydrated water, i.e., upon forming a different crystal form. This is indeed an excellent reminder that (pseudo-)polymorphism issues should always be considered in CIDT. The authors determined that the equilibration rate for the salt was much faster than for the free acid. Closely related examples were later reported by Adams et al.[38−40]

A CIDT with a biphenyl derivative was reported by the Adams group in 1932 as part of their studies on the correlation between the structure and rate of racemization of atropisomers (Scheme 8).[41] Thus, crystallization of the

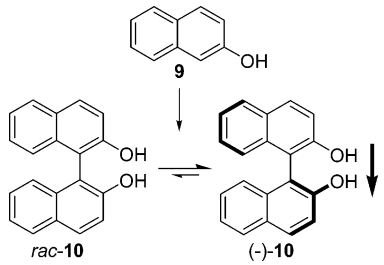
Scheme 8



salt of *rac*-**8** and 1 equiv of brucine from water at room temperature yielded the diastereomerically pure product (−)-**8** as a monohydrate in 94% yield in three fractions. The rate of racemization of this salt, as well as the corresponding free acid and sodium salt, was studied in a variety of organic solvents. Many other examples have been reported for biphenyl derivatives by the same[42−45] and other research groups.[46−53] Likewise, CIDT have also been reported for binaphthyl[54] and phenylnaphthyl derivatives.[55] CIDT has also been used for the atropisomer-selective preparation of *N*-benzoyl diphenylamines.[56,57] Attempts have also been made to develop CIDT processes for various biphenyl derivatives which lack an ionizable group by using a chiral solvent, albeit with very limited success.[58]

A CIDT also forms the basis of a preparation of the important ligand 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) as shown in Scheme 9. Thus, in situ formation of *rac*-**10** via

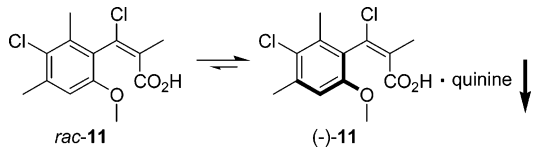
Scheme 9



oxidative coupling of 2-naphthol (**9**) with $CuCl_2$ in the presence of (+)-amphetamine (in a 1:2:8 molar ratio) in methanol afforded crystals of the near enantiopure product (−)-**10** as the corresponding copper complex.[59] Temperature proved critical in this process, possibly due to its effect on the rate of equilibration. When the procedure was carried out at <10 °C the product was almost racemic; however, at >20 °C the solids yielded (−)-**10** (96% ee) after decomplexation.[60] A similar process using (−)-sparteine instead of (+)-amphetamine has also been reported.[61] In this case the enantiopurity of the decomplexed (−)-**10** was 80% ee. It proved difficult to upgrade this purity as it is known that this compound crystallizes as a racemic compound rather than the more desirable conglomerate. Similar results were obtained in an oligomeric series.[62]

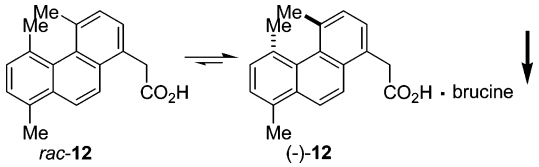
Two related examples of CIDT are reported in Schemes

Scheme 10



10 and 11. When Adams and Gross as part of their atropisomerism studies mixed *rac*-**11** with quinine in acetone at room temperature, the diastereomerically pure salt with (−)-**11** was obtained in three crops with 76% overall yield.[63]

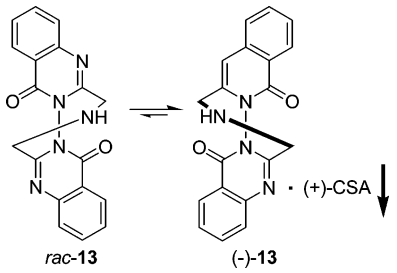
Scheme 11



Even though the mechanism of equilibration in the CIDT of phenanthrene acid derivative **12** is not based on rotation around a sterically crowded single bond as in the cases above, it is nevertheless conceptually very similar. Thus, upon treatment of *rac*-**12** with brucine in a mixture of ethanol and ethyl acetate at room temperature, the levorotatory salt with (−)-**12** was obtained in 74% yield.[64] The authors reported that the salt rapidly racemizes in solution.

When biquinazolinone *rac*-**13** was heated under optimized conditions with 2 equiv of (+)-camphorsulfonic acid (CSA) in benzene at reflux for 40 h, the resulting solids provided the (−)-amine with 93% ee and 82% yield upon a salt break (Scheme 12).[65] The authors report that the racemization of

Scheme 12

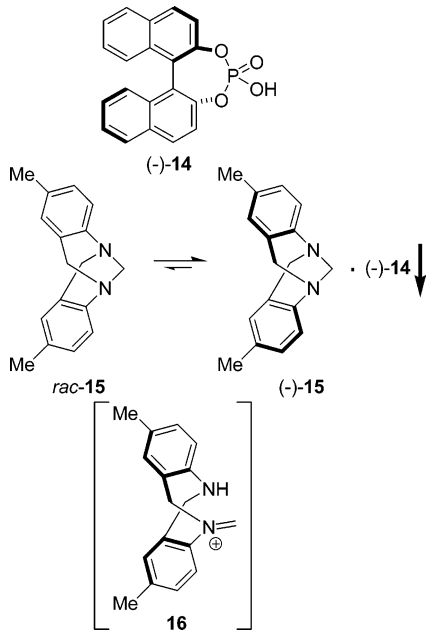


(−)-**13** in the presence of an acid is much faster than for the corresponding free base.

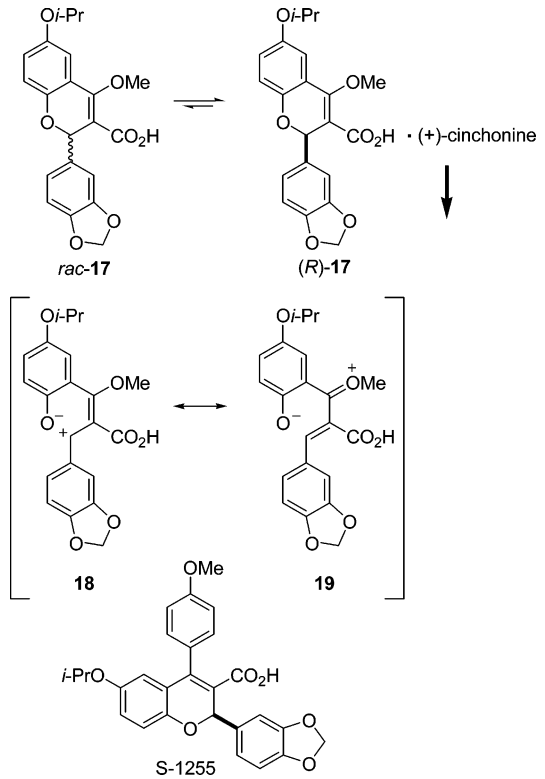
In the following example the mechanism of equilibration is undoubtedly based on the facile rupture (to give intermediate **16**) and restoration of a carbon−nitrogen bond under acidic conditions (Scheme 13). Thus, in an attempt to resolve Tröger's base via slow cooling of a mixture of equimolar quantities of *rac*-**15** and (−)-**14** in absolute ethanol to 0 °C, the diastereomerically pure salt (−)-**15**·(−)-**14** was obtained in 93% yield in two crops.[66]

A Shionogi group developed a CIDT for the preparation of a key intermediate in the synthesis of endothelin receptor antagonist S-1255 (Scheme 14).[67] When racemic acid **17** was heated with (+)-cinchonine (1.0 equiv) in a 1:1 mixture of methanol and 2-propanol at 70 °C for 20 h and then at 45 °C for 5 h, the desired salt could be isolated in 99% de purity and 83% yield. The authors present some data which seem to indicate that the equilibration in this process occurs via the resonance-stabilized structures **18** and **19**.

Scheme 13

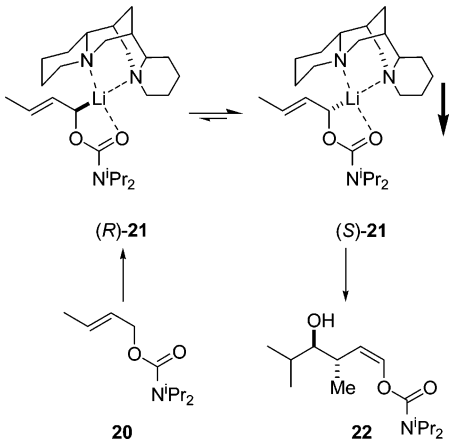


Scheme 14



A very modern CIDT was discovered by Hoppe et al. as part of their exploration of the use of lithiated *O*-2-alkenyl carbamates in asymmetric synthesis (Scheme 15).[68] These workers discovered that addition of a solution of carbamate **20** in pentane to *n*-BuLi/hexane (1.25 equiv) and (−)-sparteine (1.1 equiv) in a mixture of pentane and cyclohexane below −70 °C resulted in the crystallization of diastereomerically pure (*S*)-**21**. This crystallization is complete after approximately 30 min under these conditions. The lithium sparteine complex (*S*)-**21** could not be isolated and characterized by X-ray crystallography unlike related compounds. However, through a series of elegant studies the Hoppe group characterized the structure of (*S*)-**21** and abundantly dem-

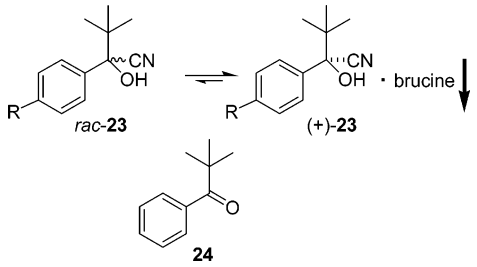
Scheme 15



onstrated its synthetic utility. For example, trans-metalation of (*S*)-**21**with titanium tetraisopropoxide followed by reaction with 2-methylpropanal provides **22** in 90% yield and enantiopurity.

Several examples of CIDT have been reported wherein the equilibration is based on other known facile bond-breaking/making processes. Toda et al. reported that, when solutions of several cyanohydrin derivatives *rac*-**23** (R = H, Cl, CH_3) and 1 equiv of brucine in methanol were left to evaporate slowly at room temperature over a period of 24 h, the corresponding enantiopure products (+)-**23** were obtained in near quantitative yield (Scheme 16).[69] It should

Scheme 16

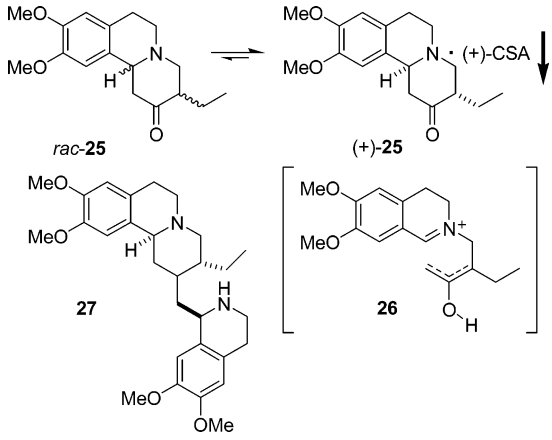


be noted that (+)-**23** is not a salt in the classical sense but an inclusion complex. This result nicely illustrates that CIDT using chiral inclusion complexes or clathrates should be contemplated when dealing with enantiomers that do not contain an ionizable functional group. The possibility that (+)-**23** was produced by an enantioselective addition of HCN to ketone **24** was discounted by bubbling HCN into a solution of **24** and brucine in MeOH. In this case *rac*-**23** was obtained in quantitative yield with no evidence of induction.

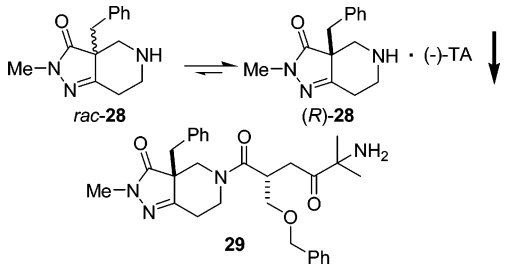
In a landmark publication, Openshaw and Whittaker reported on a spectacular CIDT as part of their total synthesis of natural emetine **27**.[70] When they heated racemic **25** with 1 equiv of (+)-CSA in ethyl acetate at reflux for 28 h, they obtained diastereomerically pure (+)-**25** salt in 81% yield (Scheme 17). In this process two stereogenic centers have equilibrated (!), most likely via acid-catalyzed formation of retro-Mannich-type intermediate **26** as the authors suggest. Similar examples were reported much later by other groups.[71,72]

A Pfizer group reported on a related CIDT in their approach to the growth hormone secretagogue **29** (Scheme 18). When racemic pyrazolopyridine derivative **28** was stirred overnight with (−)-tartaric acid ((−)-TA; 1.1 equiv) in a mixture of dichloromethane, acetone, and water at 38 °C the diastereomerically pure (*R*)-**28** was obtained in 88%

Scheme 17



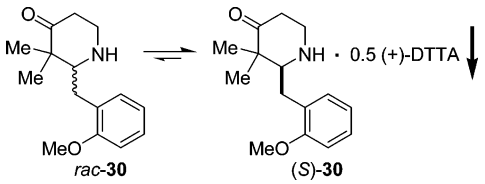
Scheme 18



yield.[73] The authors do not speculate on the mechanism of equilibration, but this is likely to occur via a retro-Mannich reaction as in the example above.

A Boehringer-Ingelheim group recently described a CIDT for the preparation of piperidone derivatives (Scheme 19).[74]

Scheme 19

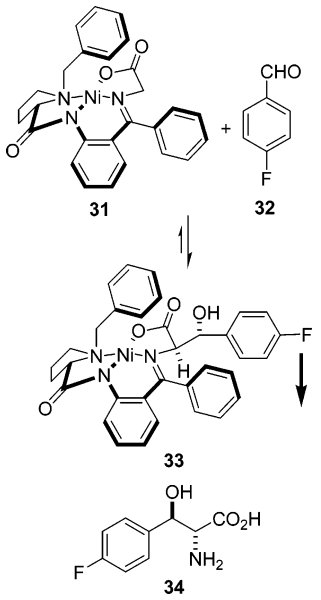


When the racemic piperidone derivative **30** is warmed with an equimolar amount of (+)-ditoluoyltartaric acid ((+)-DTTA) in acetonitrile at 55−60 °C for 24 h the diastereomerically pure hemi-tartrate salt (*S*)-**30** can be isolated in 85% yield. Once again, it is likely that in this case the equilibration occurs via a retro-Mannich/Mannich reaction sequence.

Aldol/retro-aldol reactions can also constitute the equilibration step in a CIDT. Soloshonok et al. reported on the reaction of enantiopure nickel complex **31** with an excess of 4-fluorobenzaldehyde **32** in a 1:1 mixture of methanol and triethylamine at room temperature for 18 days, which provided product **33** in 63% yield (Scheme 20).[75] Under homogeneous conditions **33** can be detected in only minute amounts. Conversion of **33** into the corresponding amino acid **34** can be achieved in 89% yield.

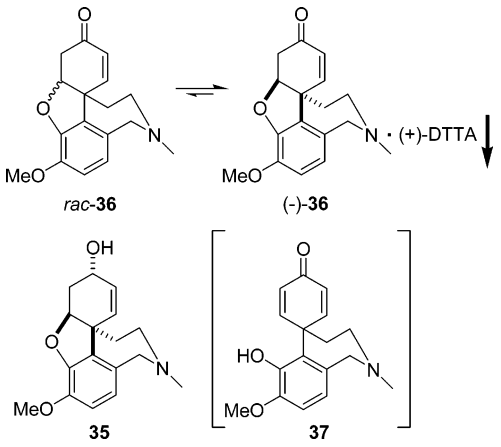
The natural product (−)-galanthamine (**35**) has received significant attention as a potential treatment for Alzheimer's disease. A variety of crystallization-induced processes have been used for the synthesis of (−)-narwedine **36**, which is a key late-stage intermediate on the way to **35**. While some of these processes are based on a CIET[76] and therefore not considered within the scope of this review, an interesting

Scheme 20



CIDT was reported by a group from the former Chiroscience corporation (Scheme 21).[77] These workers showed that when

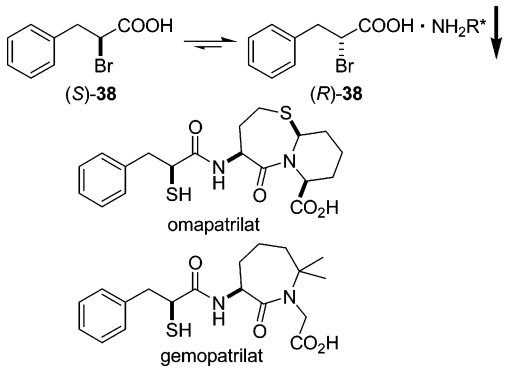
Scheme 21



racemic narwedine **36** was treated with either 0.5 or 1.0 equiv of (+)-DTTA in warm ethanol, the corresponding 2:1 and 1:1 salts are formed with good enantiopurity (98% and 97% ee, respectively) and yield (79% and 92%, respectively). The equilibration is likely to occur via acid-catalyzed formation of prochiral dienone **37** followed by conjugate addition.

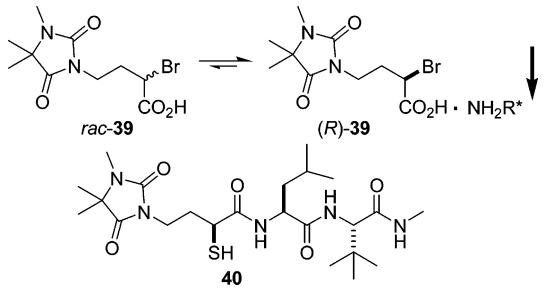
Two CIDT examples reported by Bristol-Myers Squibb groups use a degenerate nucleophilic substitution reaction in the equilibration step. In the first example an economical approach to (*R*)-**38**, which can be used in the synthesis of vasopeptidase inhibitors omapatrilat and gemopatrilat, is described.[78] Thus, when (*S*)-**38** was aged with 0.95−1.0 equiv of (*R*)-bornylamine (R*-NH_2 in Scheme 22) in acetonitrile at 50−60 °C in the presence of 0.1 equiv of tetraethylammonium bromide for 48 h, the (*R*)-**38** salt (96% de) was isolated in 76% yield. As the starting (*S*)-**38** is readily available from the inexpensive L-phenylalanine, this process provides for an economic inversion of stereochemistry at the α-stereocenter. The solubility difference between the diastereomeric salts is reported to be approximately 3-fold. The tetraalkylammonium salt functions as a soluble halide source to effect degenerate substitution reactions, as will be seen several more times in this review.

Scheme 22



In the second example another Bristol-Myers Squibb group required compound (*R*)-**39** for a synthesis of the dipeptide analogue **40**. In a detailed description of a thorough CIDT development effort,[79] the authors report that under carefully optimized conditions *rac*-**39** was heated for 24 h with 1.0 equiv of (1*R*,2*S*)-2-amino-1,2-diphenylethanol and 2.5 mol % of tetrabutylammonium bromide as the inversion catalyst in a 1:1 mixture of isopropyl acetate and MTBE at 55−60 °C to afford the (*R*)-**39** salt (88% de) in 90% yield (Scheme 23).

Scheme 23

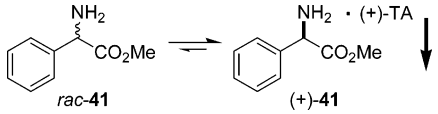


4.2. Amino Acids and Related Compounds

Amino acids are not only the building blocks of life but are also often critical components of pharmaceutical and other important manmade products. It is therefore not surprising that in recent decades CIDT can be frequently encountered as a practical method to prepare amino acids and related compounds, often on very large scale.

A variety of methods have been reported for the preparation of enantiopure phenylglycine and its derivatives using a CIDT in the key step. A landmark example was reported by a Glaxo group which undertook a systematic study of the resolution of (substituted) phenylglycine esters with (+)-tartaric acid.[80] A key finding by this group, which was later emulated by many others, was that addition of a variety of carbonyl additives facilitated equilibration by forming an imine intermediate which enhances the acidity of the proton attached to the α-amino acid carbon.[81,82] Thus, enantiopure methyl (+)-phenylglycinate could be isolated in 85% yield by adding 1 equiv of benzaldehyde to a mixture of racemic methyl phenylglycinate and (+)-TA in ethanol at 70 °C (Scheme 24).[83] Other, less configurationally labile

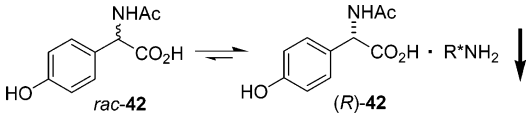
Scheme 24



amino acids were also investigated but with less useful results. For example, racemic methyl methioninate could be converted to the (+)-tartrate salt in 82% yield in the presence of anisaldehyde, but the reaction took 28 days to proceed to completion at 20 °C. The phenylglycinate result was later reproduced by Lopata et al., who found that a successful CIDT could also be achieved using only a catalytic amount of cyclohexanone at room temperature.[84] Grigg explored the mechanism of the racemization of α-amino acids in the presence of aldehydes in some detail.[85] Several patents have been awarded to DSM for production of enantiopure phenylglycine amide via a CIDT. The diastereomerically pure (+)-phenylglycine amide can be obtained with either 2-pyrrolidone-5-carboxylic acid or (−)-*N*-acetyl phenylglycine from hot acetone containing a small amount of water in 86% and 90% yield, respectively.[86] Alternatively, this compound can also be obtained using (*S*)-mandelic acid (MA) and benzaldehyde in 97% yield with >99% de.[87]

Enantiopure phenylglycine can also be accessed without using an equilibration catalyst.[88] Racemic α-amino-α-phenylacetonitrile is sufficiently labile in acetic acid at room temperature that a resolution with (+)-TA can provide the corresponding (+)-hemitartrate salt in 83% yield. The nitrile can be hydrolyzed to phenylglycine without loss of enantiopurity. A CIDT can also be accomplished directly on phenylglycine itself, albeit under much more drastic conditions. Heating the racemic amino acid with 1 equiv of (+)-CSA in propionic acid at 100 °C provides the enantiopure amino acid in 82% yield after breaking the salt.[20]

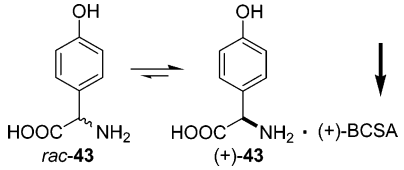
Scheme 25



p-Hydroxyphenylglycine **43** has attracted special attention from various groups, due to its utility as a side chain in semisynthetic penicillins and cephalosporins such as amoxicillin, cefadroxil, cefatrizine, cefaparole, and cefoperazon. In a systematic study Shiraiwa and co-workers[89] found that the rate of racemization of *N*-acetyl-amino acids increases proportionally with Taft's polar substituent constant (σ^*) of the amino acid side chain and also with increasing amounts of the (*R*)-α-methylbenzylamine (R*NH_2) resolving agent. On this basis they developed a CIDT in which racemic *N*-acetyl-4-hydroxyphenylglycine **42** is converted in 95% yield to the (*R*,*R*)-salt (90−93% de) via heating with at least a 5-fold excess of the amine in a 5:1 mixture of cumene and 1-hexanol at reflux (150 °C) for 3 h (Scheme 25). Enantiopure *N*-acetyl- and *N*-benzoyl-phenylglycine could be obtained in a similar process.[90,91]

Another notable example was reported by a Hoechst group (Scheme 26).[92] Heating of racemic *p*-hydroxyphenylglycine

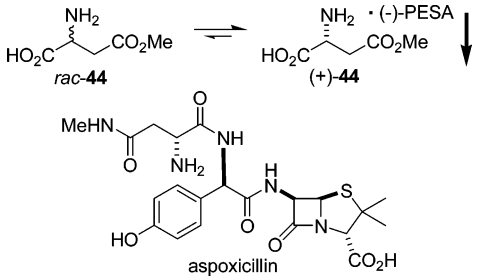
Scheme 26



43 with (+)-3-bromocamphor-8-sulfonic acid ((+)-BCSA) in the presence of 10 mol % of salicylaldehyde in acetic acid at 70 °C furnished the (+)-**43** salt (98% de) in 99% yield. Critically, even trace amounts of water were detrimental to this process, and a small amount of acetic anhydride (1 mol %) was added to trap any residual water. As (+)-BCSA is only commercially available as the corresponding ammonium salt, addition of 1 equiv of HCl (dissolved in HOAc) was also required to operate this process. A similar process using ketones as the equilibration catalysts was reported by a Beecham chemist in the patent literature.[93]

Examples of successful CIDT for amino acids which do not contain an α-aryl side chain are less abundant as their chiral center is invariably significantly more configurationally stable. Yoshioka et al. reported a process for preparation of the β-methyl ester of (+)-aspartic acid (**44**), which is an important component of the semisynthetic penicillin aspoxicillin (Scheme 27).[94] The unusual chiral acid (−)-

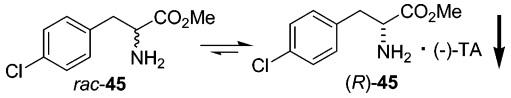
Scheme 27



phenylethanesulfonic acid (PESA) proved to be the best auxiliary. Interestingly, this acid was also successfully used in a CIDT of 4-hydroxyphenylglycine **43**,[95−97] which is another key component of aspoxicillin. Thus, heating of 1.05 equiv of *rac*-**44** with 1.0 equiv of (−)-PESA in acetonitrile (or 1,4-dioxane) at 80 °C for 6 h in the presence of salicylaldehyde (0.1 equiv) produced the (+)-**44** salt (96% de) in 92% yield. The slight excess of the aspartic acid component, the presence of salicylaldehyde, and the temperature (interestingly, the solubility difference between the two diastereomeric salts was reported to increase significantly with increasing temperature) are all critical to the success of this CIDT as they facilitate the equilibration.

A Johnson and Johnson group reported a CIDT to prepare methyl (*R*)-4-chlorophenylalaninate **45** (Scheme 28).[98] Thus,

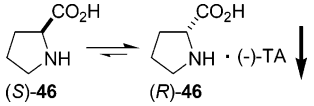
Scheme 28



rac-**45** was heated with (−)-TA (0.5 equiv) and salicylaldehyde (0.1 equiv) in refluxing methanol to yield the (*R*)-(−)-tartrate salt (98% de) in 68% yield.

The Shiraiwa group described a number of similar CIDT for a variety of amino acids. Scheme 29 provides a method

Scheme 29

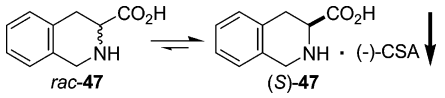


to access (*R*)-proline from the less expensive (*S*)-enantiomer.[99,100] Thus, when an equimolar mixture of (*S*)-**46** and (−)-TA was heated in butanoic acid at 80 °C for 3−4 h in

the presence of 10 mol % of butanal, the 93% de pure (*R*)-(−)-salt was obtained in 97% yield. Development of a similar process for the preparation of (*S*)-pipecolic acid has also attracted significant attention because this compound is an intermediate in the synthesis of the local anesthetic levobupivacaine.[101,102]

The Shiraiwa group also reported on the preparation of 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid, a useful intermediate in the synthesis of antihypertensive agents (Scheme 30).[103] Heating of the racemic amino acid **47** with

Scheme 30

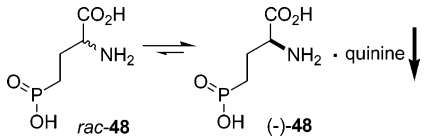


(−)-CSA in hexanoic acid at 120 °C provided the (*S*,*S*)-salt (90% de) in 86% yield. Hexanoic acid is preferred over lower carboxylic acids due to the lower solubility of the (*S*,*S*)-salt at the high temperature required to achieve equilibration.

The same group described a number of similar CIDT for histidine,[104] 4-thiazolidinecarboxylic acid,[105] and 2,2-dimethyl-4-thiazolidinecarboxylic acid[106] (the latter two are precursors to cysteine) as well as for 1,3-thiazane-3-carboxylic acid[107] (a precursor to homocysteine) and 1,4-thiazane-3-carboxylic acid[108] (a precursor to the natural product chondrine). In each case the amino acid is heated with a tartaric acid in the presence of salicylaldehyde in a carboxylic acid solvent at an elevated temperature and the diastereomerically pure salt is obtained in high yield and purity.

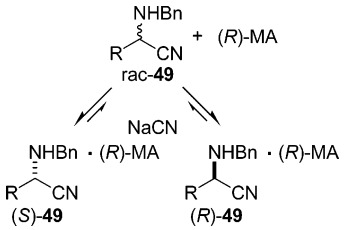
A group from Hoechst reported on a process to prepare (−)-homolalanine-4-yl-(methyl)phosphinic acid (**48**).[109] The ammonium salt of this compound is a herbicide. When *rac*-**48** and quinine (1.0 equiv) are warmed in a mixture of water and *tert*-butyl alcohol at 50 °C for 9−10 h in the presence of 1 mol % of 3,5-dinitrosalicylaldehyde, the (−)-**48** quinine salt (>99% de) can be obtained in 85% yield (Scheme 31).

Scheme 31



Amino nitriles can be readily prepared from aldehydes via a Strecker synthesis and hydrolyzed to amino acids. Jochims et al. performed a study on the correlation between the structure of a series of aryl and alkyl amino nitriles and their propensity to undergo CIDT (Scheme 32).[16] Thus, 1:1

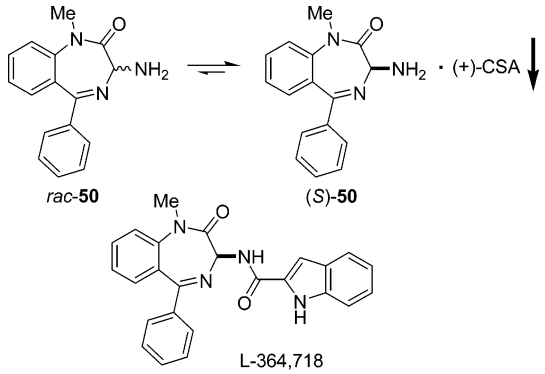
Scheme 32



mixtures of benzylamino nitriles **49** and (*R*)-mandelic acid were stirred in ethanol at 23 °C. It was noted that most aryl benzylamino nitriles produced a CIDT within hours. For example, with R = Ph, the (*S*,*R*)-salt (>99% de) was obtained in 90% yield after 12 h. Most alkyl benzylamino nitriles required a much longer time for complete conversion, presumably due to a slower equilibration. Interestingly, in these cases the (*R*,*R*)-salts were produced instead. A CIDT did not occur in all cases examined. For example, with R = *tert*-Bu the diastereomeric salts did not appear to be formed. For R = 4-ClPh solids were produced but there was no selectivity, and the authors speculate that a solid solution was produced. The analogous process using (−)-CSA instead of (*R*)-MA did not result in CIDT either, possibly because equilibration does not occur with this stronger acid.

The 3-aminobenzodiazepinone and related structures are part of many pharmaceutically interesting compounds, and it is therefore not surprising that CIDT has been successfully used as the key step in the development of practical syntheses for these compounds. An often-cited early example was developed by a Merck group (Scheme 33).[110] Under excep-

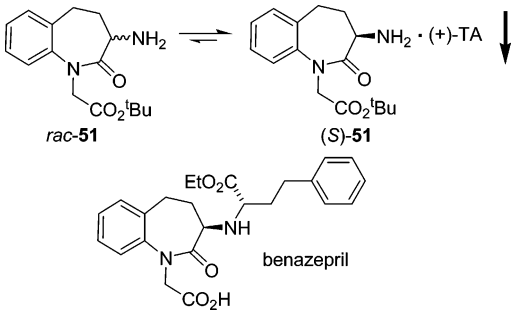
Scheme 33



tionally mild conditions (stirring with 0.92 equiv of (+)-CSA in the presence of 3 mol % of 3,5-dichlorosalicylaldehyde in a mixture of isopropyl acetate and acetonitrile at room temperature) racemic **50** was converted to the (*S*)-(+) salt (>99% de) in 91% yield. The slight excess of the amine and optimization of the aldehyde equilibration promoter are key to the success of this CIDT. Compound (*S*)-**50** was used to prepare the potent CCK antagonist L-364,718.

A Ciba Geigy group reported a CIDT in the closely related aminoazepinone structural series (Scheme 34).[111] Heating

Scheme 34

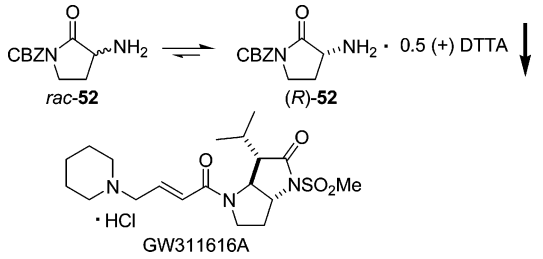


racemic **51** with (+)-tartaric acid (1.0 equiv) and benzaldehyde (0.2 equiv) in ethanol at 65 °C for 14 h resulted in production of diastereomerically pure 1:1 salt with (*S*)-**51**. The latter is a key component in the synthesis of ACE inhibitor benazepril. Several related examples in both structural series were later reported by groups from Merck[112,113] and Bristol-Myers Squibb.[114]

The above-cited work in the benzodiazepinone series inspired a GlaxoSmithKline group in developing a CIDT for α-aminolactam **52**, which is useful in the synthesis of

selective serine protease inhibitor GW311616A (Scheme 35).[115,116] Diastereomeric salts with a large number of chiral

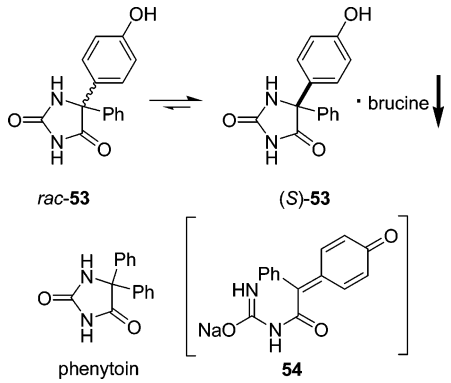
Scheme 35



acids were prepared and rapidly screened on the basis of their melting points. A large difference in melting point between diastereomeric salts is indicative of a useful solubility difference. Thus, (+)-ditoluoyltartaric acid (0.5 equiv) was identified as the optimal resolving aid. After *rac*-**52** was stirred with this acid and 4 mol % of 3,5-dichlorosalicylaldehyde in wet ethyl acetate at 66 °C for 3.5 h, the diastereomerically pure (*R*)-**52** (+)-DTTA salt could be isolated in high yield. A very similar CIDT was also reported by a Monsanto group.[117]

Vogel et al. recently reported a CIDT to prepare the metabolite (−)-**53** of the anticonvulsant phenytoin.[118] In this case the equilibrating center is quaternary and equilibration cannot occur via proton transfer as in the previous examples. The group capitalized on the known classical resolution of **53** with brucine and postulated that when this crystallization is carried out in the presence of a base a CIDT could be achieved. Indeed, when *rac*-**53** was treated with an equal amount of brucine in a minimum amount of boiling methanol in the presence of 10 mol % of NaOH, the diastereomerically pure brucine complex (*S*)-**53** could be isolated in 59% yield (Scheme 36). It is postulated that the epimerization of the

Scheme 36

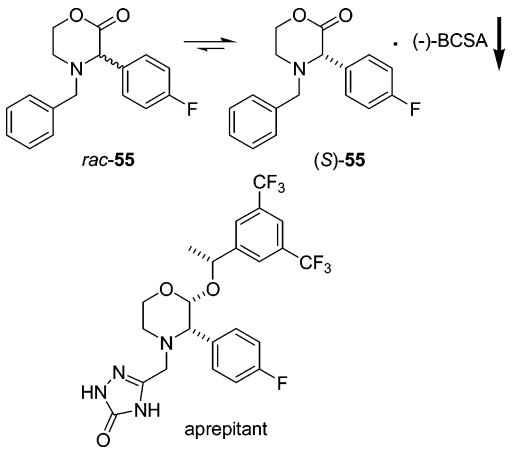


quaternary center occurs via **54** after deprotonation of the phenol.

Process chemists from Merck reported on a CIDT related to their extensive work on approaches to aprepitant, the active ingredient in Emend, which was recently approved for treatment of chemotherapy-induced nausea and vomiting. When racemic oxazinone **55** is heated with a slight excess of (−)-BCSA in isopropyl acetate at 89 °C for 48 h, the diastereomerically pure salt (*S*)-**55** can be isolated in 90% yield (Scheme 37).[119] This process has been successfully operated on >100 kg scale.

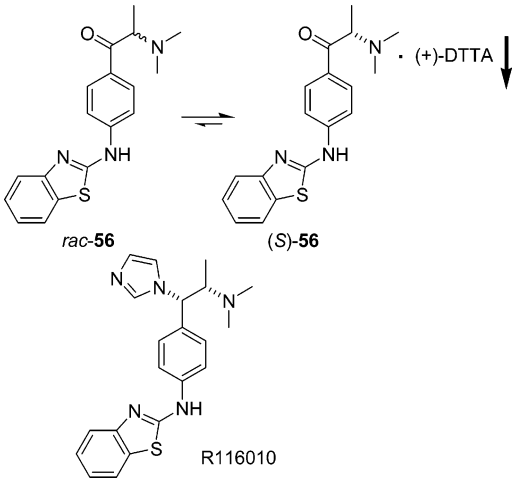
A group from Janssen Pharmaceutica reported that heating *rac*-**56** with a slight excess of (+)-ditoluoyltartaric acid in a

Scheme 37



mixture of ethyl acetate and methanol at 50 °C for 7 h yielded the diastereomerically enriched salt with (*S*)-**56** in 92% yield (Scheme 38).[120] It would appear that further optimization of

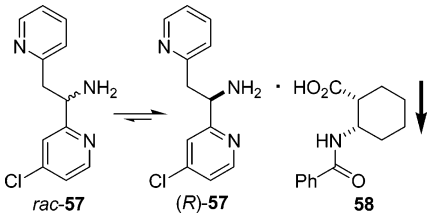
Scheme 38



the conditions could improve the relatively low diastereomeric purity of isolated (*S*)-**56** (80% de). Compound (*S*)-**56** can be used in the preparation of the selective all-trans-retinoic acid metabolism inhibitor R116010. Hu et al. reported on a CIDT of another aminoketone derivative as a practical approach to the broad-spectrum antibiotic chloramphenicol.[121]

Even though pyridylamine **57** is strictly speaking not an amino acid derivative, the conditions chosen for the CIDT involving this compound borrow significantly from the amino acid examples reported above.[122] A group from Eisai Co. stirred racemic **57** and enantiopure **58** (0.9 equiv) in DMF at room temperature for 2 days in the presence of 5 mol % of 3,5-dichlorosalicylaldehyde (Scheme 39) and obtained the

Scheme 39



diastereomerically pure product in significantly higher yield

(42% after several recrystallizations) than in an ordinary resolution with the same acid. Presumably, once again, formation of an imine intermediate further facilitates the equilibration at a position which is already partly activated by the neighboring pyridine.

5. Covalent Diastereomers

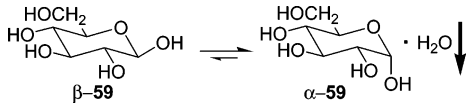
This section deals with examples of CIDT in which the equilibrating and nonequilibrating moieties of the molecule are linked through covalent bonds. The equilibrating center can be either carbon or heteroatom-based.

5.1. Carbon-Based Equilibrating Centers

The molecules in the largest subsection of this review contain a carbon-based equilibrating center which is covalently linked to the directing center. The equilibration can take place via a variety of mechanisms, including epimerization at a carbon which is activated for carbocation or anion formation by a neighboring group, rotation around hindered single bonds or *E/Z* isomerization of double bonds, reversible (conjugate) additions (including Diels−Alder cycloadditions), degenerate substitution reactions, and group transfer reactions.

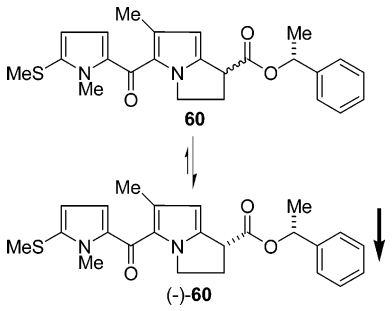
A study on the crystallization and optical rotation properties of sugars by Dubrunfaut in 1846 is often quoted as the first recorded observation of a CIDT.[123] Even though this early report does not contain structural details or a mechanistic hypothesis to explain the observations, Dubrunfaut describes in some detail the mutarotation of the isolated solids. He recognized that he isolated only a single isomer from a mixture of equilibrating isomers in solution and that this mixture could be reconstituted by dissolving the crystalline material. Since this time it has been clearly established that Dubrunfaut crystallized the less soluble α-D-glucose hydrate **59** from the mixture of anomers (Scheme 40).[124]

Scheme 40



In a large number of CIDT the equilibration occurs via epimerization of a relatively acidic carbon hydrogen bond. Hagmann from Merck reported an early example involving phenethylester derivative **60** (Scheme 41).[125] Treatment of

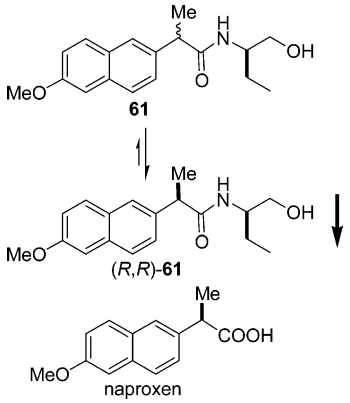
Scheme 41



a hot solution of the diastereomer mixture **60** in 25% ethyl acetate in hexanes with 10 mol % of DBN followed by cooling to room temperature gave (−)-**60** in 88% yield after a recrystallization.

In an effort to define an economical approach to the nonsteroidal antiinflammatory drug naproxen, a group from Alfa Chemicals Italiana developed a CIDT for **61**.[126] When **61** was warmed with sodium methoxide (1.1 equiv) in toluene, the diastereomerically pure (*R*,*R*)-**61** was obtained in 94% yield (Scheme 42). The product can be hydrolyzed to

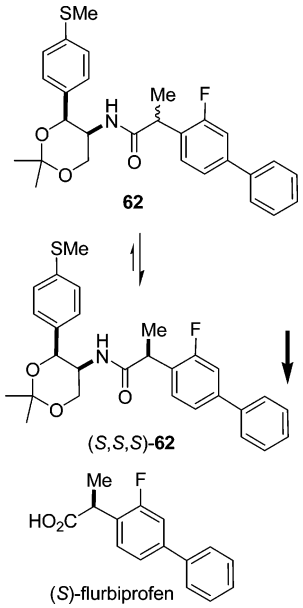
Scheme 42



naproxen in high yield and without loss of optical purity. A similar procedure used (*S*)-*tert*-butyl-2-oxazolidinone as the auxiliary, DBU as the base, and DMF as the solvent.[127]

A Zambon group found that this chemistry required a different auxiliary in the case of the related analgesic flurbiprofen.[128] When a mixture of diastereomers **62** was treated in 2-propanol with 30% sodium methoxide in methanol solution (1 equiv) and heated at 55 °C for 3 h, the diastereomerically pure (*S*,*S*,*S*)-**62** was obtained in 76% yield (Scheme 43). Compound (*S*,*S*,*S*)-**62** can be hydrolyzed to

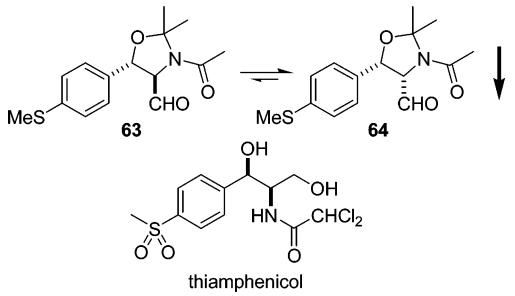
Scheme 43



(*S*)-flurbiprofen without any loss in enantiopurity.

The above amino−diol auxiliary is readily available to Zambon as it is a key intermediate in their manufacturing synthesis of the broad-spectrum antibiotic thiamphenicol. This process is based on a classical resolution. To recycle the undesired enantiomer in this process, Zambon developed a CIDT (Scheme 44).[129] Thus, neat trans isomer (*S*,*R*)-**63** is heated with 7 mol % of DABCO at 40 °C to generate a seedbed. After an age for 2 h at 35 °C the mixture is worked

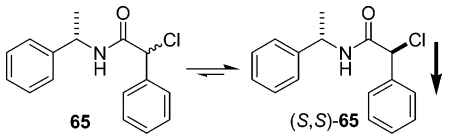
Scheme 44



up and cis isomer (*S*,*S*)-**64** is eventually obtained in 76% overall yield.

Park et al. studied the CIDT of benzylic α-halo-acetamides (Scheme 45) and found that treatment of a solution of

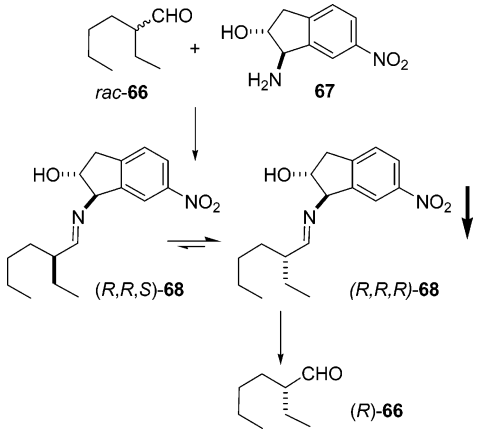
Scheme 45



diastereomeric mixture **65** in methanol at room temperature, with ammonia added on each day for 7 days, yielded (*S*,*S*)-**65** (94% de) in 95% yield.[130] The process worked in a variety of other water-miscible solvents and, to a lesser extent, also when benzethonium chloride rather than a base was used to induce the equilibration.

Košmrlj and Weigel reported on an ingenious and fairly general method to access nonracemic aldehydes and ketones using a CIDT of the corresponding imines (Scheme 46).[131]

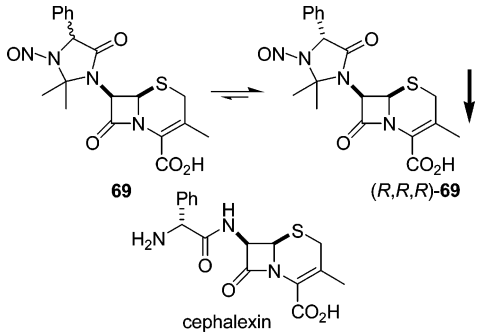
Scheme 46



For example, when *rac*-**66** was treated with 0.95 equiv of enantiopure amino-alcohol **67** in THF a 3:1 mixture of diastereomers **68** was obtained. Switching the solvent to methanol followed by slow evaporation afforded solid (*R*,*R*,*R*)-**68** (98% de) in near quantitative yield. Upon hydrolysis of the latter under carefully controlled conditions the aldehyde (*R*)-**66** (98% ee) was produced in 94% yield.

A Glaxo group described the use of a CIDT in the conversion of penicillin-G into cephalexin (Scheme 47).[132] When the diastereomeric mixture of **69** in dioxane containing 2.5 equiv of pyridine was stirred at room temperature for 14 days, the diastereomerically pure (*R*,*R*,*R*)-**69** was obtained as a solid (solvated with one molecule each of dioxane, pyridine, and water) in two crops with 75% overall yield.

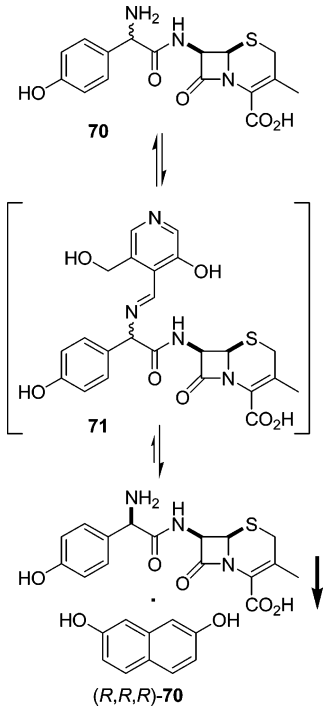
Scheme 47



The equilibrium ratio of the diastereomers was determined to be 55:45 by ^{1}H NMR in pyridine-d_5.

Zwanenburg et al. were able to epimerize the α-amino acid carbon of the cefadroxil side chain using a CIDT under exceptionally mild conditions (Scheme 48).[133] Stirring of **70**

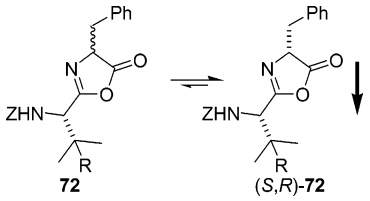
Scheme 48



in the presence of 10 mol % of pyridoxal in water at a pH between 7 and 7.5 at room temperature was shown to lead to facile epimerization, presumably via the Schiff base intermediate **71** (vide supra). To drive this equilibrium in the desired direction, 2,7-dihydroxynaphthalene (1.1 equiv) was added to the solution as this compound is known to selectively form a clathrate with cefadroxil. The crystalline 2,7-dihydroxynaphthalene complex with (*R*,*R*,*R*)-**70** could thus be isolated in 86% yield.

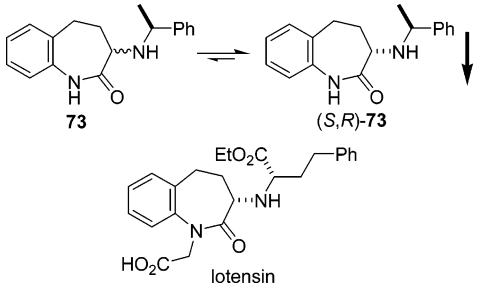
Turner et al. reported on the CIDT of oxazolone derivatives (Scheme 49).[134] When compound **72** (R = H; 12% de) was heated in a refluxing 100:1 mixture of petroleum ether (40−60) and dichloromethane for 5 min, the diastereomerically pure (*S*,*R*)-**72** could be isolated in 73% yield. The analogous process with **72** (R = Me) also worked. Acids or bases were not needed in this process due to the relatively high acidity of the proton at C-4. A similar finding was made for an α-phenylthiolactone derivative.[135]

Scheme 49



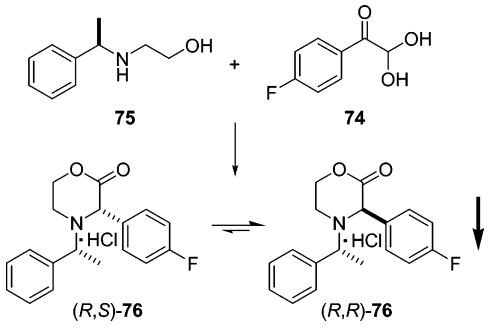
Scheme 50 shows an example of a CIDT in an aminoazepinone derivative which can be used in the synthesis of the ACE inhibitor lotensin.[136] A Novartis group heated phenethylamine derivative **73** at 140 °C in mineral spirits for 16 h and obtained diastereomer (*S*,*R*)-**73** (>98% de) in 88% yield. This process was successfully operated on a multikilogram scale.

Scheme 50



In a wide-ranging effort to define a manufacturing process for the NK-1 receptor antagonist aprepitant, a number of Merck groups reported on a variety of CIDT. In the example of Scheme 51 the mixture of oxazinones **76**, obtained by

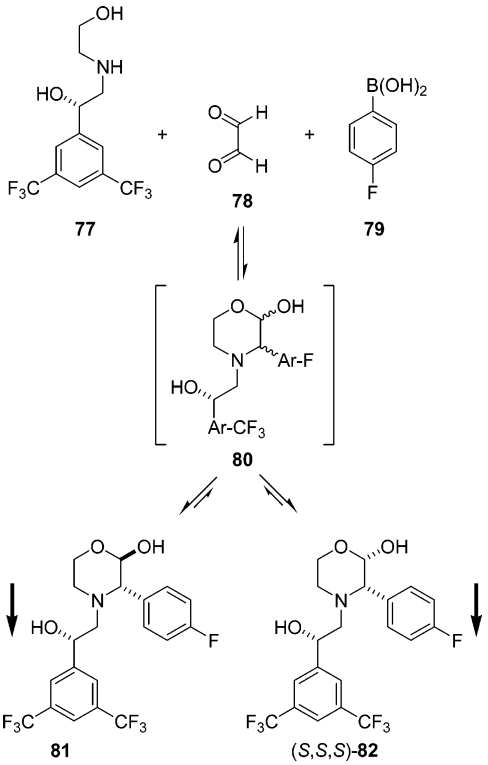
Scheme 51



condensing glyoxal derivative **74** with amino-alcohol **75**, was heated in a mixture of isopropyl acetate and acetic acid at 70−75 °C in the presence of excess dry HCl. The resulting CIDT afforded the hydrochloride salt (*R*,*R*)-**76** (>98% de) in 90% overall yield.[137]

In a conceptually very different approach,[138] a mixture of amino-alcohol **77**, glyoxal **78** (2 equiv), and 4-fluorophenylboronic acid **79** (1.25 equiv) was heated in *tert*-amyl alcohol at 40 °C to yield a complex mixture of five (!) diastereomeric components **80** (Scheme 52). Crystallization from a mixture of methylcyclohexane and ethyl acetate at 45 °C yielded lactol **81** in 65% yield when the starting **77** was racemic. However, when the identical sequence was performed with enantiopure **77**, the isomeric lactol (*S*,*S*,*S*)-**82** was obtained in 86% yield! The authors report that this component was only present to the extent of 2% in the solution equilibrium. This example shows in a dramatic way how the differing crystal properties of racemates and

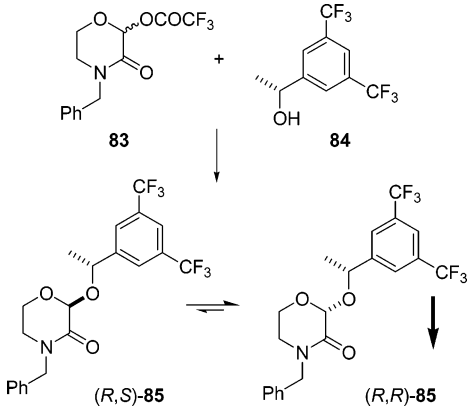
Scheme 52



enantiopure compounds can impact the outcome of a CIDT. It should be noted that the equilibration in **80** takes place at two neighboring carbon atoms, presumably via a ring-open aldehyde intermediate which was not detected.

In the final example of Merck's work on aprepitant, the equilibration takes place at a relatively nonacidic position, therefore requiring strongly basic conditions. To operate this CIDT successfully a number of significant hurdles had to be overcome (Scheme 53).[139] Under highly optimized condi-

Scheme 53

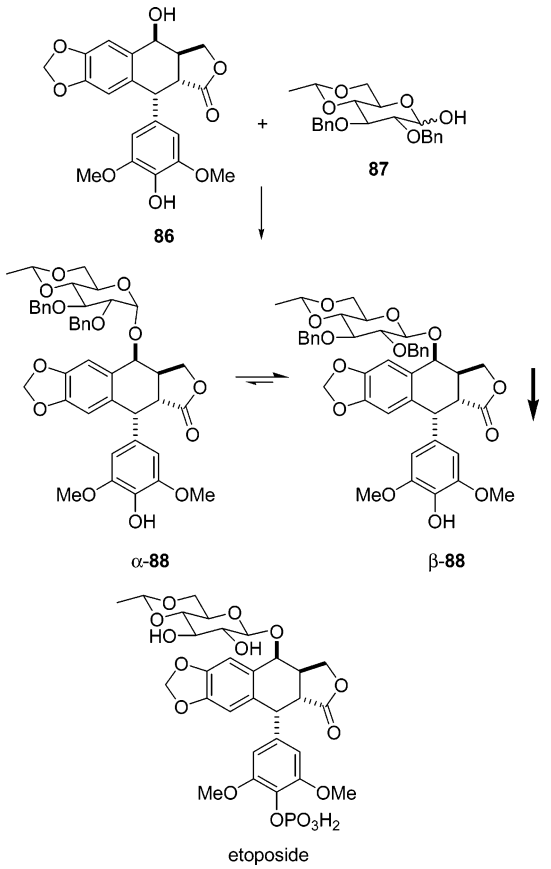


tions a 55:45 solution of diastereomers **85** (as prepared from **83** and phenethyl alcohol **84**) in heptane containing 3,7-dimethyl-3-octanol (1 equiv) was treated with the corresponding potassium alkoxide (0.3 equiv) to afford (*R*,*R*)-**85** (>99% de) in 85% yield after 6 h. Several important parameters were well characterized for this process. The equilibrium ratio of (*R*,*R*)-**85** and (*R*,*S*)-**85** under the process conditions was determined at 75:25. The (*R*,*R*)-**85** diastereomer is less soluble in the reaction medium (25 vs 51 mg/mL)[140] and shows a higher melting point (92 vs 43 °C) and melting enthalpy (64.3 vs 47.7 J/g) than (*R*,*S*)-**85**.

This CIDT forms the basis of the manufacturing process for aprepitant and is carried out on a scale of hundreds of kilograms per batch.

In a number of CIDT the equilibration occurs via relatively readily formed iminium, oxonium, or other stabilized carbocation intermediates. A Bristol-Myers Squibb group used a CIDT to effect a stereoselective glycosidation. These workers reported that treatment of **86** with a mixture of anomers **87** in the presence of boron trifluoride etherate (1.5 equiv) in acetonitrile at −10 °C yielded the β-anomer **88** selectively in 78% yield (Scheme 54).[141] The product is

Scheme 54

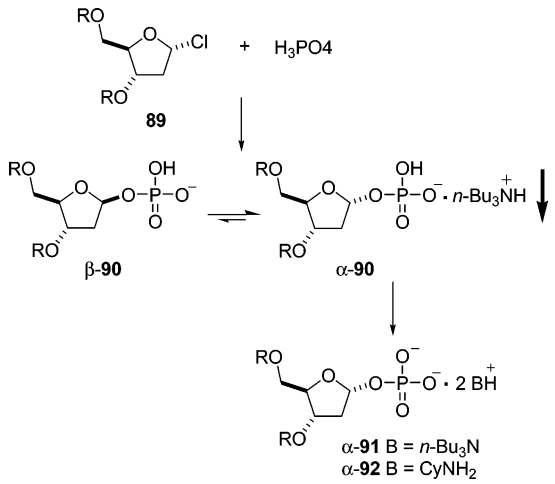


useful in the synthesis of the anticancer drug etoposide. A related procedure was reported for a derivative in which the phenol was protected.[142]

In a related CIDT a challenging phosphorylation is achieved by a Mitsui Chemicals group for the synthesis of a useful intermediate for the enzymatic preparation of 2′-deoxynucleosides.[143] Reaction of chlorosugar **89** with orthophosphoric acid (3.5 equiv) and tributylamine (1.1 equiv) in acetonitrile at room temperature in the presence of molecular sieves provides the solid mono(tributylamine) salt with α-**90** with 97% de purity (Scheme 55). The reaction is neutralized with additional tributylamine (3.5 equiv) to form the soluble bis(tributylamine) salt α-**91**. The sieves can then be filtered and, after solvent switching to 4-methyl-2-pentanone and adding cyclohexylamine (2.5 equiv), the corresponding bis(cyclohexylamine) salt α-**92** (97% de) is isolated in 99% yield. This process is successfully used for the ton-scale manufacture of 2′-deoxynucleosides.

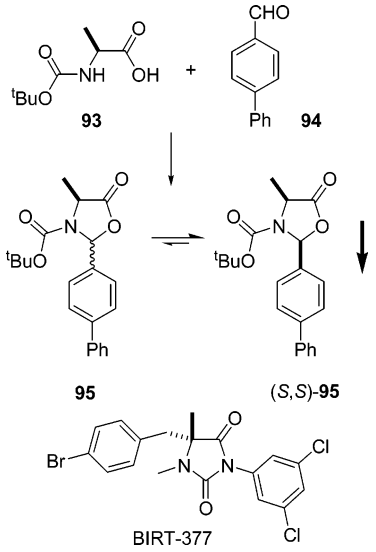
A group from Boehringer Ingelheim reported on two complementary CIDT methods to prepare an intermediate in the synthesis of antiinflammatory target BIRT-377 (Scheme

Scheme 55



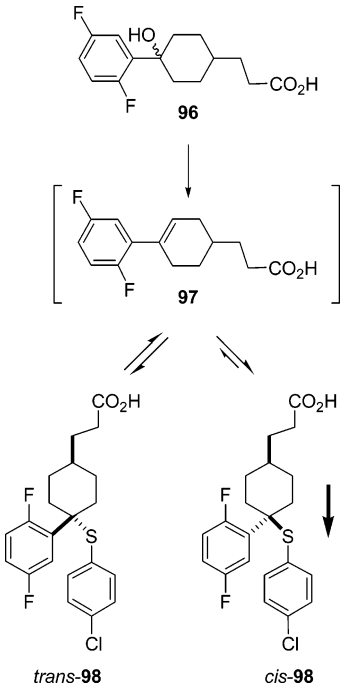
56).[144] Condensation of **93** with 4-phenylbenzaldehyde **94** in the presence of 5 mol % of *p*-toluenesulfonic acid in cyclohexane with continuous removal of water for 18 h followed by another 8 h age at the reflux temperature allowed the isolation of oxazolidinone (*S*,*S*)-**95** (>99% de) in 91% yield. Alternatively, the acid chloride corresponding to **93** was prepared with oxalyl chloride and DMF in dichloromethane. The latter was then treated with **94** and 7 mol % of $ZnCl_2$ and, after partial evaporation and addition of MTBE, (*S*,*S*)-**95** could be isolated in 88% yield. Similar examples were reported for a related imidazolidinone[145] and a tetrakis-(benzoxazine).[146]

Scheme 56



A Merck group described the use of a CIDT to selectively prepare a 1,4-substituted cyclohexane derivative which can be used in the synthesis of a γ-secretase inhibitor (Scheme 57).[147] This example is particularly noteworthy as neither the starting material nor the product are chiral. Thus, when carbinol diastereomers **96** and 4-chlorothiophenol were warmed overnight in methanesulfonic acid containing 11 vol % of water in methanesulfonic acid at 40 °C, **98** (94:6 cis/trans) was obtained in 85% yield. A simple recrystallization from acetonitrile afforded diastereomerically pure product (>99% de). It was shown that the ratio of the carbinols was irrelevant as they are rapidly converted into olefin **97** in the strongly acidic medium. The acid-catalyzed addition of the

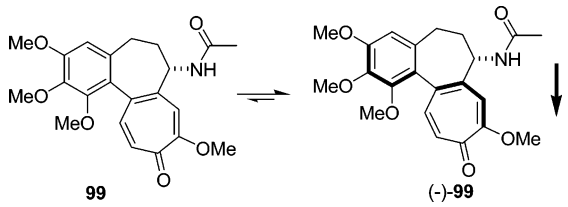
Scheme 57



thiol to **97** was shown to be reversible under the chosen conditions, thus allowing the selective transformation of the starting materials to the desired product *cis*-**98**. The solubilities of *cis*- and *trans*-**98** were measured in more than 50 solvents and solvent combinations and their ratio varied between 1.1 and 1.7.[148] This difference was also reflected by their melting points (147 and 127 °C, respectively). A high-throughput screen did not produce any other polymorphs for either compound. Interestingly, the 1:1 mixture of sulfides also showed a sharp melting point (110 °C).

Just as was noted in the diastereomeric salt section, CIDT can also be used for the selective conversion of atropisomers containing covalent directing centers. Rapoport et al. studied the mutarotation of isocolchicine **99** and determined that this phenomenon is most likely caused by the hindered rotation around the biaryl axis.[149] Thus, a CIDT of **99**, induced by heating in ethyl acetate, yielded diastereomerically pure (−)-**99**, which upon dissolution reverts back to the mixture of diastereomers (Scheme 58).

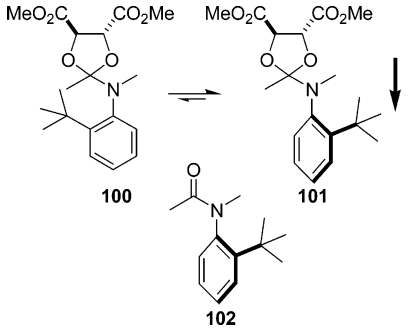
Scheme 58



Curran et al. used a CIDT to prepare diastereomerically enriched **101**, a precursor to enantioenriched axially chiral **102** (Scheme 59).[150] When a 1.1:1 mixture of **100** and **101** was recrystallized from hot hexane, two crops of solids were obtained in 95% combined yield which contained **101** as a 20:1 mixture with **100**. The mother liquors contained both atropisomers in the starting 1.1:1 ratio. A similar observation was made by Herradon et al. in their studies of the properties of peptide−biphenyl hybrids.[151,152]

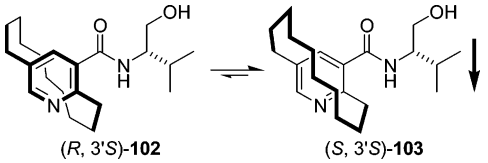
Kanomata et al. discovered in their study of molecular rope jumping of pyridinophanes that heating a neat 1:1

Scheme 59



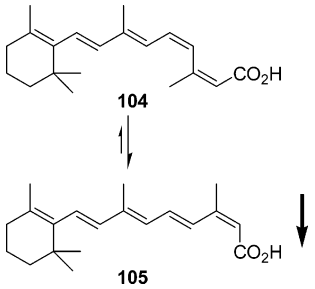
mixture of (*R*,3′*S*)-**102** and (*S*,3′*S*)-**103** at 110 °C for 3 days yielded (*S*,3′*S*)-**103** (96% de; Scheme 60).[153] The authors determined that (*S*,3′*S*)-**103** is a solid with a high melting point while its diastereomer (*R*,3′*S*)-**102** is an oil.

Scheme 60



The following two examples highlight relatively unusual cases of CIDT since in the equilibration step rotation occurs around a double bond of an achiral substrate. A pioneering case has been described by a Hoffman-La Roche chemist who used this transformation in the synthesis of *cis*-retinoic acid **105** (Scheme 61).[154] When a 12/82 mixture of 11-*cis*-

Scheme 61

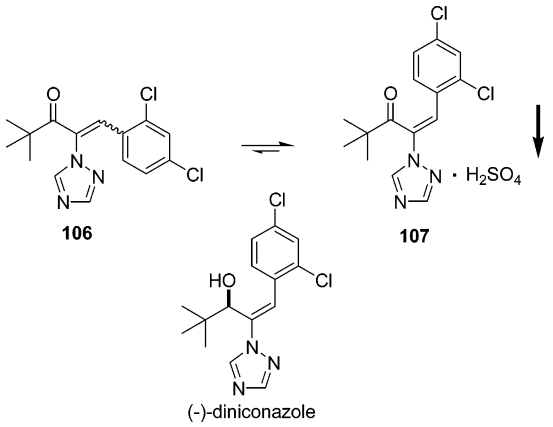


104 and 11-*trans*-**105** is heated in a mixture of THF and acetonitrile at 50 °C in the presence palladium nitrate (0.1 mol %), triethylamine (0.2 mol %), and triphenylphosphine (0.4 mol %), the 11-*trans* product **105** (92% de) was obtained in 97% yield.

A Sumitomo group used a CIDT to prepare **107**, which is a useful intermediate for the synthesis of antimicrobial (−)-diniconazole (Scheme 62).[155] The *E*/*Z* mixture **106** is readily available from a Knoevenagel condensation between 3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanone and 2,4,-dichlorobenzaldehyde. When this mixture is heated with anhydrous sulfuric acid (1.0 equiv) and 3 mol % of bromine in dry dichlorobenzene at 95 °C for 4 h the pure *E*-isomer **107** can be obtained as the hydrogen sulfate salt in 93% yield.

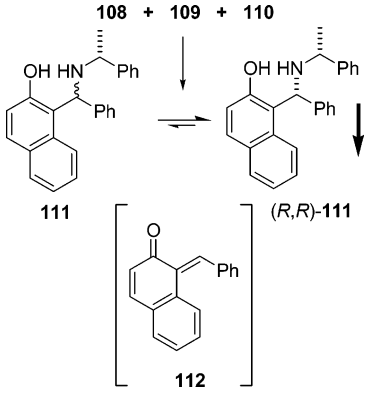
In the next series of examples the equilibration takes place via elimination−addition reactions. Palmieri et al. reported on a number of examples of CIDT as part of a study of the aminoalkylation of phenol[156] and 2-naphthol.[157] Thus, when a mixture of 2-naphthol (**108**), benzaldehyde (**109**;1.2 equiv), and (*R*)-1-phenethylamine (**110**; 1.05 equiv) was heated at 60 °C for 8 h, (*R*,*R*)-**111** crystallized with 98% de purity

Scheme 62



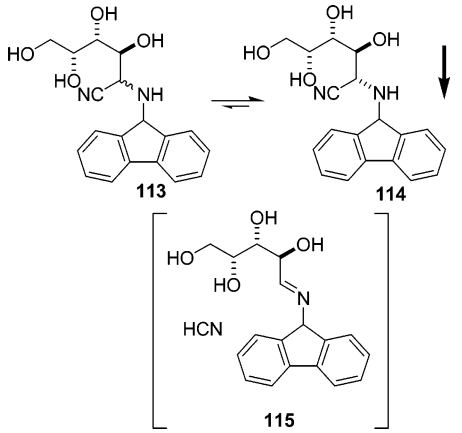
and 93% yield (Scheme 63). The authors speculate that the equilibrium occurs via enone **112**.

Scheme 63



Several CIDT have been reported for the synthesis of amino nitriles. These compounds can be readily prepared via Stecker-type reactions which are known to be reversible. Pioneering studies were carried out by Kuhn and Jochims in their preparation of amino sugars.[158] When ribose derivative **113** is stirred for 13 h in dry 2-propanol at 65 °C the diastereomerically pure allose derivative **114** can be isolated in 90% yield, presumably via addition−elimination of HCN to imine **115** (Scheme 64). This process works well for a

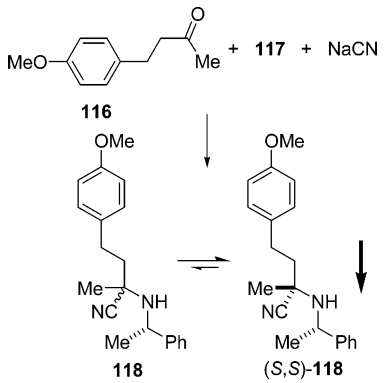
Scheme 64



number of sugar derivatives and provides for a convenient preparation of the homologous amino sugar derivatives.

Wenges et al. described a number of related examples in their studies of the Strecker chemistry of arylalkyl methyl ketones.[159] For example, when they added acetic acid to a solution of ketone **116**, sodium cyanide (1.1 equiv), and (*S*)-1-phenethylamine (**117**, 1.0 equiv) in methanol at room temperature and aged the resulting mixture at 60 °C for 24 h they were able to isolate (*S*,*S*)-**118** in 91% yield (Scheme 65).

Scheme 65



The preparation of pyrethroid insecticides such as deltamethrin (Figure 2) is carried out on multiton scale. These

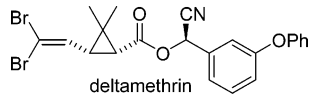
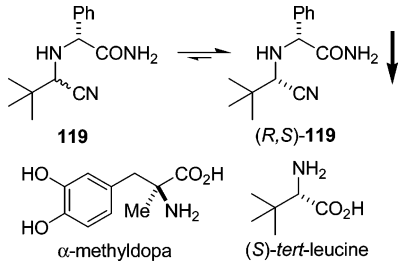


Figure 2.

compounds are often marketed as a mixture of diastereomers and/or enantiomers. A number of CIDT processes for their selective preparation have been described in the patent literature. This work has been reviewed by Martell.[160]

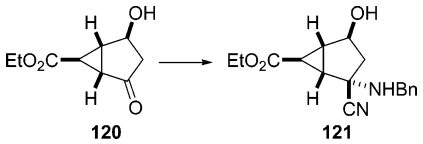
A DSM group used similar chemistry in practical approaches to (*S*)-*tert*-leucine and α-methyldopa.[161] Compound **119** is readily available as a mixture of diastereomers from (*R*)-phenyl-glycinamide. Warming **119** in water at 70 °C for 24 h gives (*R*,*S*)-**119** (>99% de) in 93% yield (Scheme 66).

Scheme 66



A group from Eli Lilly described a CIDT for the preparation of amino nitrile **121**, which is an intermediate in the synthesis of prodrugs of excitatory amino acids for the treatment of neurological disorders (Scheme 67).[162]

Scheme 67

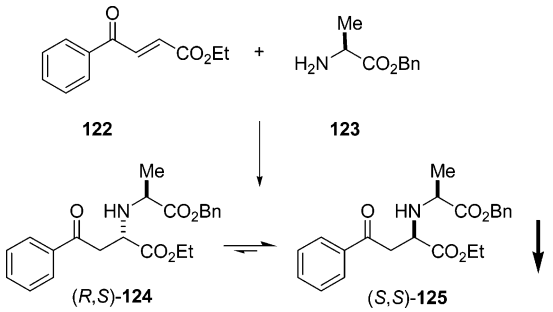


Subjecting racemic **120** to typical Strecker conditions with

a variety of amines yielded products with poor diastereoselectivity. However, amino nitrile **121** crystallized from solution in 80% yield upon using benzylamine. When this reaction was repeated with enantiopure **120** the product did not crystallize under the reaction conditions and the selectivity returned to the low levels previously observed. As noted above, crystal properties of racemic and enantiopure compounds can differ greatly.

A Hoechst group described the use of a CIDT in the preparation of (*S*,*S*)-**125** which can be used to synthesize a number of ACE inhibitors.[163] Treatment of **122** with the benzyl ester of (*S*)-alanine **123** in ethanol at room temperature in the presence of triethylamine provided a mixture of diastereomers. The desired (*S*,*S*)-**125** diastereomer is less soluble in this medium and crystallized out in 77% yield (Scheme 68). It was demonstrated separately that (*R*,S)-**124**,

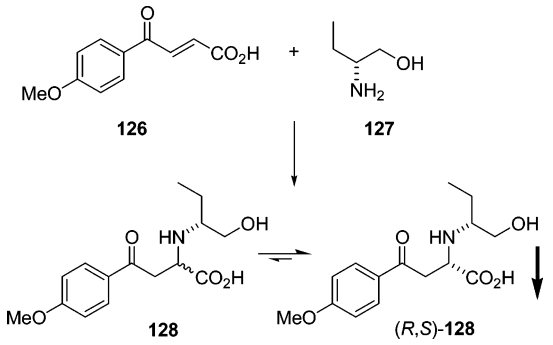
Scheme 68



which is an oil, converts to crystalline (*S*,*S*)-**125** upon standing at room temperature.

Berkeš et al. reported on a number of closely related CIDT examples.[164−167] For example, when **126** was treated with **127** (1.1 equiv) in dichloromethane at 25−30 °C for 7 days, (*R*,*S*)-**128** (>90% de) was obtained in 83% yield (Scheme 69).[168] The excess amino-alcohol presumably promotes the

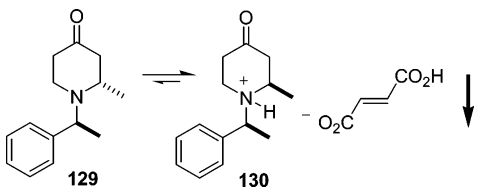
Scheme 69



reversibility of the conjugate addition reaction.

An example in which a reversible intramolecular conjugate addition was used to epimerize a 2-methylpiperidin-4-one derivative has recently been described by an Eli Lilly group (Scheme 70).[169] After heating of a mixture of **129** with

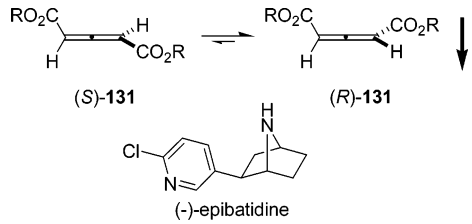
Scheme 70



fumaric acid (0.9 equiv) in acetone at 46 °C followed by an age at 20 °C for 16 h, the diastereomerically enriched salt **130** (82% de) was obtained in 66% yield. The mother liquors contained the diastereomers in a near 1:1 ratio. It should be pointed out that a retro-Mannich/Mannich sequence, as described for related compounds in Schemes 17 and 19, could also be the mechanism of equilibration in this case. Compound **130** was used in the synthesis of a number of 5-HT_{1F} receptor agonist candidates for the treatment for migraine.

An allene derivative which is useful for the synthesis of (−)-epibatidine was prepared using a CIDT (Scheme 71).[170]

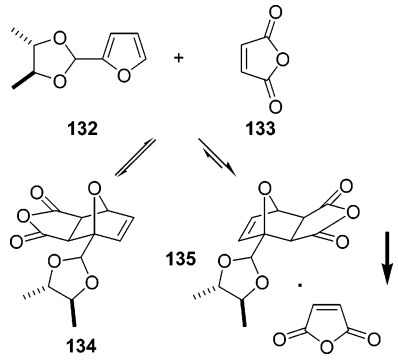
Scheme 71



When a mixture of isomeric **131** (R = (−)-menthyl) was treated with triethylamine (0.01 equiv) in pentane at −20 °C for 2 days, the diastereomerically pure (*R*)-**131** (>98% de) could be isolated in 90% yield. It is likely that triethylamine undergoes a transient conjugate addition, thus facilitating rotation around the double bond.

The Vogel group reported several examples of CIDT which are based on the reversibility of Diels−Alder reactions of olefinic dienophiles with furan derivatives at relatively low temperatures. When the enantiopure butanediol acetal of furfural (**132**) was heated with an excess of maleic anhydride (**133**) for 1 week at 55 °C and the resulting mixture was diluted with toluene, the diastereomerically pure **135** could be filtered as an interesting 1:1 complex with maleic anhydride in 78% yield (Scheme 72).[171] Treatment of the

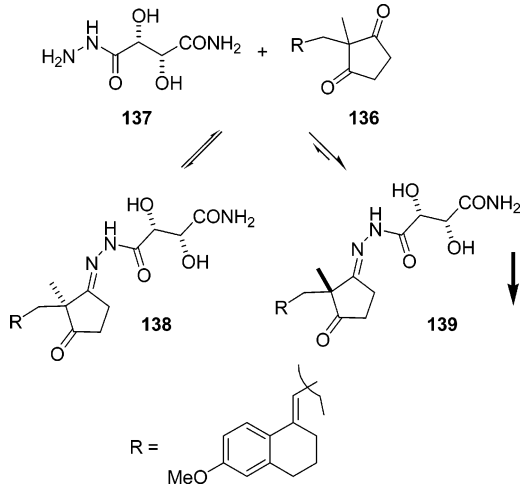
Scheme 72



isolated complex with an excess of isoprene at 20 °C allowed isolation of pure **135** in 60% overall yield after recrystallization. Similar results were reported on a reaction between maleic anhydride and (−)-furfuryl-(1′*S*)-camphanate and between 1-cyanovinyl-(1′*S*)-camphanate and 2,4-dimethylfuran.[172,173] In each case the Diels−Alder products have been used in natural product synthesis.

In a few examples of CIDT a group transfer occurs in the equilibration step. An ingenious asymmetric approach to steroids was reported in 1967 by a Roussel-Uclaf group using a CIDT of a hydrazone derivative (Scheme 73).[174] When dione **136** and (−)-tartaric acid hydrazide **137** (1.15 equiv)

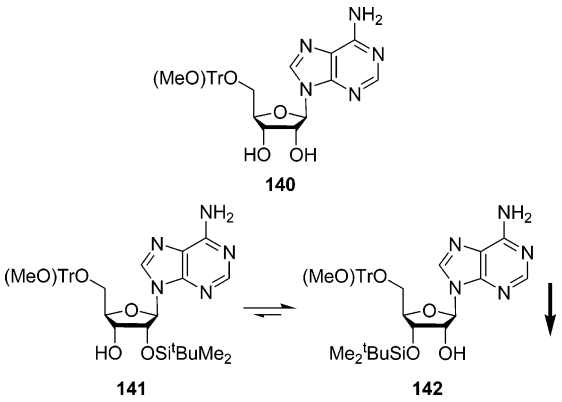
Scheme 73



were stirred in a mixture of methanol, acetic acid, and water (79:5:16 ratio) at room temperature for 3 days, the diastereomerically pure **139** was obtained in 84% yield. The solvent mixture for this process was optimized to allow facile formation and hydrolysis of the diastereomeric hydrazides **138** and **139** while crystallizing the less soluble one.

Noyori et al. used a CIDT in a regioselective preparation of a silyl-protected adenosine which can be used in the synthesis of 2′-5′-linked oligoadenylates.[175] Silylation of **140** under standard conditions yielded a 1:1 mixture of regioisomers **141** and **142** (Scheme 74). When a solution of the

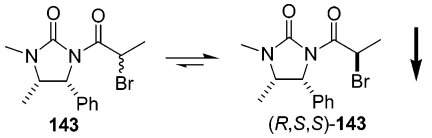
Scheme 74



latter in a 4:4:5:100 mixture of triethylamine, methanol, ethyl acetate, and diethyl ether was allowed to evaporate slowly over a period of 3−5 days the desired 3′-silylated derivative was obtained in 88% yield. Silyl transfer between neighboring hydroxyl groups is known to occur readily under these conditions.

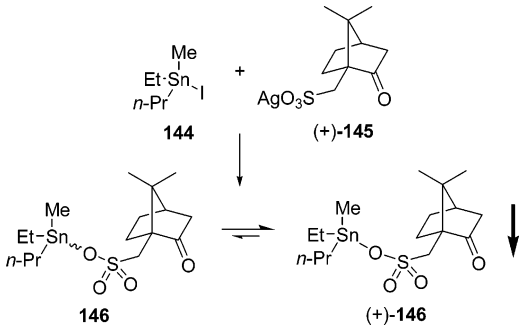
Just as was described in Schemes 22 and 23, degenerate nucleophilic substitutions can also be used to equilibrate covalent diastereomers. Caddick et al.[176] reported that subjection of a 1:1 mixture of imidazolidinone diastereomers **143** to tetrabutylammonium bromide (0.2 equiv) in THF while allowing slow evaporation of the solvent led to the formation of >98% de pure (*R*,*S*,*S*)-**143** in 91% yield (Scheme 75).

Scheme 75



A significant number of examples have been described for organometallic complexes, most of which are considered outside the scope of this review. An exception is made for the example of Scheme 76, which has great historic

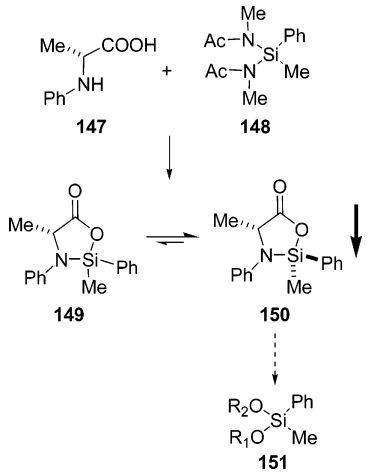
Scheme 76



significance as it is one of the first reported examples of CIDT.[177] During an investigation into optically active tin compounds, Pope and Peachey observed that upon reaction of iodide **144** with silver salt **145** in water only the dextrotatory product (+)-**146** was obtained after filtration of the silver iodide and concentration of the filtrate to induce crystallization. The authors noted that upon further concentration of the mother liquors only additional dextrotatory product (+)-**146** was obtained. All attempts to isolate the levorotatory compound were unsuccessful.

CIDT has been noted for stereogenic silicon-containing compounds. A General Electric group studied the condensation of *N*-phenylamino acids with bis(*N*-methylacetamido)-methylphenylsilane **148**.[178] For example, when (*R*)-*N*-phenylalanine **147** is reacted with **148** in benzene at room temperature, a mixture of siloxazolidinone diastereomers **149** is formed (Scheme 77). Vacuum distillation of the solvent

Scheme 77



and the *N*-methylacetamide byproduct affords the diastereomerically pure **150** in 92% overall yield. This product can be used to prepare enantiopure silane derivatives **151**. Corey

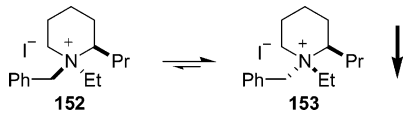
5.2. Heteroatom-Based Equilibrating Centers

CIDT have been observed for molecules in which the equilibrating stereocenter is not carbon but heteroatom based.

et al. noted a CIDT which converts *racemic* 1,2-difluoro-1,2-diaryl-1,2-dimethyldisilanes into their *meso* counterparts.[179]

A landmark nitrogen-based CIDT example was described in 1905 by Scholtz as part of his studies of quaternary coniine salts.[180] Scholtz heated a mixture of products **152** and **153**, which he obtained by treating *N*-ethylconiine with benzyl iodide, near their melting points (Scheme 78). He observed

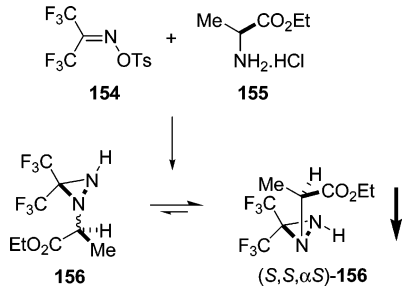
Scheme 78



that this resulted in the transformation of the lower melting isomer **152** (179 °C) into the higher melting **153** (208 °C). Even though the recovery was only 70% in this experiment, Scholtz noted that he could not find any trace of the lower melting isomer. In contrast, when he heated the pure higher melting isomer, Scholtz recovered his starting material and only noticed some decomposition. He also noted the smell of benzyl iodide in his experiments. These seminal observations are still compelling 100 years later. Related observations were made by Wedekind et al.[181,182]

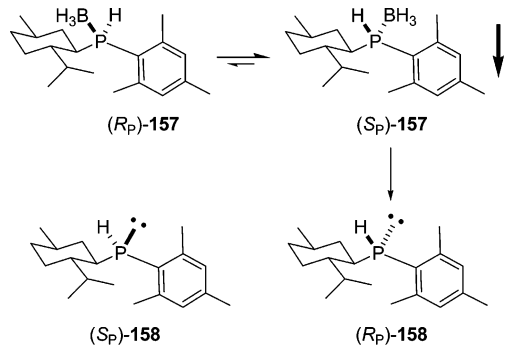
A different kind of stereogenic nitrogen atom is involved in a CIDT which was reported by Shustov et al. as part of their study of the structure and properties of diaziridine derivatives.[183] Reaction of *O*-tosyloxime **154** with an equimolar amount of the L-alanine ester hydrochloride **155** in dry DMF at 0 °C for 24 h in the presence of triethylamine (2 equiv) provided a mixture of diastereomers **156**, which after workup and distillation yielded the diastereomerically pure (*S*,*S*,α*S*)-**156** in 65% yield (Scheme 79).

Scheme 79



Several examples of stereogenic phosphorus-based CIDT have been described. Wild et al. described the preparation of the secondary phosphine (*R*P)-**158** (Scheme 80).[184] Crys-

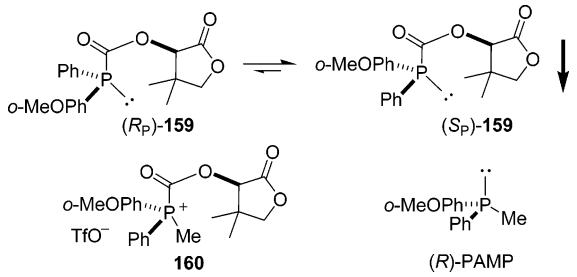
Scheme 80



tallization of a mixture of diastereomers (*R*P)-**157** and (*S*P)-**157** (prepared by treatment of a 1:1 mixture of (−)-menthylmesitylphosphine diastereomers (*R*P/*S*P)-**158** with borane dimethyl sulfide in benzene) from hexane yielded (*S*P)-**157** in 66% yield. The equilibrium ratio of (*R*P)-**157** and (*S*P)-**157** was determined at 28:72. Treatment of (*S*P)-**157** with diethylamine yields (*R*P)-**158** in quantitative yield.

In the past decade the Vedejs research group reported on several CIDT as a means to control the configuration of several heteroelements. The group described two different methods for the preparation of trisubstituted phosphorus compounds. *P*-Alkoxycarbonylphosphines (*R*P)-**159** and (*S*P)-**159** can be readily prepared as a 1:1 mixture of diastereomers via reaction of the (*R*)-pantolactone-derived chloroformate with *o*-anisylphenylphosphine (Scheme 81).[185] Crystallization

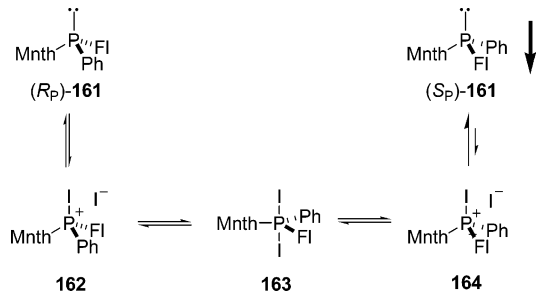
Scheme 81



of this mixture of diastereomers from ethanol at room temperature yielded (*S*P)-**159** (96% de) in two crops with an overall yield of 85%. Interestingly, the purity of the solids improved upon extended storage at room temperature (98% de after 2 wks) or brief heating at 50 °C (99% de after 22 h of heating). When (*S*P)-**159** is dissolved, it rapidly equilibrates to a mixture of diastereomers. Compound (*S*P)-**159** can be converted to **160**, which is useful in the synthesis of (*R*)-PAMP, a precursor to the (*R*,*R*)-DIPAMP ligand.[186]

In a second report the group described how CIDT can be used to directly control the phosphorus configuration in tertiary phosphines.[187] Thus, when a 3:1 mixture of diastereomers (*S*P/*R*P)-**161**, which contain a nonequilibrating (−)-menthyl ligand (Mnth) and a 9-fluorenyl (Fl) moiety (the latter was shown to impart a high degree of crystallinity), was warmed in acetonitrile at 50 °C in the presence of 4 mol % of iodine and powdered 3 Å molecular sieves while allowing the solvent to slowly evaporate over 30 h, the diastereomerically enriched (95% ds) (*S*P)-**161** could be isolated in 83% yield after a quench with H_2O/K_2CO_3 (Scheme 82). The equilibration is thought to take place via

Scheme 82

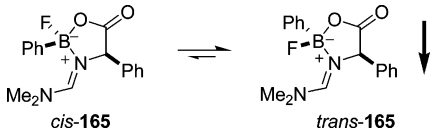


intermediates **162**−**164**.

The group also reported on a number of boron-based CIDT in their development of chiral amino acid enolate equivalents. Treatment of the sodium salt of (+)-phenylglycine with dimethylformamide dimethyl acetal followed by KBF_3Ph (1.0

equiv) and TMSCl (2.3 equiv) affords **165** as a 3.5:1 mixture of trans and cis diastereomers, respectively (Scheme 83).[188−190]

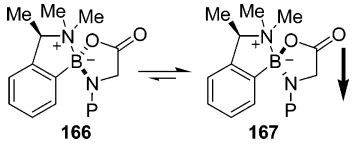
Scheme 83



Crystallization of this mixture from dichloromethane at 30 °C with slow evaporation of the solvent yields the diastereomerically pure *trans*-**165** (99:1 mixture) in 85% yield. This process appears to be fairly general for a number of amino acids.

Similar results were obtained in a related salicylaldimine-derived series. However, exploration of another series showed that quasi-racemate formation can occur depending on the *N*-protecting group, thwarting successful CIDT. When the *N*-protecting group in diastereomers **166** and **167** is either BOC or Cbz, quasi-racemate formation was observed. However, in the case of sulfonyl-based protecting groups a CIDT was successful (Scheme 84).[191]

Scheme 84



6. Conclusions

This review highlights the use of crystallization-induced diastereomer transformations (CIDT) in organic synthesis. The many examples were divided into two main classes of CIDT: those in which the equilibrating and directing centers reside on different counterions of a salt and those in which they are part of the same covalent backbone. While most examples of CIDT take place due to a facile equilibration of the configuration at a carbon center, heteroatom-based equilibrations have also been described.

While many examples of CIDT are based on serendipitous findings, recent reports from both academic and industrial groups have shown that CIDT can also be methodically developed, even though this typically requires a significant effort. When attempting to design a CIDT it is often critical that the two main challenges (i.e., equilibration and crystallization) are studied separately before an integrated process can be worked out.

As this review has shown, the mechanism of equilibration is based on either rotation around hindered bonds or facile cleavage and formation of bonds which are activated in some way. Examples of the latter included proton transfer to/from relatively acidic carbon−hydrogen bonds, facile formation of stabilized carbocations (iminium, oxonium, benzylic etc.), (conjugate) addition/elimination reactions (including Diels−Alder cycloadditions), and degenerate substitution reactions. However, many other mechanisms can be envisaged.[192] In many cases equilibration can be accomplished simply by raising the temperature. However, when the temperature becomes too high the product may decompose. Since the temperature also impacts solubility, careful optimization of the process temperature is important for most CIDT processes. When temperature alone is not sufficient to effect equilibration, additives may be used. These can vary from Brönsted and Lewis acids and bases to a number of special additives. The best-known example of the latter is the use of aldehydes and ketones to facilitate equilibration of amino acids and related compounds via intermediate imine formation. When additives are used in a process, careful quenching of the CIDT may become critical. Often isolation of the desired solids with high purity can only occur when further equilibration is stopped.

The selective crystallization of one component from a mixture requires the meticulous manipulation of its physicochemical properties. Chromatography often provides the first quantities of pure compound which can be used to conduct these studies. If the compound is ionizable, salt formation can be considered. If the compound is nonionizable, clathrate formation can be contemplated. High-throughput techniques are increasingly used to determine the potential for crystallization as well as for determination of the melting point and solubility of the crystalline phases. Knowledge of the latter as a function of solvent composition and temperature is critical. When the solubility of the desired product in the process medium is too low, the CIDT often does not occur and/or affords solids with a relatively low purity. On the other hand, if the solubility is too high the yield will be relatively low. It should always be kept in mind that formation of solvates or polymorphs can have a profound impact on solubility. With detailed knowledge of the equilibration and crystallization parts of the process in hand, development of a successful CIDT can be contemplated. Often this will require another round of significant process optimization.

The amount of time and effort which is typically needed to develop a successful CIDT may limit its use in the pursuit of an academic synthesis. However, CIDT can be one of the most powerful tools available to a process chemist charged with development of a large-scale synthesis for a commercially important molecule. A CIDT-based process typically offers significant capital and operating expense savings compared to alternatives. It is our hope that this review will inspire new generations of chemists to use these exceedingly useful transformations in the planning of truly practical syntheses.

7. Acknowledgments

We acknowledge the help of our librarians Jane Bilson and Margaret Allen in searching the literature for crystallization-induced processes.

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