PROLINE CATALYZED ENANTIOSELECTIVE RETRO-ALDOL REACTION

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by

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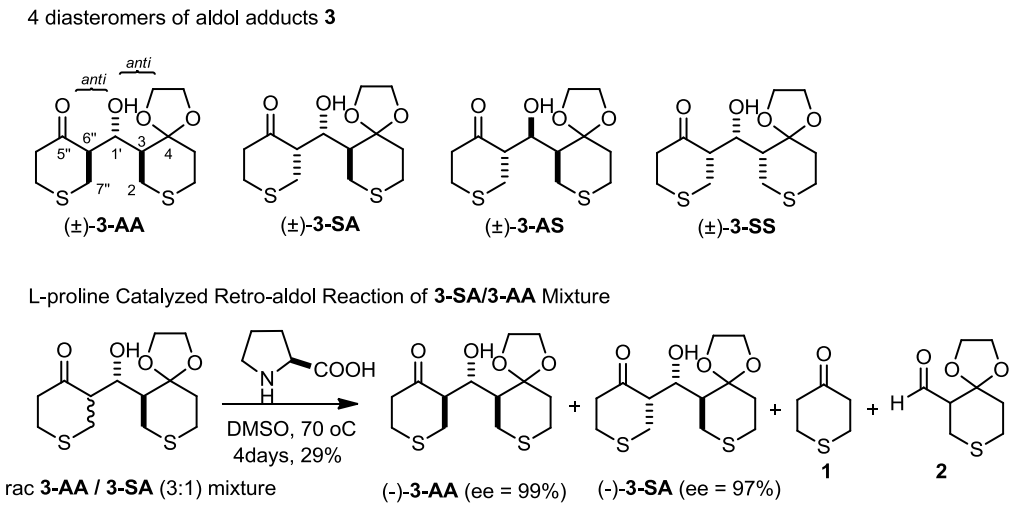
CANADA

ABSTRACT

In the Ward Group, stereoselective aldol reactions of thiopyran derived templates play an important role in polypropionate natural product syntheses. Central to this approach is the diastereo- and enantioselective synthesis of all possible aldol adducts **3** arising from tetrahydro-4*H*-thiopyran-4-one (**1**) and 1,4-dioxa-8-thiaspiro[4.5] decane-6- carboxaldehyde (**2**). There are four possible diastereomers of **3** indicated by the relative configurations at positions 3 and 1' (*syn* or *anti*) and positions 1' and 6' (*syn* or *anti*).

Up to date, the asymmetric aldol reaction of **1** with **2** catalyzed by L-proline or its tetrazole analogue **12** provides efficient access to 3,1'-*anti*-1',6'-*syn*-3 (**3-AS**) without need for chromatography (>40 g scale; 75% yield, >98% ee) and 3,1'-*syn*-1',6'-*syn*-3(**3-SS**) (via isomerization of **3-AS**; >75% yield, 2 cycles); however, the preparation of enantiopure 3,1'-*anti*-1',6'-*anti*-3 (**3-AA**) and 3,1'-*anti*-1',6'-*syn*-3 (**3-SA**) still requires the use of enantiopure aldehyde **2** in a diastereoselective synthesis. Without a simple and scalable route, access to enantioenriched iterative aldol adducts and polypropionate natural products that are based on **3-AA** and **3-SA** skeletons are hindered. It was observed that conducting the asymmetric aldol synthesis of **3-AS** on large scale gave enantioenriched **3-AA** as a very minor product. This observation triggered the hypothesis of using L-proline to resolve racemic **3-AA** via a retro-aldol reaction.



Diastereomers of 3 and the Enantioselective Retro-Aldol Reaction

In this thesis, the development, optimization, and application of an unprecedented L-proline catalyzed enantioselective retro-aldol reaction is described. Interesting mechanistic insights were uncovered. An unexpected isomerization process between **3-AA** and **3-SA** occurs in parallel with the retro-aldol process. The method was demonstrated to be a robust, flexible, and readily scalable process to access highly enantioenriched **3-AA** (ee > 95%) and **3-SA** (ee > 95%). To the best of our knowledge, this reaction represents the only reported enantioselective retro-aldol reaction catalyzed by L-proline.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Conc	concentration
Conv	conversion
^{13}C NMR	carbon nuclear magnetic resonance
d	day(s)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
ee	enantiomeric excess
Et3N	triethylamine
equiv	equivalent(s)
1H NMR	proton nuclear magnetic resonance
h	hour(s)
HPLC	high performance liquid chromatography
M	molar
Me	methyl
mg	milligram(s)
min	minute(s)
Ph	phenyl
PTSA	para-toluenesulfonic acid
rac	racemic
rt	room temperature
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMS	trimethylsilyl (or trimethylsilane)

INTRODUCTION

1.1 The Thiopyran Route to Polypropionates

Polyketides are a large class of natural products found in bacteria, fungi, and plants. Compounds in this class have been shown to have various biological activities including antibiotic, immunosuppressant, anti-parasitic, cholesterol-lowering, and anti-tumor effects.[1] While continuing to be an important source for new drug discovery, the polyketide class of natural products includes many currently marketed therapeutics such as rapamycin, actinorhodin, erythromycin, and lovastatine. Their potential pharmacological applications and intriguing structural complexities have fueled numerous researchers to develop efficient synthetic access to polyketides.

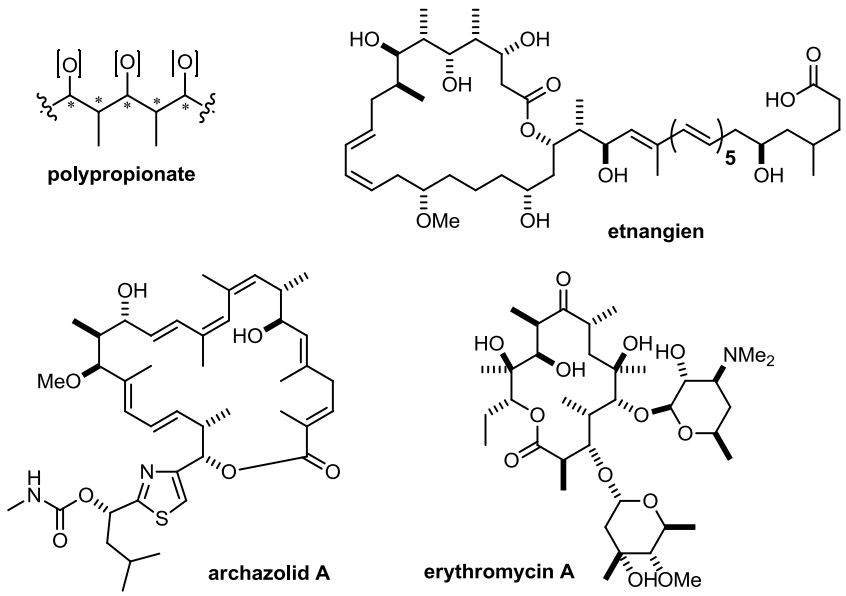


Figure 1. Characteristic Structure of Polypropionate (* indicates a stereogenic center) and Examples of Polypropionate Natural Products

When the carbon chain of a polyketide features alternating methyl and oxygen

substituents such as in erythromycin,[2] archazolid A,[3a] or etnangien,[3b] the ensuing polyketide is termed a polypropionate (Figure 1). The polypropionate name correlates with the main building block in biosynthetic pathway where methylmalonyl-CoA precursors are iteratively condensed by decarboxylative addition onto a growing acyl carrier protein, a process mediated by polyketide synthases.[4] The densely arranged stereogenic centers in a polypropionate chain create a large number of possible stereoisomers. Efficiently controlling the formation of stereogenic centers is of key importance in polypropionate syntheses. A large number of synthetic methods have been devised to assemble the characteristic chain of polypropionates, including those based on crotylation, allenylation, epoxide opening, Wittig rearrangement, aldol reaction, and so on.[5] Mechanistically similar to the biosynthetic pathway, the aldol reaction is by far the most important tool for stereoselective construction of polypropionate chains. In the Ward Group, advances in the modern aldol chemistry field were developed and utilized in a comprehensive approach to polypropionate syntheses.

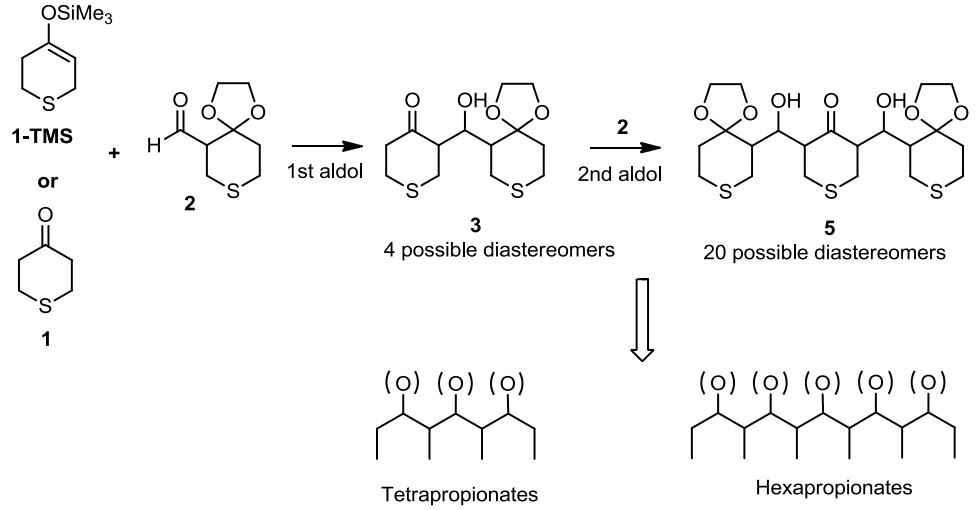


Figure 2. The Thiopyran Route to 1st and 2nd Aldol Adducts[6]

Within the Ward Group, the challenges in efficient and selective assembly of polypropionate chains were met in part through strategic iterative aldol coupling of thiopyran

derived scaffolds such as **1**, **2**, **3** or **5** (Figure 2). These sulfur containing templates offer advantages in controlling the transformations and the sulfur atom(s) could be easily removed to afford the polypropionate chain.[6] By exploiting a variety of metal mediators, Lewis acids/bases, organocatalysts, and substrate stereo-control elements, stereoselective synthesis of a library of thiopyran aldol adducts was established. Desulfurization transformed the thiopyran aldol adducts into a polypropionate chain. In just a few steps from inexpensive and commercially available material, a stereochemically diverse set of tetrapropionate and hexapropionate synthons can be selectively prepared.[7,8] Various derivatives of the tetra- and hexapropioantes such as protected, oxidized or reduced forms served as excellent candidates for further study as well as strategic building blocks for use in total synthesis of natural products.

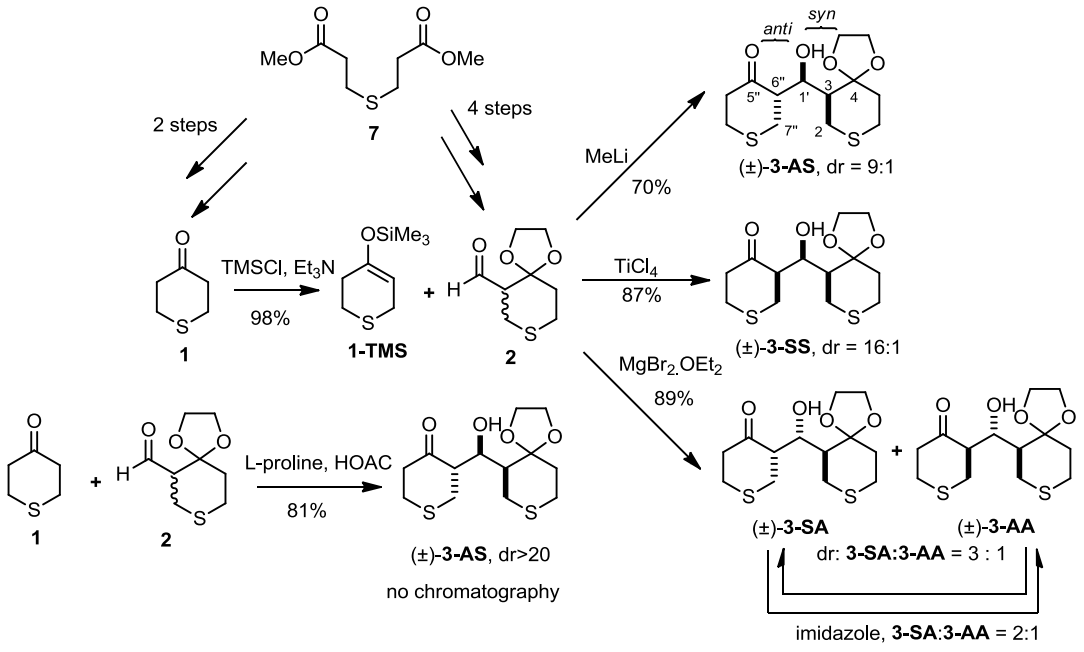


Figure 3. Diastereoselective Synthesis of the **3** Series of Aldol Adducts

Fundamental to this approach is the diastereoselective aldol coupling of ketone **1** with aldehyde **2** to produce the four possible first diastereomeric aldol adducts (Figure 3).[9] **1** and **2** can both be prepared from the commodity starting material **7**,[10] making the first aldol adducts synthesis very economical. The four possible diastereomers of **3** are indicated by the relative configurations at positions 3 and 1' (*syn* or *anti*) and positions 1' and 6' (*syn* or *anti*). Diastereomer 3,1'-*anti*-1',6'-*syn*-**3** (**3-AS**) was prepared through addition of the 'amine-free' lithium enolate of **1** to **2** via a closed transition state as expected for this reaction.[9] Diastereomer 3,1'-*syn*-1',6'-*syn*-**3** (**3-SS**) was prepared through a Mukaiyama type aldol reaction of **1** with **2** mediated by the $TiCl_4$ presumably via an open transition state.[9] The synthesis of both **3-AS** and **3-SS** proceeded through a selective addition to the Felkin face of chiral aldehyde **2**. The diastereomers 3,1'-*syn*-1',6'-*anti*-**3** (**3-SA**) and 3,1'-*anti*-1',6'-*anti*-**3** (**3-AA**) were prepared as a 3:1 mixture from non-Felkin addition of **1-TMS** to **2** mediated by $MgBr_2 \cdot OEt_2$.[9] The selective addition to the Felkin face of aldehyde **2** observed in the preparation of **3-AS** and **3-SS** was reversed when $MgBr_2 \cdot OEt_2$ was used because of the simultaneous coordination of the Mg (II) with the aldehyde carbonyl and cis oxygen of the ketal (chelation control). The yield of **3-AA** could be further increased by taking advantage of the much lower solubility of **3-SA** and the ability to isomerize **3-SA** and **3-AA** in the presence of imidazole. Recently, a more convenient and scalable method was developed to access **3-AS** with high diastereoselectivity (dr>20) without the need of chromatography.[11] The reaction was catalyzed by L-proline and acetic acid to produce the racemic **3-AS**.

A synthetically useful isomerization phenomenon of the aldol adducts was explored.[12] The pairs of aldol adducts **3-AS**/**3-SS** and **3-AA**/**3-SA** are linked by keto-enol tautomerism

(Figure 4). Under appropriate conditions (e.g., in the presence of imidazole), these adducts pairs can be induced to undergo isomerization under thermodynamic control. A similar isomerization process is also applicable to bisaldol adducts **5**; in these cases, producing an equilibrium mixture of three or four diastereomers (depending on the starting diastereomer of **5**). This isomerization process has been used for structure elucidation and to access certain diastereomers or to increase the yield of certain minor diastereomer on preparative scale.[12]

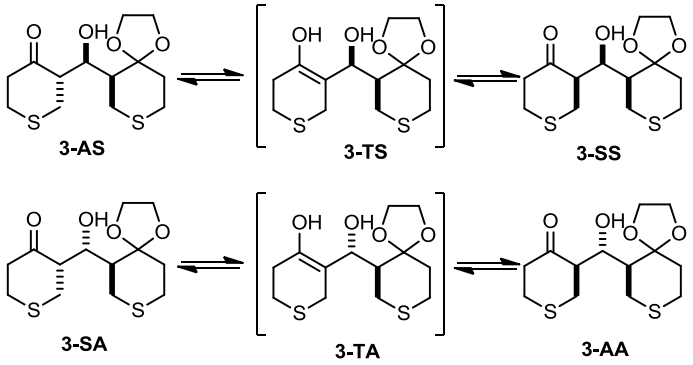


Figure 4. Isomerization of First Aldol Adducts in the Presence of Imidazole or Et_3N, SiO_2

Enantioselective synthesis of the first aldol adducts **3** took two different approaches. All four aldol adducts diastereomers could be synthesized enantioselectively through the use of enantioenriched aldehyde **2**.[13] Under conditions similar to the diastereoselective syntheses of the racemic compounds, each enantiomer could be prepared by Mukaiyama aldol coupling of **1-TMS** with enantioenriched **2**. The enantioenriched aldehyde **2** was prepared by enantioselective protonation of the achiral lithium enolate derived from **(±)-9** with chiral aminoalcohol **10** followed by oxidation state adjustment (Figure 5). Under the optimized conditions, **11** was obtained as a 10:1 mixture of enantiomers (82% ee). The enantiopurity of **11** could be further increased by recrystallization (up to 95% ee; ca. 50% yield).

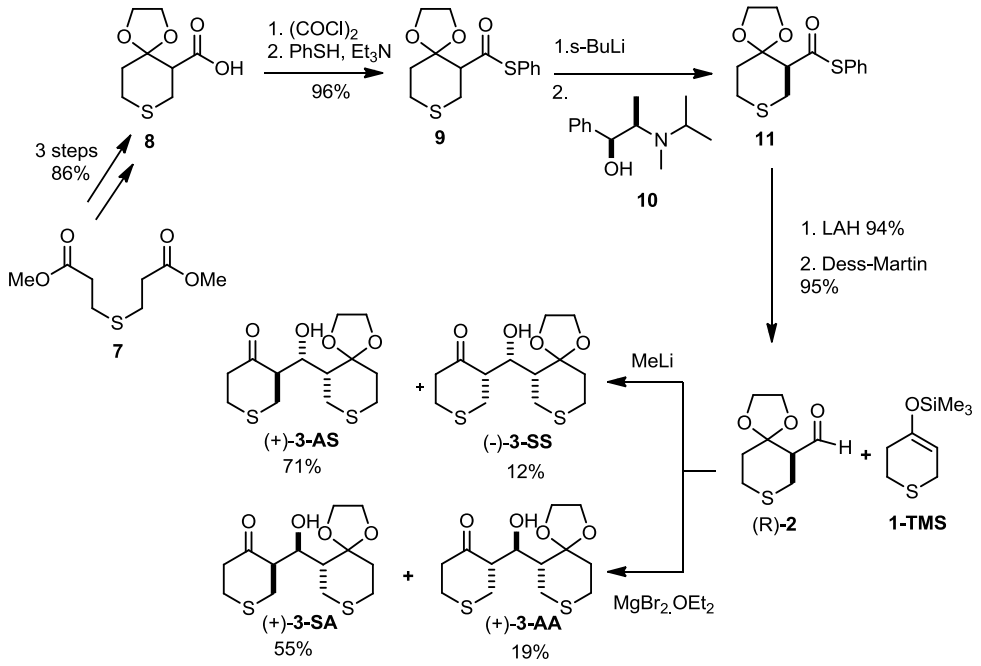


Figure 5. Preparation of Enantioenriched **3** by Use of Enantioenriched Aldehyde **2**

The availability of enantioenriched aldehyde **2** allowed access to enantioenriched aldol adducts **3**. However, the additional steps required to prepare enantioenriched **2** made this route less efficient. In addition, the protonation step was done at -100 ^{o}C in highly diluted solution making scale up difficult. Finally, the aldehyde **2** undergoes racemization upon standing which imposes additional challenges to material management. A more efficient and scalable enantioselective synthesis of aldehyde **2** and aldol adducts **3** would be very beneficial.

1.2 Direct Asymmetric Synthesis of 3-AS and 3-SS

An alternative approach was found for enantioselective access to **3-AS**. This was accomplished via a direct asymmetric aldol reaction with dynamic kinetic resolution. Enantiopure proline or 5-[(2S)-pyrrolidine-2-yl]-1H-tetrazole (**12)** (Figure 6) catalyzed this remarkably stereoselective (dr>20, er>20) and scalable transformation (>40 g) (Figure 6).[11,14] The reaction proceeded through dynamic kinetic resolution because aldehyde **2** readily underwent racemization in the reaction conditions. Taking advantage of isomerization process between **3-AS** and **3-SS**, enantiopure **3-SS** could be easily obtained from enantiopure **3-AS**. The availability of these enantiopure materials facilitated the synthesis of several natural products by the Ward Group: serricornin[15], baconipyrone A,[16] baconipyrone C,[16] siphonarin B,[15] caloundrin B,[17] and muamvatin.[18]

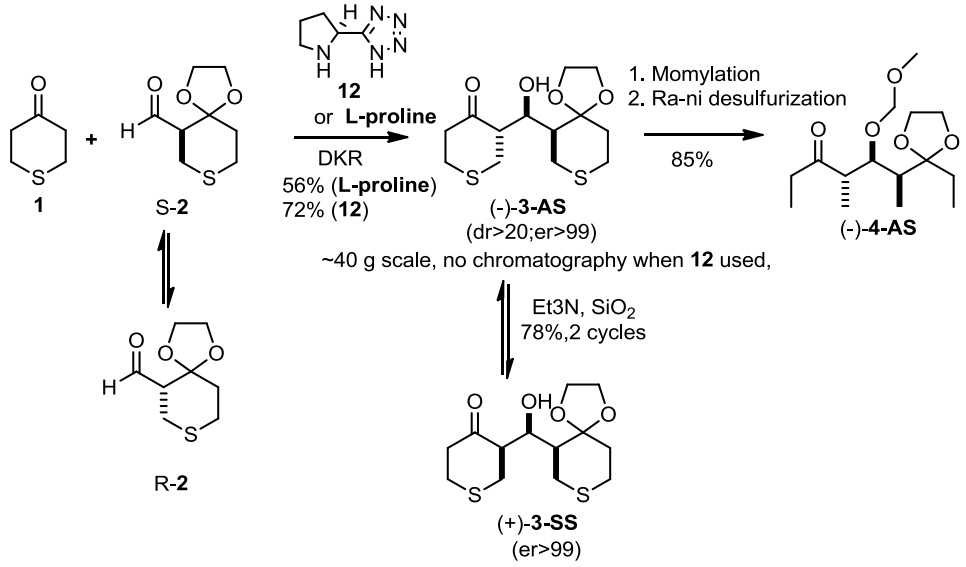


Figure 6. Organocatalyzed Enantioselective Synthesis of (-)-**3-AS** and Isomerization to (+)-**3-SS**

The aldol coupling of unmodified ketone **1** and aldehyde **2** promoted by a chiral catalyst is an example of the *direct* asymmetric aldol reaction. Before moving onto a more detailed

discussion of the *direct* aldol reaction, a brief summary of the more traditional stereoselective aldol reaction, the *directed* aldol reaction, is useful.

An aldol reaction couples an enolizable carbonyl compound with aldehyde or ketone to produce a beta-hydroxy carbonyl compound (Figure 7). In this process, one C-C bond and up to two new stereogenic centers are formed. Under some conditions (e.g. acidic), this initial product can undergo dehydration to furnish an α, β-unsaturated carbonyl compound. The ketone and/or aldehyde substrates are commonly the enolizable partners. They undergo coupling with themselves and/or cross coupling depending on the conditions. Aldol reactions can be catalyzed by simple acids and bases; however, the lack of control over stereoselectivity makes these conditions undesirable from a synthetic chemistry viewpoint. In addition, the intrinsic reversibility of simple acid and base catalyzed aldol reaction also limits their utility.

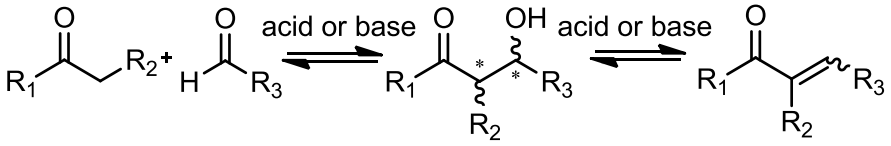


Figure 7. An Acid Base Catalyzed Aldol/Retro-Aldol Reaction

To address the various challenges in selectivity and reversibility, the *directed* aldol reaction relies on controlled and stoichiometric conversion of the enolizable carbonyl compound (pre-nucleophile) into an enolate prior to coupling (Figure 8). Diastereoselectivity in *directed* aldol reaction is achievable through the use of a variety of metal enolates, Lewis acids and base mediators, as well as by exploiting factors that promote substrate control of stereoselectivity. Excellent enantioselectivity is also achievable by employing tools such as

chiral auxiliaries, chiral ligands, and catalytic enantioselective reactions (Mukaiyama-type).[19a]

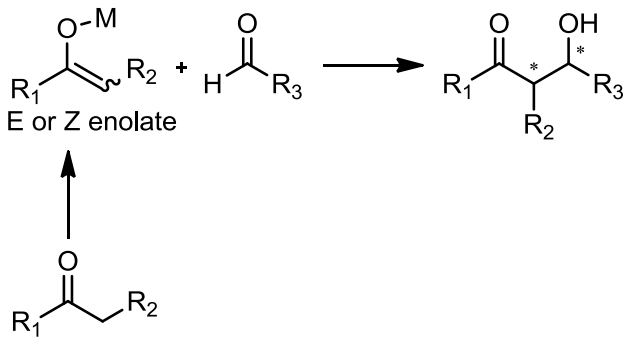


Figure 8. A Typical Directed Aldol Reaction

On the other hand, the *direct* aldol reactions achieve stereoselectivity through the use of catalysts and the carbonyl partners are coupled without prior modification. Excellent enantioselectivity can be induced by chiral catalysts rather than using enantiopure reactants derived from a "chiral pool", a practice that results in added steps and decreased efficiency. Clearly, avoiding the pre-formation of activated reactants brings benefits to both step economy and overall efficiency.

Many catalysts were reported to catalyze asymmetric aldol reactions of unmodified carbonyl partners. The main classes include enzymes, metal complexes and small organic molecules. Though it is the prevalent form of aldol reaction in biochemical environment, the small molecule catalyzed asymmetric aldol reaction is relatively new compared to the well established *directed* aldol approach.

Enzymes have been increasingly recognized as useful catalysts for chemical synthesis. Aldolases are a group of lyases that typically catalyze reversible addition of a ketone to an aldehyde.[20] Many examples of the use of aldolases in chemoenzymatic aldol synthesis have

been reported.[21,22] The high selectivities (chemo, regio- and stereo-) exhibited by enzymatic agents are certainly attractive, yet the relatively narrow substrate scope imposes significant limitations on their use. The preparation or cost of the enzymes often also inhibits their use in organic synthesis. Catalytic antibodies are another type of biochemical agent that catalyzes stereoselective aldol reactions.

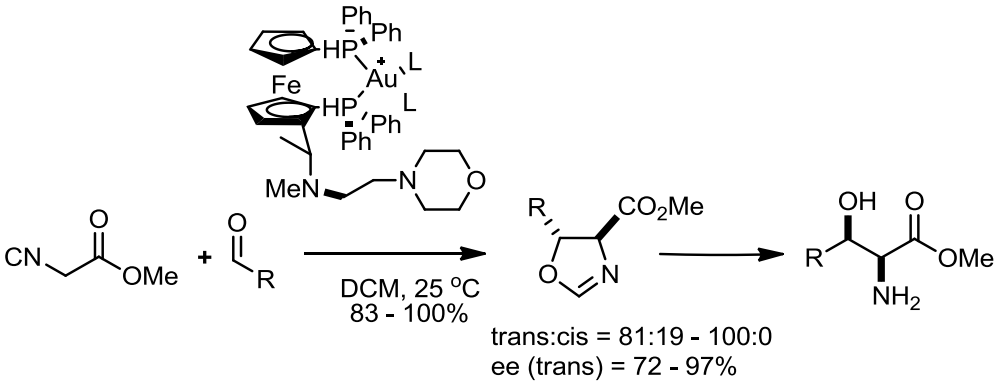


Figure 9. Ito's Gold-Catalyzed Asymmetric Aldol Reaction.

The first metal complex catalyzed direct asymmetric aldol was reported in 1986.[23] The reaction coupled an isocyanoacetate with a series of aldehydes through the catalysis of chiral ferrocenylphosphine-gold (I) complexes (Figure 9). The oxazoline products could undergo hydrolysis to afford α-amino-β-hydroxyesters. A wide variety of other metal complexes were subsequently reported to directly catalyze enantioselective aldol reactions. BINOL based metal complexes account for a major portion of these catalyts.[24]

The first small organic molecule catalyzed direct enantioselective aldol reaction was reported by two industrial groups: Hajos and Parrish as well as the group of Eder, Sauer, and Wiechert in 1971 (Figure 10). [25,26] This L-proline catalyzed aldol cyclization produces a bicyclic ketol in high enantiomeric excess without dehydration and subsequently was applied

extensively in steroid synthesis.

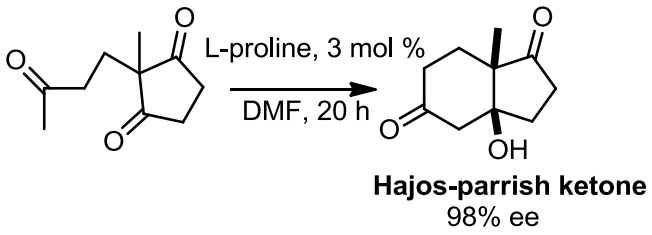


Figure 10. The Hajos-Parrish-Eder-Sauer-Wiechert Reaction

Three decades after the work of Hajos *et al*., the intermolecular counterpart of the reaction was reported. List and co-workers reported the first L-proline catalyzed intermolecular enantioselective aldol reaction in 2000.[27] In this initial account, L-proline catalyzed the coupling of a handful of mostly aromatic aldehydes with acetone to form aldol adducts enantioselectively. Enantiomeric excesses as high as 96% were achieved with isobutyraldehyde aldehyde in near quantitative yield (Figure 11, a). This rediscovery of L-proline-catalyzed aldol marked a milestone of the development of organocatalysis in synthetic chemistry. The simplicity, the abundance of enantiopure amino acids, and the concept of small organic molecule to catalyze asymmetric transformations inspired a new surge of research in organocatalysis.

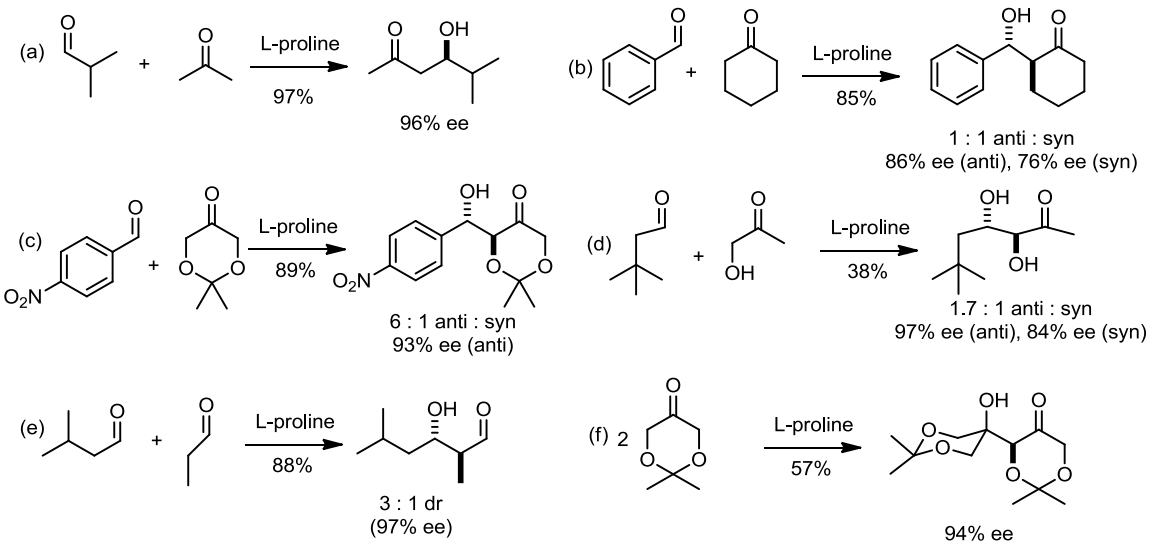


Figure 11. Examples of L-Proline Catalyzed Enantioselective Aldol Reactions.

An explosive growth in the field of small organic molecules catalyzed enantioselective aldol reactions was seen in the last ten years. In this field, L-proline and its derivatives represent the most commonly used catalysts. The scope of L-proline catalyzed enantioselective aldol reactions has been largely expanded. Cyclic, heterocyclic, and hydroxyl ketones were demonstrated to be viable substrates. Self-condensation of ketone as well as ketone-ketone cross coupling were observed under the catalysis of L-proline. In addition, aldehydes can also be used as donors in L-proline catalyzed aldol reactions. However, in many cases the reactivity remained low. A large excess of ketone is often required in L-proline catalyzed aldol reaction and simple achiral ketones and aldehydes remain the primary substrates.[28]

Mechanistically, aldol reactions catalyzed by secondary amines are rooted in well known principles. The currently accepted mechanism of L-proline catalyzed aldol reaction proceeds through the imine-enamine tautomerism cycle (Figure 12). The cycle starts with the

condensation of the secondary amine with the ketone (or aldehyde) donor to produce the nucleophilic enamine **13**. Carbonyl addition activated by the carboxylic acid of L-proline followed by hydrolysis of the iminium ion **15** gives the aldol adduct **16**.

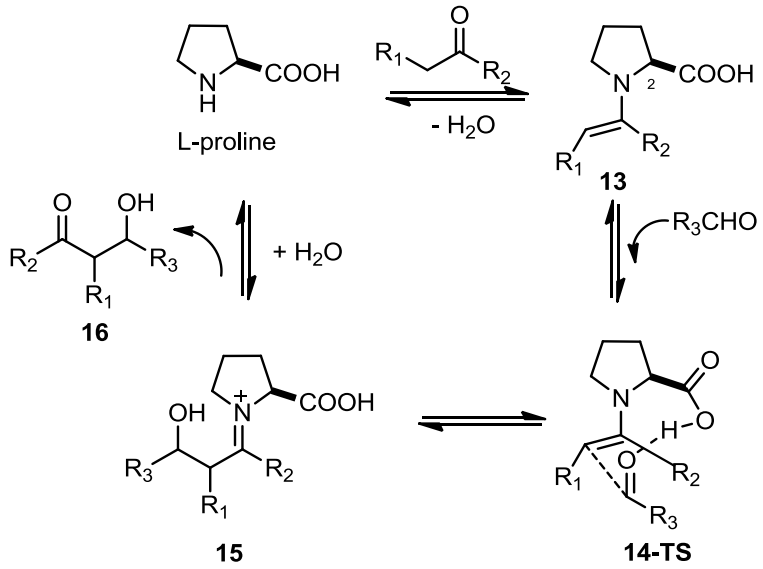


Figure 12. Enamine Mechanism of L-Proline Catalyzed Aldol Reaction

As indicated in the catalytic cycle (Figure 12), L-proline is a bifunctional catalyst that achieves rate acceleration by activating both the donor and acceptor of an aldol reaction. The excellent level of enantioselectivity was attributed to L-proline's ability to form a highly organized transition state with an extensive H-bonding network. To establish the origin of stereoinduction, the enamine transition state was thoroughly studied. The generally accepted configuration of the enamine is (*E*) (cf. R1 vs. N in **13**) with the preferred conformation being s-*trans* (i.e., the C=C-N-C2 torsion is 180°). The trajectory of the incoming carbonyl acceptor was proposed to be directed by an H-bonding interaction of the carboxylic acid "arm" (cf. **14-TS**) with the aldehyde carbonyl.[29,30]

A great deal of work has been dedicated to the discovery of new catalysts for the

enantioselective aldol reaction. A large number of catalysts that operate via an enamine catalytic cycle similiar to that illustrated in Figure 12 were developed. Catalysts with a modified L-proline structure represent the most popular type. Common modifications include increasing hydrophobicity to increase solubility in organic solvents, changing the carboxylic acid group to other hydrogen bonding groups, or increasing the steric-bulkness and adding new stereogenic centers to enhance enantioselectivity (Figure 13). A variety of non-proline-based catalysts have been reported as well. Non enamine based catalysts such as tertiary and quaternary ammonium salts were also reported to catalyze the aldol reaction.[24,28]

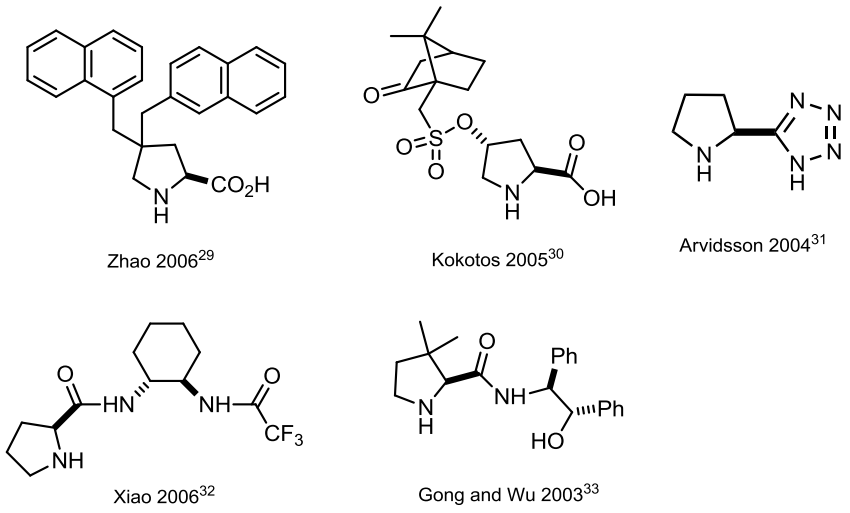


Figure 13. Some Proline Based Organocatalyst

Organocatalysis has now matured and is recognized as a main class of catalysts along side with the well established enzymatic and organometallic catalysts. Aside from offering comparable diastereo- and enantioselectivity to enzymatic or metal containing catalysts, organocatalysts are often more stable, easier to handle, and less demanding in terms of reaction condition. Clearly, the absence of heavy metals in organocatalysts as well as their higher tolerance for water and oxygen promises a very favorable future for industrial use of organocatalysis.

1.3 Retro-Aldol Reaction

The reversibility of the aldol reaction is one of its key features. A main advantage of the use of pre-formed enolates in the directed aldol reaction is to make this reversibility less favorable. In Heathcock's book chapter on general aldol chemistry[19b], he offered a brief summary on the thermodynamics of the acid and based catalyzed aldol reaction. The key point in that summary is that acid and based catalyzed aldol reaction generally lacks a strong driving force with some examples being endothermic reactions. The common driving force is the lowered energy in the product resulting from replacing a C-H ($\Delta H°$ = 98 kcal/mol) bond for an O-H ($\Delta H°$ = 108 kcal/mol) bond. An additional driving force for aldol addition is the stronger acidity of secondary (e.g., *i*-PrOH pKa = 16.5) or tertiary (e.g., *t*-BuOH pKa = 17.0) alcohols compared to ketones (e.g., methyl ketone pKa = 20). On the other hand, the main structural factor that favors aldol reversibility is the higher steric compression in the product compared to starting materials (e.g., branching at α or β position). Entropy also disfavors aldol adducts compared starting materials.

Therefore, the ease of reversibility of the aldol reaction makes the retro-aldol a readily available process. However, quite contrary to the extensive work in asymmetric aldol reactions, the retro-aldol reaction has remained rather underdeveloped. Conceptually, the retro-aldol reaction can proceed enantioselectively in the presence of a chiral catalyst. This process could provide an alternative access to enantioenriched aldol adducts that are hard to obtain from the forward pathway (Figure 14). For example, when the desired product is the minor diastereomer in a forward asymmetric synthesis, it could first be prepared using racemic synthesis then resolved by asymmetric retro-aldol. Also, very often only one

enantiomer of catalyst is readily available. Therefore, the forward aldol reaction only provides access to one enantiomer. If the synthesis of the racemic aldol adduct is facile, the racemic adduct may be subjected to retro-aldol reaction to gain enantioenrichment. The same chiral catalyst in principle should kinetically resolve the racemate therefore provide the complementary aldol enantiomer.

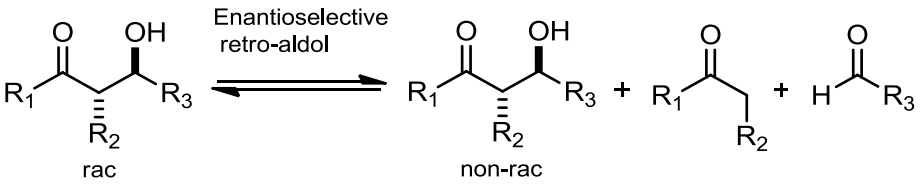
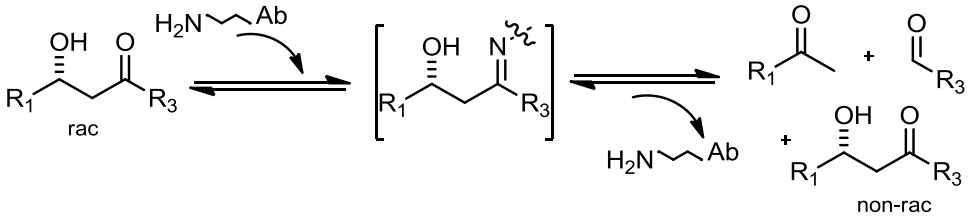


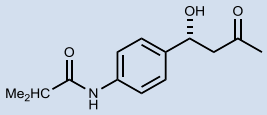
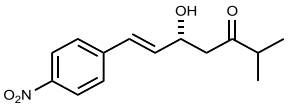
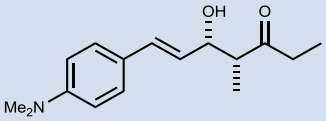
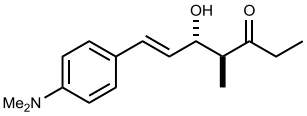
Figure 14. Enantioselective Retro-Aldol Reaction

However, this potentially powerful approach has not seen much development and there are only a handful of examples. Many factors may have contributed to the current underdeveloped state of the asymmetric retro-aldol reaction. Catalysts engineered for forward reaction were designed to avoid promoting retro-aldol reactions. Stereoselectivity could be a challenge, L-proline and its derivatives representing the most studied organo catalyst have been shown not to catalyze retro-aldol reaction enantioselectively.[36]

A major class of asymmetric retro-aldol reaction is enzymatic. Barbas, Lerner and co-workers used aldolase antibodies 38C2 and 33F12 to resolve racemic aldol substrates.[37] By selectively catalyzing retro-aldol reactions of one enantiomer, racemic aldol adducts were resolved to produce enantiomerically pure materials (Table 1).[37] The method was also demonstrated as a practical means to prepare enantiopure starting material in the total synthesis of epothilones.[38]

Table 1. Barbas and Lerner's Anti-Body Catalyzed Retro-Aldol Reaction (selected entries)



Product	Conversion (%)	ee (%)
	52	>99
	51	>99
	59	>99
	50	58

Small molecules have been reported to catalyze enantioselective retro-aldol reaction. Matsunaga, Masakatsu, and co-workers reported a kinetic resolution in a retro-nitroaldol (retro-Henry) reaction. This reaction was catalyzed by mixed organo La–Li heterobimetallic complexes to afford highly enantioenriched material.[39]

Examples of using retro-aldol reactions to generate enantioenriched fragments from racemic aldol adducts have been reported. Breslow and co-workers reported a series of tetrahydroquinoline based pyridoxal-like catalysts.[40] These catalysts were designed to have the amine held rigidly away to modulate the intrinsic transamination reactivity of their parent catalyst. Compounds **17** and **18** were able to catalyze enantioselective retro-aldol reaction on a mixture of 1-methyl-2-phenyl-serine diastereomers (Figure 15). Moderate enantiomeric

excess was observed in the *alanine* generated from the retro-aldol process. However, the potentially much more useful enantioenrichment of the starting aldol adducts was not reported.

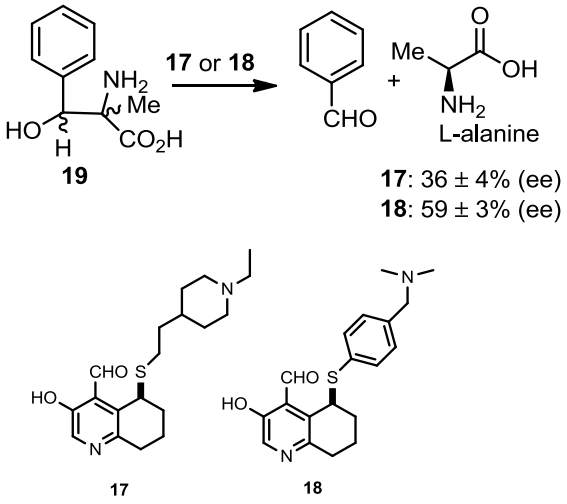
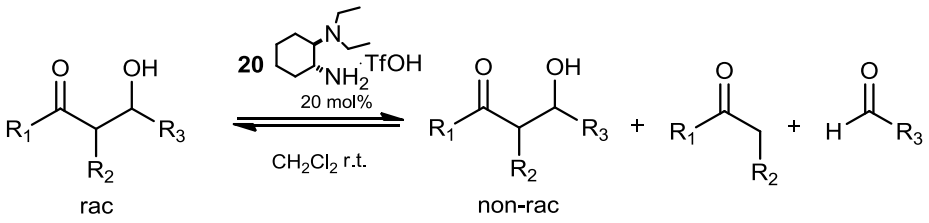
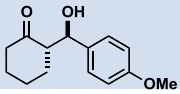
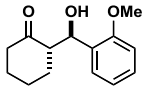
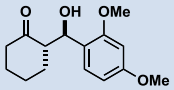
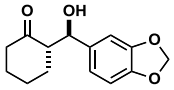
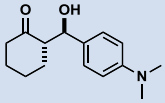
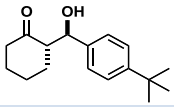
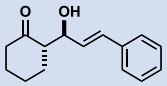
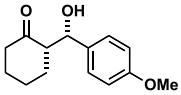
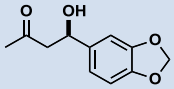
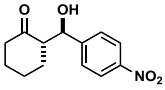
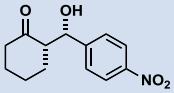


Figure 15. The Retro-Aldol Reaction of **19** Catalyzed by Pyridoxal-like Catalysts

To date, the only asymmetric retro-aldol reaction catalyzed by an enantiopure organocatalyst was reported by Cheng and co-workers.[41] They used a primary-tertiary-diamine catalyst (Table 2) to effect kinetic resolution on a series of racemic aldol adducts. The reaction worked well on aldol adducts derived from electron rich aldehydes (entries 1-7 & 9); however, the reactions were sluggish on adducts from electron-poor aldehydes (entries 10 & 11). Notably, the *syn*-aldol diastereomer was also demonstrated to be a viable substrate (entry 8). The diastereomeric ratio of the recovered starting material was little changed in all cases.

Table 2. Cheng's Catalytic Kinetic Resolution

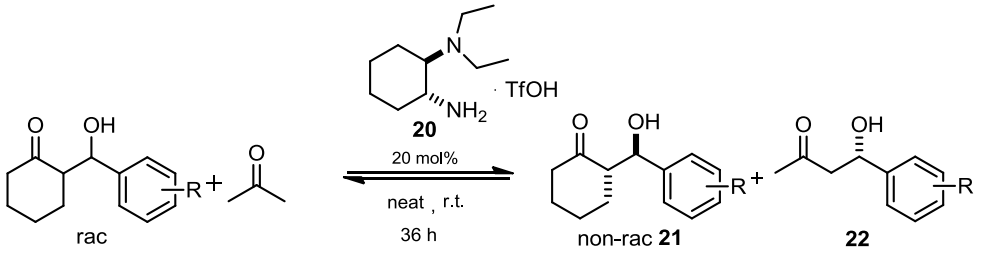


Entry	Product	t(h)	Yield (%)	anti/syn	ee(%)
1		8	48	98 : 2	99
2		12	46	98 : 2	95
3		12	43	94 : 6	96
4		9	41	98 : 2	98
5		6	40	99 : 1	>99
6		24	47	95 : 5	97
7		12	45	95 : 5	93
8		22	33	99 : 1	98
9		36	45	-	91
10		36	35	98 : 2	50
11		36	16	95 : 5	18

Note: Racemic anti-aldol adducts used as starting material except in entries **8 and 11** where syn-aldol were adducts used

Apart from retro-aldol reactions, enantioselective transfer-aldol reactions were also demonstrated (Table 3). Because **20** catalyzes both the forward and reverse aldol reaction, addition of a reactive ketone could trap the in situ generated aldehyde. This displacement of aldehyde would shift the equilibrium to favor the retro-aldol reaction. Upon successful application, they observed net transfer-aldol reaction when acetone was used as the reactive ketone donor. The originally sluggish substrates were able to proceed much more selectively under these conditions. The aldol **22** was, as expected, enantiomericlly enriched.

Table 3. Cheng's Transfer-Aldol Reactions



Entry	R	Yield (%) 21	anti/syn 21	ee (%) 21	Yield (%) 22	ee (%) 22
1	4-NO_2	50	98:2	98	50	78
2	2-NO_2	48	98:2	98	50	83
3	4-NO_2	46	89:11	94	50	11

Note: Racemic anti-aldol in entries **1** and **2**, racemic syn-aldol in entry **3**, heating at 50 ^{o}C in entry **3**.

An enamine transition state model similar to the forward aldol reaction was proposed to account for the stereoinduction. They reasoned that the shown configurations (Figure 16)

were kinetically more favored hence leaving the other enantiomer enriched through the retro-aldol process.

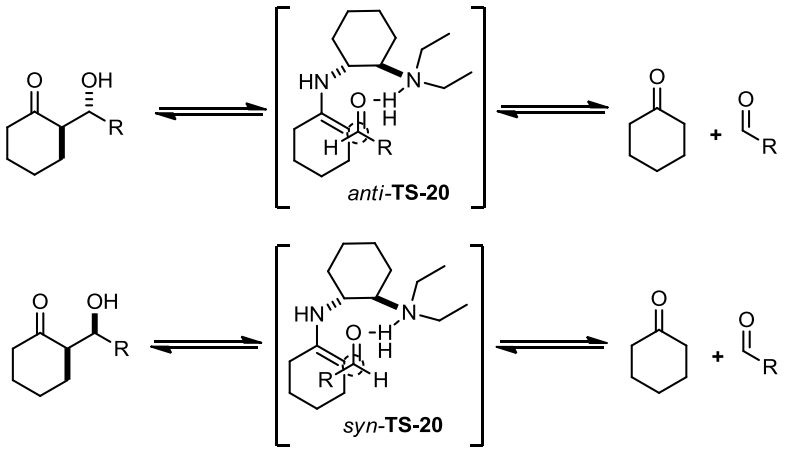


Figure 16. Proposed Transition State of Cheng's Retro-Aldol reaction

It was proposed that an asymmetric retro-aldol reaction might be utilized to prepare the non-Felkin first aldol adducts **3-AA** and **3-SA**. In the enantioselective synthesis of **3-AS (**Figure 6**)**, researchers identified that highly enantioenriched **3-AA** was a minor product (<5 %). Given the very high diastereoselectivity in favor of **3-AS**, this procedure was obviously impractical in producing enantioenriched **3-AA**.

As discussed above, the enantioselective retro-aldol reaction, could serve as a method to resolve racemic aldols. Although **3-AA** was a minor product from the reaction of **1** and (±)-**2** catalyzed by L-proline or **12**, its enantioselective formation implies that the transition state leading to it is accessible with these organocatalysts through the enamine catalytic cycle. In principle, the retro-aldol reaction on **3-AA** catalyzed by L-proline should be enantioselective (Figure 17). Such a process could provide access to enantioenriched **3-AA** and **3-SA** (via isomerization). Because racemic **3-AA** is easily prepared on large scale, a preparative method to obtain **3-AA** and **3-SA** would be in hand.

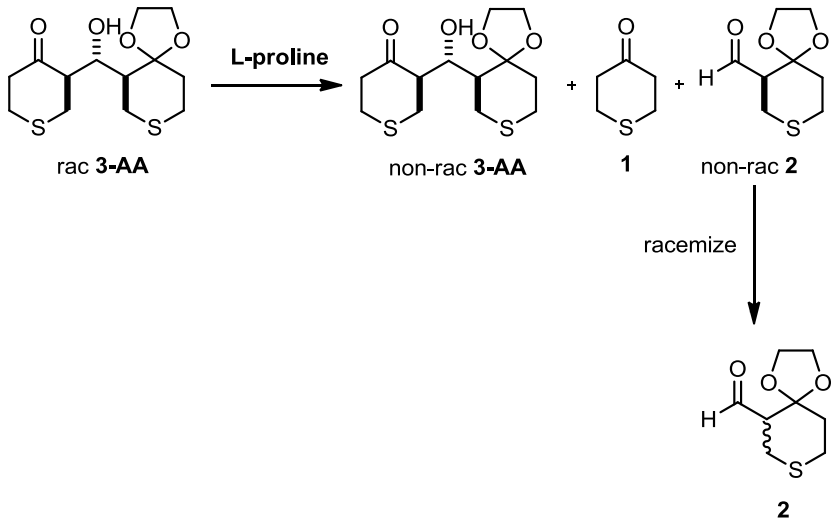


Figure 17. Proposed Enantioselective Retro-Aldol Reaction of **3-AA**

On a practical aspect, promoting the reversal of aldol reaction on **3-AA** is highly possible. In the forward synthesis of **3-AS** catalyzed by L-proline, 56% yield was obtained only when large amount of **1** (6 equiv to **2**) was used to drive the equilibrium in favoring the product. It is well known that in a combination reaction, higher concentration favors the product. The high concentration (**2** = 1 M) required to bring up the yield also suggested potential of reversing the aldol when lower concentration of product was subjected to the catalyst. In summary, the low equilibrium constant of the L-proline catalyzed synthesis of **3-AS** and **3-AA** made inducing retro-aldol reaction a reasonable plan.

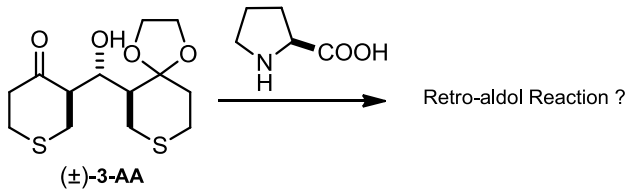
To explore this hypothesis, a new project unfolded. A detailed discussion of the experimental approach and interpretation of results is presented in the *Results and Discussion* chapter.

RESULTS AND DISCUSSION

2.1 Preliminary Trials of Retro-Aldol Reaction

Preliminary experiments were carried out to test retro-aldol reactivity of **3-AA** in the presence of L-proline and if retro-aldol were observed, determine if the reaction was enantioselective. Following the published procedure, reaction of silyl ether **1-TMS** with aldehyde **2** gave a 3:1 mixture of racemic **3-SA** and **3-AA**, respectivelly.[9,10,11] The adducts were readily separated by a combination of fractional crystallization and chromatography.

Table 4. Attempted Retro-Aldol Reactions of (±)-**3-AA** at Room Temperature



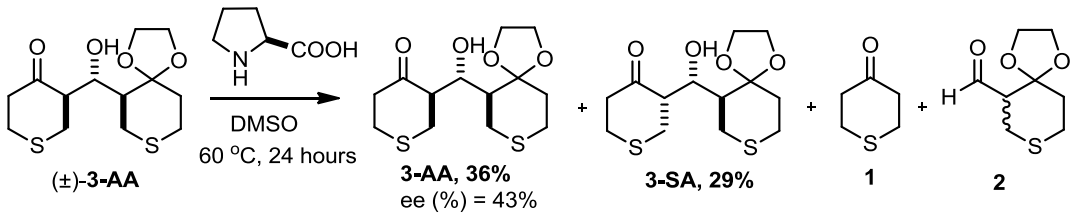
(±)-3-AA

Entry	Solvent	[a] L-proline (equiv)	Time (d)	Retro-Aldol Reaction
1	DMSO	1	1	no
2	DMF	0.6	4	no
3	MeOH/H_2O (3:1)	3	2	no
4	EtOH/H_2O (3:1)	3	3	no
5	THF/H_2O (3:1)	3	4	no
6	DMSO/H_2O (3:1)	3	5	no

Reaction conditions: racemic **3-AA** (0.2 M), stirred at room temperature with L-proline. [a] Equivalents with respect to **3-AA**.

At room temperature, (±)-**3-AA** was mixed with L-proline in DMSO or DMF to induce retro-aldol reaction. However, even after prolonged reaction time (Table 4, entries 1 & 2), little change was observed. The absence of aldehyde **2** in the ^{1}H NMR spectrum of the crude product suggested that retro-aldol reaction did not occur. Starting materials were recovered after work up in nearly quantitative yield. Similar results were obtained with less polar solvents. Due to the excellent solubility of L-proline in water, organic solvents with added water were tested (Table 4, entries 4-7). However, despite complete dissolution of L-proline in these mixed solvents, no retro-aldol reaction was observed under these conditions even after several days.

Figure 18. The L-proline Catalyzed Retro-Aldol Reaction of (±)-**3-AA** at 60 °C

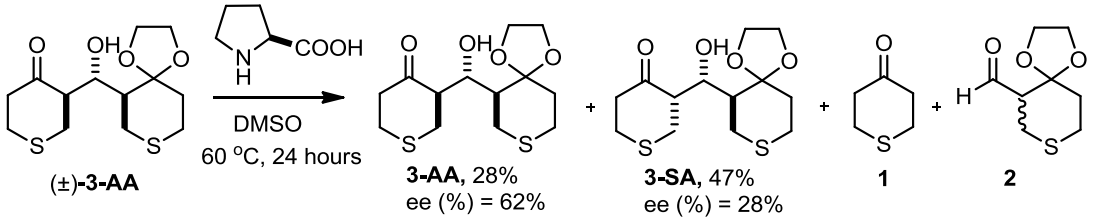


Reaction conditions: **3-AA** (0.12 M) and L-proline (0.11 M) mixed and stirred in dry DMSO at 60 °C; yield based on ^{1}H NMR using an internal standard; ee determined by chiral phase HPLC.

To cope with the observed low reactivity, reactions at high temperature were investigated. A reaction at 60 °C for one day afforded a crude product that, after work up, suggested consumption of starting material. The presence of aldehyde **2** and ketone **1** in the ^{1}H NMR spectrum of the crude product confirmed that retro-aldol reaction had taken place. Analysis of the recovered **3-AA** by chiral phase HPLC revealed the remaining **3-AA** was enantiomericlly enriched (Figure 18). This result established the feasibility of inducing enantioselective retro-aldol reaction with L-proline.

Closer inspection of the crude product suggested that a large amount of **3-SA** was also present. An obvious question at this point was if the **3-SA** was enantioenriched. Given that **3-SA** accounted for a significant portion of the product, the enantiomeric excess of **3-SA** became critical in determining the overall efficiency of the enantioselective process.

Figure 19. Retro-aldol Reaction of (±)-**3-AA** Afforded Enantioenriched **3-AA** and **3-SA**



Reaction conditions: **3-AA** (0.05 M), L-proline (0.15 M) and water (0.75M) mixed and stirred in DMSO at 60 °C; yield based on isolated mass; ee determined by chiral phase HPLC.

Using chiral phase HPLC, the **3-SA** was found to be enantioenriched, although with lower ee compared to that of **3-AA** (Figure 19). As discussed above, **3-AA** and **3-SA** are related by keto-enol tautomerization and can be isomerized under thermodynamic control by imidazole, DMAP or other amine bases. The predominant product of L-proline catalyzed aldol coupling of **1** and **2**, is **3-AS**. Therefore, the **3-SA** generated was likely the result of isomerization of **3-AA** rather than from a retro-aldol followed by re-aldol reaction. Two possible hypotheses were considered to account for the enantioenrichment of **3-SA**, one being isomerization of non-racemic **3-AA**, and enantioselective retro-aldol reaction of **3-SA**.

2.2 The Isomerization Process of 3-AA and 3-SA

A time course study on the progress of the L-proline catalyzed retro-aldol reaction was performed to probe the development of enantioenrichment and the possible isomerization process between **3-AA** and **3-SA** (Table 5).

Table 5. Time Course of the Retro-Aldol Reaction Starting from **3-AA** or **3-SA**

Entry	**Starting material**	**Time (day)**	[a] **Yield 3-AA (%)**	[b] **ee 3-AA (%)**	[a] **Yield 3-SA (%)**	[b] **ee 3-SA (%)**
1	(±)-**3-AA**	1	25	59	45	30
2	(±)-**3-SA**	1	20	31	66	11
3	(±)-**3-AA**	4	15	74	33	65
4	(±)-**3-SA**	4	16	72	40	52
5	(±)-**3-AA**	10	10	91	21	75
6	(±)-**3-SA**	10	10	96	21	79

Reaction conditions: **3-AA** or **3-SA** (0.05 M), L-proline (0.15 M) and water (0.75M) mixed and stirred in DMSO at 60 °C. [a] Based on isolated mass, [b] Determined by chiral phase HPLC.

A few trends were reflected in the results in Table 7. Starting from either **3-AA** or **3-SA,** an ca. 2:1 mixture of **3-SA** and **3-AA**, respectively was obtained after prolonged reaction time (Table 5, entries 5 and 6). This observation suggested that a thermodynamic equilibrium between **3-SA** and **3-AA** occurs in parallel with the retro-aldol reaction. Additionally, the observed 2:1 ratio is very similar to the equilibrium ratios measured for the isomerization catalyzed by imidazole in a variety of solvents.[12]

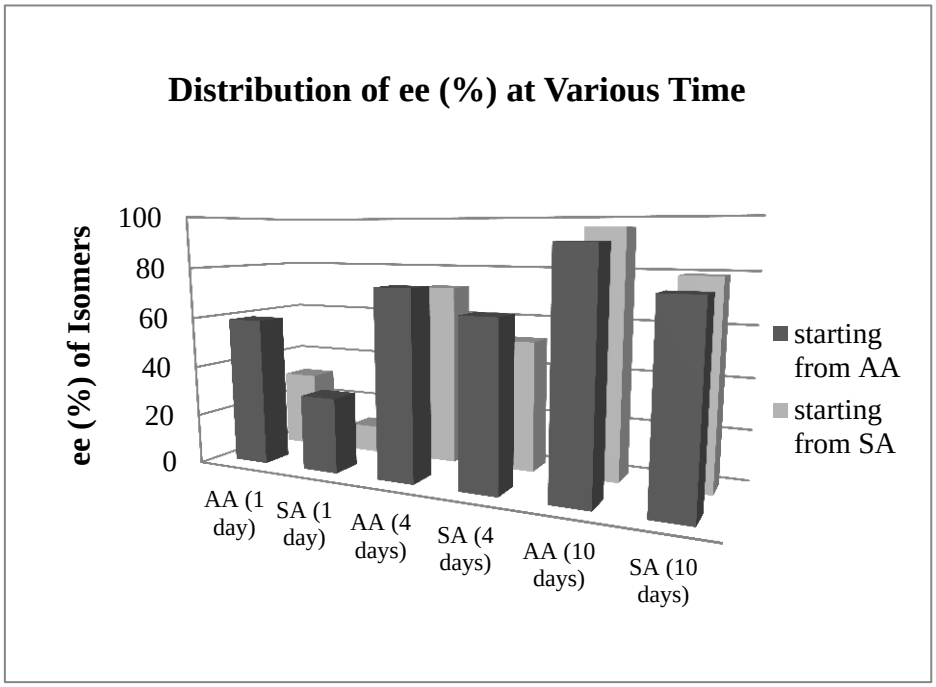
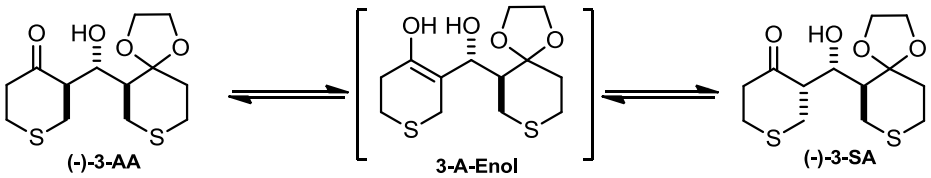


Figure 20. Evolution of Enantioenrichment of **3-AA** and **3- SA**

It was observed that regardless of whether the reaction started with **3-AA** or **3-SA**, the enantiomeric excess of **3-AA** was higher than that of **3-SA** at any given point. Meanwhile, all reactions starting from **3-SA** had a lower conversion compared to their counterparts, starting from **3-AA** (Figure 20). Both of these results indicated that **3-AA** underwent the retro-aldol reaction faster than **3-SA.** However, whether **3-SA** underwent enantioselective retro-aldol at all, lacked definitive evidence. As mentioned above, the enantioenrichment of **3-SA** can be attributed to two sources: 1) continuous isomerization from enriched **3-AA**; 2) enantioselective retro-aldol of **3-SA**. It is unclear whether enrichment of **3-SA** is a combination of both processes or solely the outcome of isomerization.

Table 6. Retro-Aldol Reactions on Highly Enantioenriched **3-AA** and **3-SA**



Entry	Substrate ee & Concentration	Time	3-SA/3-AA Ratio	[a] ee 3-AA	[a] ee 3-SA	[b] Yield (%)
1	(-)-**3-AA** = 0.033 (M) ee (%) = 94%	24 h	1.1 : 1	99%	95%	80
2	(-)-**3-SA** = 0.033 (M) ee (%) = 94%	24 h	1.9 : 1	99%	94%	91

Reaction conditions: **3-AA** or **3-SA,** L-proline (0.9 M) and water (0.45 M) mixed, stirred at 60 °C. [a] ee of recovered **3-AA** and **3-SA** determined by HPLC chiral column. [b] Based on isolated mass of **3-SA** and **3-AA**

To better focus on the isomerization reaction, highly enantioenriched (-)-**3-AA** and (-)-**3-SA** (94% ee) were separately subjected to the retro-aldol reaction (Table 6). At low conversion, a significant amount of the other diastereomer was generated via isomerization; and the diastereomers, produced by isomerization, were observed to have an ee equal to or higher than that of the starting material.

In agreement with the results from reactions starting with racemic substrates, the ee enhancement of **3-AA** was significantly more than that of **3-SA** regardless of the starting diastereomer. After 24 hours, the reaction that started with (-)-**3-AA** gave a 1.1:1 mixture of (-)-**3-SA** (95% ee) and (-)-**3-AA** (99% ee), respectively, in 80% yield (Table 6, entry 1). By comparison the reaction starting with (-)-**3-SA** gave, after 24 h, a 1.9:1 mixture of (-)-**3-SA**

(94% ee) and (-)-**3-AA** (99% ee), respectively, in 91% yield (Table 6, entry 2). Thus, the reaction starting with (-)-**3-SA** had a significantly lower conversion (9%) than that starting with (-)-**3-AA** (20%) but in both cases the majority of the ee enhancement occurred in (-)-**3-AA** with little change in the enantiopurity of (-)-**3-SA**. In contrast, the reaction starting with (-)-**3-SA** had reached equilibrium with (-)-**3-AA** within 24 h whereas the isomerization of (-)-**3-AA**was only ca. 80% complete in the same time. These results suggest that the L-proline catalyzed isomerization of (-)-**3-SA** is faster than that of (-)-**3-AA** and that enantioselective retro-aldol of (-)-**3-SA** under these conditions is negligible.

2.3 Optimization of the Reaction Conditions

2.3.1 Solvent Screening and the Effect of Water Additive

The enantioselective retro-aldol reaction was observed in a variety of solvents, with DMSO giving the best selectivity. Having a small amount of added water was found to be beneficial for the retro-aldol reaction both in terms of rate and selectivity.

Water is well-known to affect L-proline mediated aldol reactions. In 2004, [42] Pihko and co-workers reported rate acceleration with the addition of water. A few weeks after Pihko's paper, Ward and Jheengut published a related study where significantly increased conversions were observed in some (but not all) reactions when 5 equivalents of water were added.[14] The observation that water would accelerate the aldol reaction is counter-intuitive given that water would disfavor enamine formation in the catalytic cycle (Figure 21). [43,44]

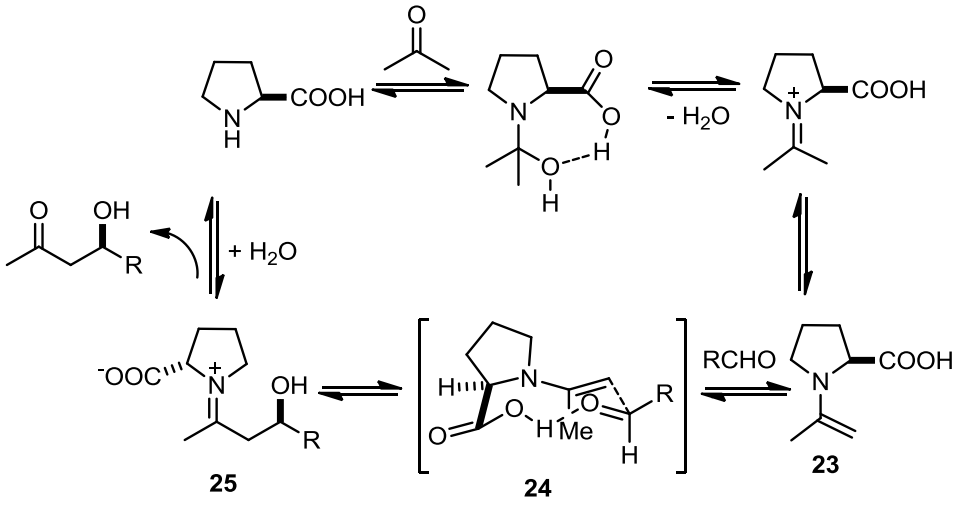


Figure 21. Mechanism of the L-Proline Catalyzed Aldol Reaction[30]

Armstrong and Blackmond studied the mechanistic role of water in proline catalyzed aldol reactions. They identified the opposing effects of suppressing both the productive enamine cycle and a parasitic off–cyc le, that drains L-proline and aldehyde into

oxazolidinone and oxazolidine byproducts (Figure 22). They found that when L-proline and an aromatic aldehyde were mixed, oxazolidinone **27** was formed reversibly. Also, in the cases of electron deficient aromatic aldehydes, **26** can undergo decarboxylation followed by addition of another molecule of aldehyde to form oxazolidine **29** irreversibly. Both processes would lower the concentration of the proline catalyst, thereby affecting the rate or progress of the catalyzed reaction. By Le Chatelier's principle, water suppresses the formation of iminium ions **23** and **26**. Depending on the relative concentration of **23** and **26**, the net aldol rate can benefit from addition of a small amount of water.[45]

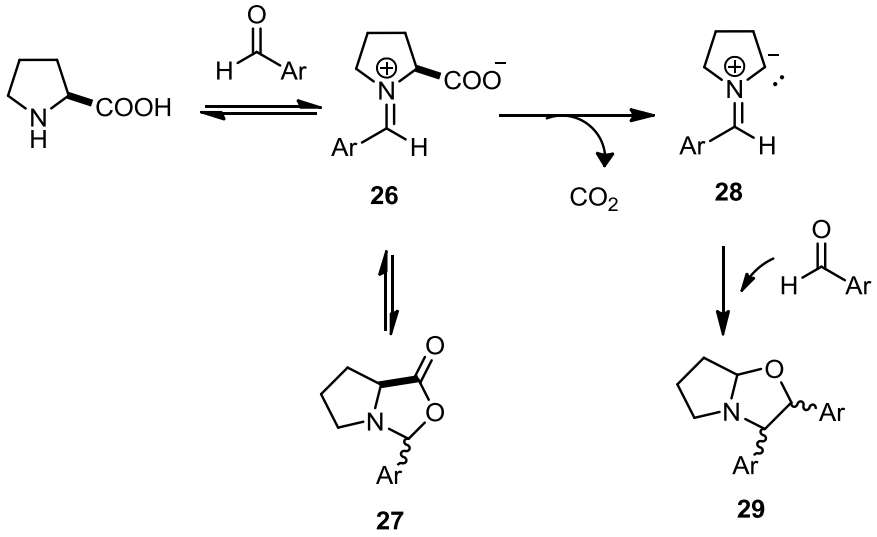


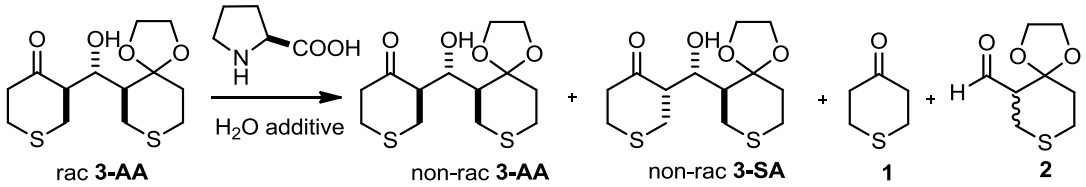
Figure 22. Off-Cycle Process Forming Oxazolidinone and Oxazolidine

Addition of five equivalents of water to L-proline was found to largely increase the apparent enantioselectivity of the retro-aldol reaction (Table 7, entries 1 & 2). Increasing to 10 equivalents of water did not affect much change but demonstrated a high tolerance of the reaction towards moisture (Table 7, entry 3). Using a mixture of ethanol and DMSO as solvent, the beneficial effect of water was even more dramatic. Reactions done without added

water proceeded faster but with much lower selectivity (Table 7, entry 4). An increase in the apparent enantioselectivity was observed on adding one to five equivalents of water (Table 7, entries 5 & 6); however, additional water did not improve the result (Table 7, entries 7).

The combined ee (Comb ee) parameter is used in Table 7 and later tables. This value is computed based on enantiomer ratios (er) and mole fractions (mf) of **3-AA** and **3-SA** in the product mixture to represent the overall ee of the products (combined ee = [$\mathbf{3\text{-}AA}_{er} \times \mathbf{3\text{-}AA}_{mf}$ + $\mathbf{3\text{-}SA}_{er} \times \mathbf{3\text{-}SA}_{mf} - 1$] ÷ [$\mathbf{3\text{-}AA}_{er} \times \mathbf{3\text{-}AA}_{mf}$ + $\mathbf{3\text{-}SA}_{er} \times \mathbf{3\text{-}SA}_{mf}$ + 1]). This description is useful because of the enriched enantiomers of **3-AA** and **3-SA** are connected through the isomerization pathway discussed above. In other words, the combined ee is equivalent to the ee of the product if the **3-AA**/**3-SA** product mixture was isomerized to a single diastereomer (either **3-AA** or **3-SA**).

Table 7. The Effects of Solvent and Water on the Retro-Aldol Reaction



Entry	Solvent	Temp (°C)	Water (equiv)	Time (h)	[a] Yield (%)	[b] Comb ee (%)	[c] Selectivity factor
1	DMSO	70	0.0	40	43	36	2.4
2	DMSO	70	5.0	40	51	52	5.5
3	DMSO	70	10	40	52	51	5.7
4	[d]EtOH/DMSO	60	0	96	10	80	2.3
5	[d]EtOH/DMSO	70	1	70	12	89	3

6	[d]EtOH/DMSO	70	5	70	28	94	7
7	[d]EtOH/DMSO	70	10	70	32	88	6
8	DMSO	70	5	70	34	95	9.9
9	EtOH	70	5	70	22	75	3
10	EtOH	70	10	70	33	57	3
11	DMSO	70	5	48	40	76	7
12	2-Propanol	70	5	48	30	71	4
13	DMF	70	5	48	41	61	4
14	DMF	70	0	48	26	50	2
15	DMSO	40	5	115	55	38	4
16	Acetone	40	5	115	no reaction	5	n.d.

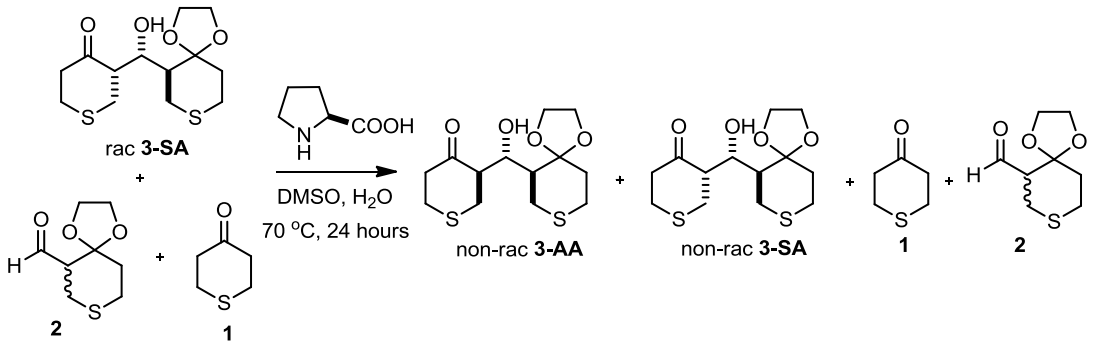
Reaction conditions: **3-AA** (0.05 M); L-proline (0.075 M in entries **1**-**3**; 0.15 M in entries **4**-**16)**; water; stirred and heated. [a] Combined mass of recovered **3-SA** and **3-AA**, (for entries **5-10**, determined by ^{1}H NMR using an internal standard. [b] Combined ee based on the weighted ee's of the recovered **3-AA** and **3-SA** determined by chiral phase HPLC. [c] The selectivity factor computed based on the combined ee and conversion (C = 1-yield) according to the equation: $s = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$. [d] EtOH/DMSO 1:1 (v/v).

Among the above studies, DMSO was found to be the optimum solvent for the reaction. DMSO with EtOH as co-solvent gave results similar to those with DMSO alone but provided an additional benefit of higher solubility of L-proline. This property was useful in optimization and mechanistic study when higher concentrations of L-proline were employed. Other solvents showed inferior selectivity or low reactivity (Table 7, entries 8-15).

2.3.2 L-Proline Stoichiometry and Reaction Order

Overall, the rate of the reaction was insensitive to the concentration of L-proline above a certain threshold. Sub-stoichiometric amounts of L-proline could not be used because the two by-products, the aldehyde **2** and the ketone **1**, deactivated the L-proline, presumably by forming adducts.

Table 8. The Effect of Added **1** and **2** on the Retro-Aldol Reaction

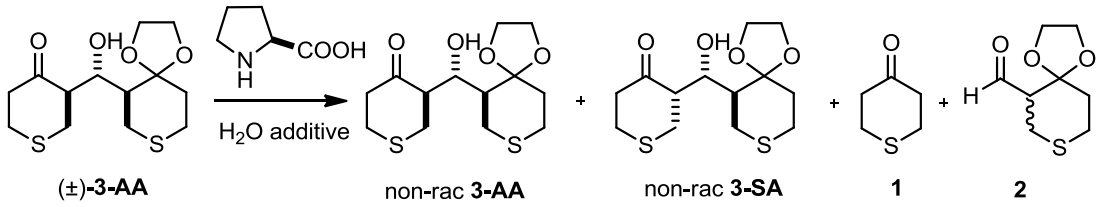


Entry	3-SA (M)	L-proline (M)	2 (M)	1 (M)	[a] Yield (%)	SA : AA Ratio
1.	0.05	0.05	0	0	58	2.3 : 1.0
2	0.05	0.05	0.06	0	100	2.0 : 1.0
3	0.05	0.05	0	0.05	75	2.7 : 1.0
	0.05	0.05	0.05	0.05	100	2.3 : 1.0

Reaction conditions: **3-SA**, L-proline, and water (0.25 M) in DMSO:EtOH (1:1), stirred and heated at 70 °C, [a] Based on ^{1}H NMR using an internal standard.

Reactions conducted with added aldehyde **2** were completely inhibited (Table 8, entries 2 and 4). The retro-aldol reaction occurred in the presence of added ketone **1** as evidenced by the presence of aldehyde **2** in the crude product, but at a significantly slower rate (Table 8, entry 3). In both cases, the isomerization reaction occurred as usual.

Table 9. The Effect of L-Proline Stoichiometry on Rate and Selectivity



Entry	3-AA (M)	L-proline (Equiv)	Temp (°C)	Time (h)	[a] Yield (%)	[b] Comb ee (%)
1	0.05	0.5	60	15	94	n.d
2	0.05	0.5	60	24	83	n.d
3	0.05	0.5	60	44	85	n.d
4	0.05	1.5	60	24	57	43
5	0.05	3	60	24	57	45
6	0.05	1.5	60	90	40	60
7	0.05	3	60	90	38	77
8	0.10	3	70	64	33	90
9	0.05	3	70	64	39	89

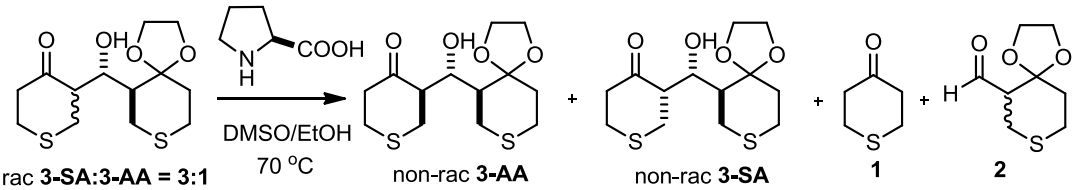
Reaction conditions: **3-AA,** L-proline and water (5 equivalents with respect to L-proline), in DMSO stirred at 60 °C. [a] Combined mass of recovered **3-SA** and **3-AA** (for entries **1-3**, based on ^{1}H NMR using an internal standard). [b] Combined ee of the recovered **3-AA** and **3-SA** determined by HPLC chiral column.

In accord with L-proline being deactivated by retro-aldol products **1** and **2** (Table 8), using sub-stoichiometric amounts resulted in catalyst quenching (Table 9, entries 1-3). Higher amounts of L-proline were needed to bring the reaction to practical conversion. Reactions with 1.5 and 3 equivalents of L-proline did not differ in their initial rates or selectivities

(Table 9, entries 4-5). At prolonged reaction time, three equivalents of L-proline appeared to give higher ee at similar conversions (Table 9, entries 6-7). A plausible explanation for this phenomenon is that the rate of retro-aldol reaction is zero-order to L-proline beyond a threshold concentration. Deactivation of L-proline (by the generated **1** and **2** as demonstrated in Table 8) lowers the L-proline concentration below the threshold more quickly with less initial catalyst.

At fixed stoichiometry, the concentration of reactants did not seem to affect selectivity at low conversion. With prolonged reactions times, lower concentrations gave slightly improved results (Table 9, entries 8 & 9).

Table 10. Kinetics of the Retro-aldol Reaction



Entry	[a] Conc. T_0 (M)	L-proline (M)	Time (h)	[b] Conc. T_1 (M)	k (mMol/h)
1	0.026	0.042	15	0.020	0.40
2	0.025	0.079	15	0.018	0.46
3	0.049	0.082	15	0.034	1.0

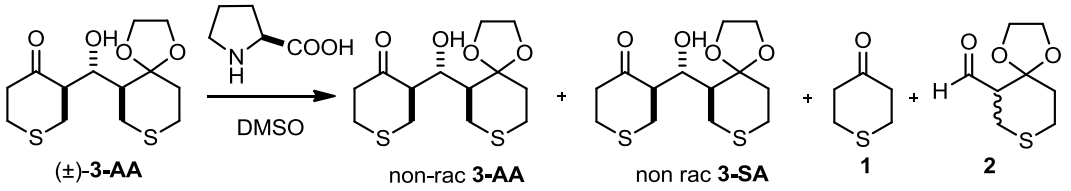
Reaction conditions: a 3:1 mixture of **3-SA** and **3-AA**, respectively, L-proline and water (5 equivalents with respect to L-proline) in EtOH/DMSO (1:1), stirred and heated at 70 °C and stirred, [a] Combined initial concentration of **3-SA** and **3-AA**. [b] Combined concentration of **3-AA** and **3-SA** after the indicated reaction, based on ^{1}H NMR using internal standard.

To test the reaction order for each reactant, a kinetic study was performed. The rates of retro-aldol from reactions with different reactant concentrations were measured and

compared (Table 10). Results showed that the rate of retro-aldol was independent of L-proline concentration. Entries 1 and 2 (Table 10) displayed very similar rates, although the L-proline concentration in entry 2 was nearly twice as of entry 1. On the other hand, the rate appeared to be 1st order in starting aldol **3-AA**/**3-SA** concentration. Comparing entry 2 with entry 3, the concentration of **3-AA** was doubled in entry 3 compared to entry 2 and the observed rate nearly doubled as well.

2.3.3 The Effect of Temperature

Table 11. The Effect of Temperature on the Retro-Aldol Selectivity



Entry	Temperature (°C)	Time (h)	[a] Yield (%)	[b] Comb ee (%)	[c] Selectivity Factor
1	40	115	55	38	3.8
2	50	44	64	39	8.1
3	60	44	63	48	16
4	70	24	58	58	17
5	100	7	31	79	5.0
6	80	40	34	90	7.7
7	70	70	34	95	9.9

Reaction conditions: **3-AA** (0.05 M), L-proline (0.15 M) and water (0.75 M) stirred at the indicated temperature. [a] Combined mass of recovered **3-SA** and **3-AA** (for entries 5-7 based on ^{1}H NMR using an internal standard). [b] Combined ee based on the weighted ee's of the recovered **3-AA** and **3-SA** determined by chiral phase HPLC. [c] The selectivity factor computed based on the combined ee and conversion (C = 1-yield) according to the equation: $s = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$.

The retro-aldol reaction rate only became practical with heating. From 40 – 70 °C, the retro-aldol reaction rate naturally increased but interestingly, the apparent enantioselectivity also increased (Table 11). At 100 °C， the reaction was even faster but occurred with low selectivity. Reactions at 80 °C were faster but moderately less selective than those at 70 °C. Therefore, 70 °C was chosen as the optimum temperature.

Comparison of ^{1}H NMR spectrums of the crude products from reactions at different temperatures did not reveal the presence of side products. Nonetheless, side reaction cycles need to be explored more extensively before a plausible reaction model can be developed.

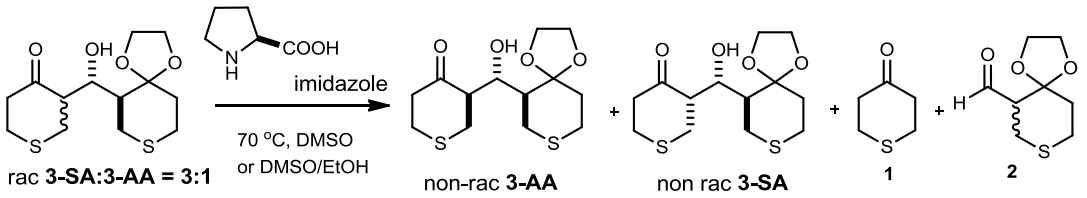
2.3.4 Enhanced Isomerization and Retro-Aldol Reaction

As discussed in section **2.2**, aldol adducts **3-AA** is the reactive species in the enantioselective retro-aldol reaction. If the isomerization process that exchanges **3-AA** and **3-SA** were fast enough, the observed enantiomeric excesses of **3-AA** and **3-SA** would be the same throughout the reaction. However, the **3-AA** was consistently found to be more enantioenriched than **3-SA**, suggesting that the isomerization and the retro-aldol reaction had comparable rates.

This relatively slow rate of isomerization imposed a limitation on the efficiency of the retro-aldol process. The slower exchange between **3-AA** and **3-SA** resulted in decreased concentration of the kinetically more reactive **3-AA** enantiomer and also a slower rate of enantioenrichment for **3-SA**. In principle, enhanced isomerization would allow more rapid regeneration of the reactive **3-AA** enantiomer, thereby increasing the efficiency of retro-aldol.

To explore this idea, the use of imidazole as an additive was tested because of its known role in catalyzing the isomerization between **3-AA** and **3-SA** (Section 1.1). The presence of 2 equivalents of imidazole resulted in an increased reaction rate (Table 12, entries 1 & 2). Noticeably, the difference in observed enantiopurities between **3-SA** and **3-AA** significantly reduced with added imidazole. The similar enantioenrichment for **3-AA** and **3-SA** suggested a faster isomerization, promoted by imidazole.

Table 12. Retro-Aldol Reactions of **3-SA/3-AA** with Varied Imidazole Concentrations



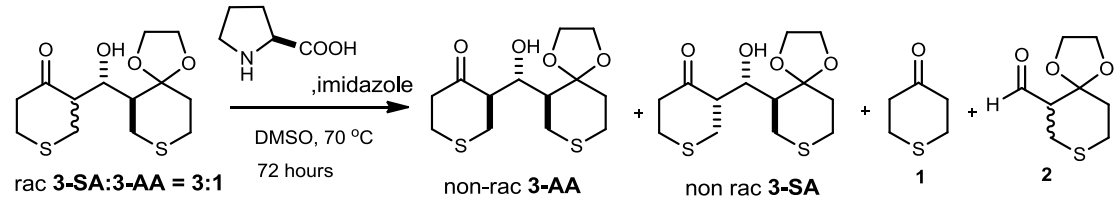
Entry	Time (h)	Imidazole (M)	[a] Yield (%)	Ratio SA:AA	ee (%) AA	ee (%) SA	[b] Comb ee (%)
1	48	0.0	49	2.3	75	58	63
2	48	0.11	44	1.9	78	72	74
3	48	0.25	45	2.0	83	82	82
4	48	0.42	43	1.9	84	84	84
5	70	0.0	41	1.9	83	74	77
6	70	0.25	36	1.8	89	90	90
[c]**7**	72	0.25	36	1.8	81	80	80

Reaction conditions: 3:1 mixture of **3-SA** and **3-AA** (0.05 M), L-proline (0.15 M), imidazole, and water (0.75 M) in DMSO, stirred at 70 °C. [a] Combined mass of recovered **3-SA** and **3-AA**, determined by ^{1}H NMR using an internal standard. [b] Combined ee based on the weighted ee's of the recovered **3-AA** and **3-SA** determined by chiral phase HPLC. [c] Reaction in a 1 : 1 mixture of DMSO/EtOH.

This faster isomerization, in accordance with the above mentioned hypothesis, led to a more efficient retro-aldol reaction. Reaction with 0.11 M and 0.25 M imidazole, despite showing closely matched rates, produced an increase in the overall ee of the product. Further increasing the concentration of imidazole to 0.42 M did not produce significant improvements in either the yield or ee of the product. A similar reaction in DMSO and EtOH as co-solvent was less selective (Table 12, entries 6 & 7).

Table 13. Retro-Aldol Reactions at Higher **3-SA**/**3-AA** Concentrations with Imidazole

Additive



Entry	Starting Material (M)	Imidazole (M)	[a] Yield (%)	Ratio SA:AA	ee (%) AA	ee (%) SA	[b] Comb ee (%)
1	0.05	0.25	35	2.0	91	88	88
2	0.1	0.25	34	2.1	95	90	92
3	0.1	0.55	31	1.8	96	93	94

Reaction conditions: 3:1 mixture of **3-SA** and **3-AA** (0.05 M), L-proline (0.15 M), imidazole, and water (0.75 M) in DMSO, stirred at 70 °C. [a] Combined mass of recovered **3-SA** and **3-AA**, determined by ^{1}H NMR using an internal standard. [b] Combined ee based on the weighted ee's of the recovered **3-AA** and **3-SA** determined by chiral phase HPLC.

Performing the reaction at higher concentration is beneficial in many ways. When the transformation needs to be done on scale, the reduced solvent adds economic gain and also eases processing, particularly with high boiling point solvents such as DMSO. Previous results suggested, in prolonged reaction, inferior selectivity was exhibited for reactions done at 0.1 M reaction compared to 0.05 M. Presumably, this was because certain side reactions were more favored at higher concentration, which caused faster loss of L-proline. Given that reaction was significantly shortened with added imidazole, higher concentration reactions with imidazole were explored (Table 13).

In the presence of imidazole, reaction at 0.1 M afforded similar performance compared to reaction at 0.05 M. Therefore, a more rapid reaction with imidazole additive allowed the use of higher concentrations, which will be beneficial in scaling up. In addition, the use of imidazole also affected some side reactions presumably due to the elevated pH. An increase in the elimination product **3-elim** (Figure 23) was observed, resulting in loss of starting material. With an optimum amount of imidazole, this loss of starting material appeared to be countered by the increased apparent selectivity. A new side product, the ketal-deprotected **2-d** (Figure 23)**,** was isolated from reactions with added imidazole. As expected, the amount of **2-d** generated was positively correlated to the concentration of imidazole additive.

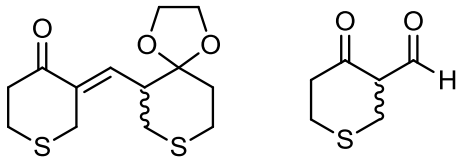


Figure 23. Retro-aldol Reaction Side Products

2.4 Application of the Retro-Aldol Reaction

2.4.1 Large Scale Reaction

The main goal of the project was to have access to high enantiopurity material on a reasonable scale. Table 14 presents a summary of results applying this reaction on a preparative scale. In general, the large scale reactions gave selectivities and yields similar to these observed on smaller scale. The highly flexible starting material combination allowed essentially any mixture of **3-SA** and **3-AA** to be used.

Table 14. Scale-Up of the Retro-Aldol Reaction

Entry	Starting Material	Time (h)	[a] Yield (%)	[b] ee (%) 3-AA	[b] ee (%) 3-SA	[c] Ratio
1	(±)-**3-SA**/**AA** (3.4: 1) 1.0 g	100	29	99	97	2.2
2	**3-AA**, ee = 71%, 0.14 g **3-SA**, ee = 57%, 0.36 g	48	65	89	89	2.4
3[d]	(±)-**3-SA**/**AA** (3.4: 1) 1.5 g	72	32	93	92	2.1

Reaction conditions: **3-AA**/**3-SA** (0.050 M in entries 1 and 2**,** 0.10 M in entry 3); L-proline (3 equivalents with respect to starting material) and water (5 equivalents with respect to L-proline), in DMSO stirred and heated at 70 °C. [a] Combined mass of recovered **3-SA** and **3-AA**, determined by ^{1}H NMR using an internal standard. [b] Determined by chiral phase HPLC. [c] The ratio of **3-SA** to **3-AA**. [d] Imidazole (0.25 M) was added along with other reactants.

The isomerization process allowed flexible use of any combination of **3-AA** and **3-SA** starting materials. Mixed **3-SA** and **3-AA** aldol products, obtained directly from the aldol

reaction of **1-TMS** with **2**, could be subjected to the retro-aldol reaction. Therefore, in just one added step from the racemic synthesis, **3-SA** and **3-AA** are now available in high enantiomeric excess. Moreover, non-racemic materials are also proper substrates, allowing further enrichment of enantioenriched **3-AA** and **3-SA**. By applying what was learned from an enhanced isomerization, a faster, more selective, and better synchronized reaction could be achieved with the addition of 5 equivalents of imidazole (Table 14, entry 3).

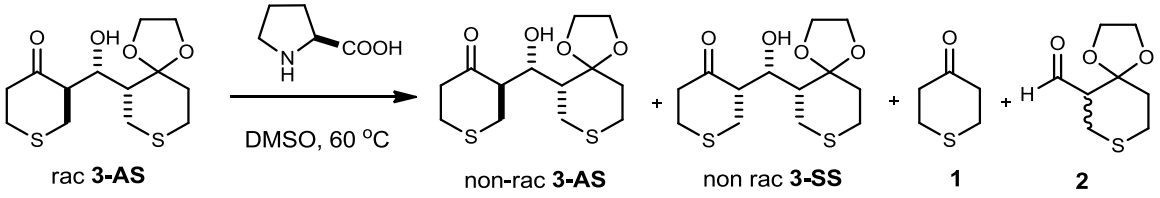
The crude product contained a mixture of **3-SA** and **3-AA** (ca. 2:1) alone with thiopyranone **1** and aldehyde **2**. The thiopyranone **1** can be removed from the crude product by extraction with warm water and (or) by sublimation under higher vacuum. Taking advantage of the much lower solubility of **3-SA**, much of the **3-SA** can be obtained by fractional recrystallization of the crude product from methanol. Utilizing the thermodynamic equilibrium between **3-AA** and **3-SA**, the yield of a particular isomer can be increased through cycles of isomerization catalyzed by bases such as imidazole.

Owing to its robustness, the scale-up of this reaction was straightforward. No exclusion of air or moisture was required. Heating at a temperature much lower than the boiling point of the DMSO removed the requirement of a condenser. Further scale-up should be achievable without much modification.

2.4.2 Applying Retro-Aldol Reaction on 3-AS

In the forward aldol coupling of **1** and **2** catalyzed by L-proline, **3-AS** was the major product (*d.r.* > 20). For the same reason as with **3-AA**, **3-AS** should undergo enantioselective retro-aldol reaction catalyzed by L-proline. To broaden the scope of L-proline catalyzed retro-aldol as well as to confirm the lessons learned from retro-aldol reaction of **3-AA** and **3-SA**, (±)-**3-AS** was subjected to the established retro-aldol condition.

Table 15. Enantioselective Retro-Aldol Reaction of **3-AS**



Entry	Starting Material	Time (h)	[a] Yield (%)	3-SS:3-AS Ratio	ee (%) 3-AS	ee (%) 3-SS	[e] Comb ee (%)
1	(±)-**3-AA**	24	75	[b] 1.7	[c] 62	[d] 28	41
2	(±)-**3-AS**	24	54	0.5	83	50	71
3	(±)-**3-AS**	48	39	1.1	94	62	78
4	(±)-**3-AS**	96	33	1.8	96	67	78

Reaction conditions: Starting material (0.05 M); L-proline (0.15 M) and water (0.75 M), in DMSO stirred at 60 °C. [a] Combined mass of recovered **3-AS** and **3-SS** (for entry 1, the combined mass of recovered **3-SA** and **3-AA** determined by ^{1}H NMR using an internal standard).[b] Determined by chiral phase HPLC), determined by ^{1}H NMR using an internal standard. [b] Determined by chiral phase HPLC. [b] The ratio of **3-SA**:**3-AA**; [c] ee of **3-AA**; [d] ee of **3-SA**; [e] The combined ee of both diastereomers computed from the weighted ee's of the individual diastereomers determined by chiral phase HPLC.

After 24 hours, the crude product from the reaction starting with **3-AS** was found to contain enantioenriched **3-AS** and **3-SS**, in which (+)-**3-AS** and (-)-**3-SS** were the enantiomers in excess (Table 15, entry 2). In the forward reaction, (-)-**3-AS** was produced in

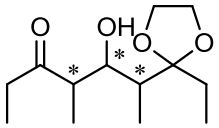
high ee. That the L-proline catalyzed retro-aldol reaction provided (+)-**3-AS** is consistent with the proposed principle. Because the transition state in the L-proline catalyzed reaction leading to (-)-**3-AS** is lower in energy, both in forward and reverse direction, the retro-aldol reaction pathway from (-)-**3-AS** has a higher rate compared to that from (+)-**3-AS**. Therefore, when racemic **3-AS** underwent retro-aldol reaction, the slow reacting enantiomer, (+)-**3-AS**, was enriched.

Presumably, a keto-enol tautomerization process was responsible for the generation of **3-SS**. It was clear that at 96 hours, the favored diastereomer via isomerization was **3-SS** (Table 15, entry 4). Compared to **3-AA** and **3-SA**, the rate of isomerization between **3-AS** and **3-SS** was slower (Table 15, entries 1 and 2). On the other hand, similar to **3-AA** and **3-SA** mixture, **3-SS** and **3-AS** have very different rates in the retro-aldol reaction. The consistently lower ee of **3-SS** compared to **3-AS** indicated that **3-SS** was less reactive towards retro-aldol.

As discussed in Section 2.34, a slow isomerization limits the efficiency of the retro-aldol reaction. This effect was more profound with **3-AS** and **3-SS**. When **3-AS** became highly enantioenriched, lacking an effective means to regenerate the reactive enantiomer of **3-AS**, the reaction essentially came to a halt (Table 15, entries 3, 4). Presumably, reagents such as imidazole would increase the efficiency by enhancing the isomerization.

2.4.3 Attempted Retro-Aldol Reaction on Acyclic Substrates

Recent research in the Ward Group has focused on developing selective aldol reactions using **4** as ketone donor. Similar to thiopyran-based aldol adducts **3**, the three stereogenic centers in **4** result in four possible diastereomers (Figure 24).



4

Figure 24. Acyclic Aldol Adducts **4** (* indicates stereogenic centers)

Encouraged by the enantioselective retro-aldol reaction on **3** series aldols, **4-AA** and **4-SA** were tested for L-proline induced retro-aldol reactivity. If similar results could be achieved, a way to access enantioenriched **4** series diastereomers would be possible.

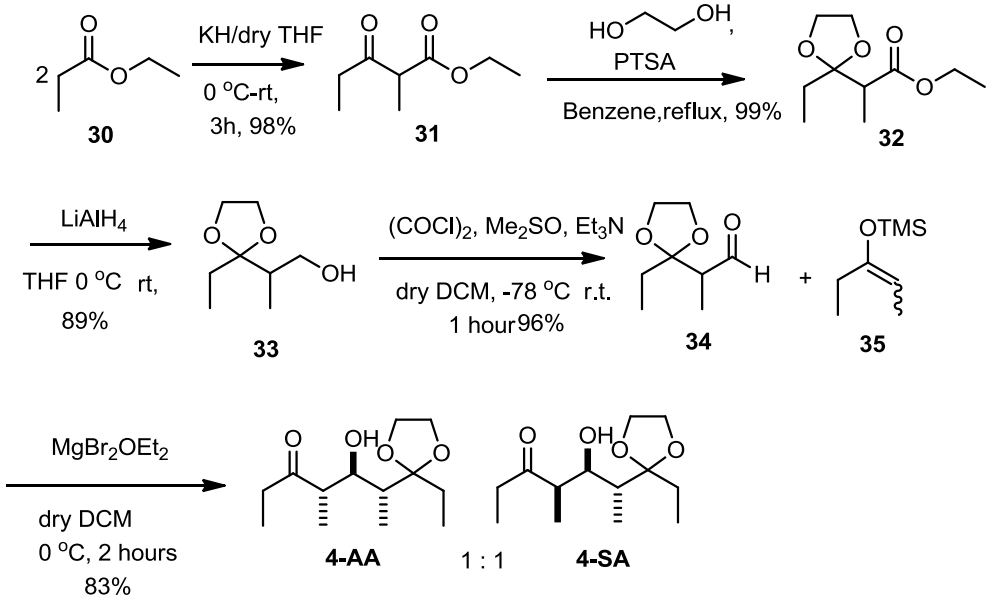
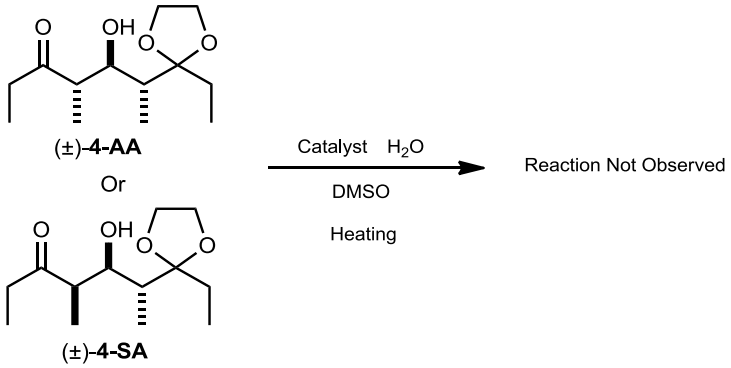
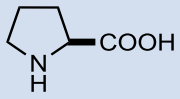
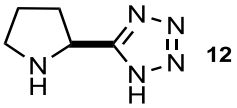
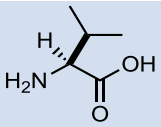
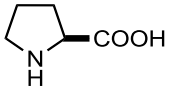
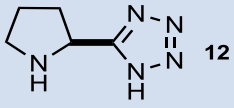


Figure 25. Outline of the Synthesis of racemic **4-AA** and **4-SA**

Aldehyde **34** was prepared from **30** following known procedures. [11,49,50] The ketone donor silly enol ether **35** was prepared from 3-pentanone and chlorotrimethyl silane following the well known procedure. The aldol coupling was done according to an unpublished procedure developed in the Ward Group (M. Biniaz and A. Karagiannis) to afford a separable 1:1 mixture of **4-AA** and **4-SA** (Figure 25).[51]

Table 16. Attempted Retro-Aldol Reaction on **4-AA** and **4-SA**



Entry	Starting Material	Catalyst	Temp (°C)	Time	[a] Conv (%)
1	(±)-**4-AA**		60	62 h	no reaction
2	(±)-**4-AA**	 **12**	60	62 h	no reaction
3	(±)-**4-AA**		60	62 h	no reaction
4	(±)-**4-SA**		70	7 days	no reaction
5	(±)-**4-SA**	 **12**	70	7 days	no reaction

Reaction conditions: **4-AA** or **4-SA** (0.10 M); catalyst (0.15 M) and water (0.75 M) mixed, stirred in DMSO. [a] Based on ^{1}H NMR of the crude product using an internal standard.

With the materials in hand, retro-aldol reactions were attempted on **4-AA** and **4-SA**. Similar to the thiopyran-based substrates, no reaction was observed at room temperature stirring with L-proline in DMSO. Heating was applied to induce reactivity (Table 16). However, the aldol adducts **4-AA** and **4-SA** were stable to these conditions (70 °C) for several days. Other catalysts such as L-valine and the tetrazole analogue **12** were tested; however, no reactivity was observed.

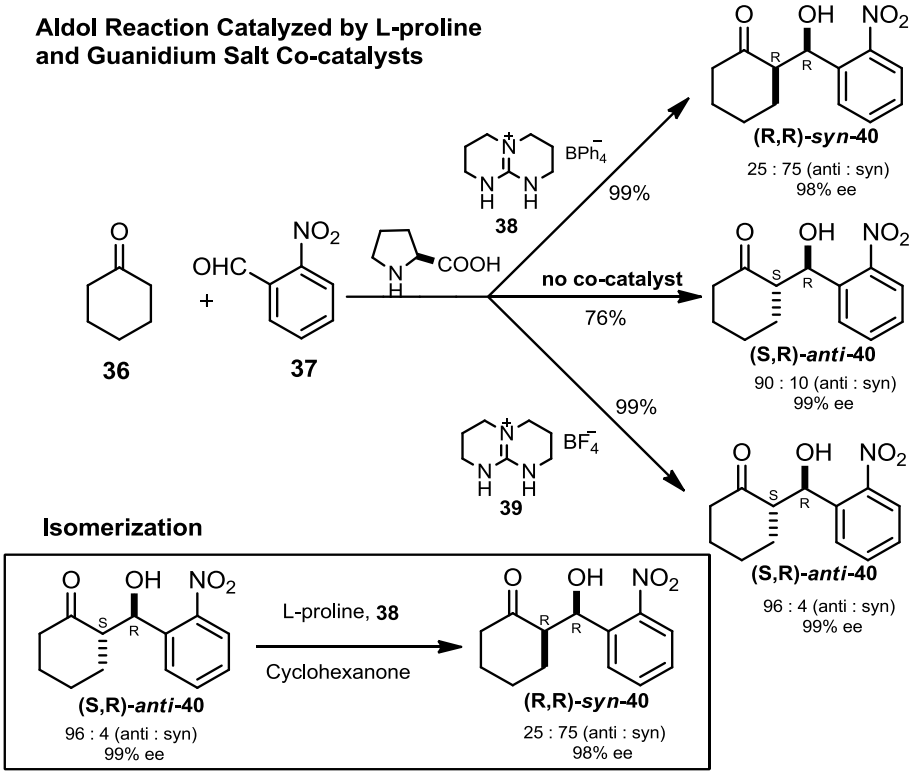


Figure 26. Amo and Concellon's Co-catalysts Promoted Proline Aldol Reaction and Isomerization.

The recent report by Amo and Concellon that certain co-catalysts (**38** and **39** on Figure 26) promoted their proline catalyzed direct asymmetric aldol reaction was of interest. Co-catalysts are often used to enhance reactivity and selectivity of a catalytic reaction. Amo and Concellon also found that the use of co-catalysts **38** and **39** either reinforced or reversed the diastereoselectivity of the aldol reaction. Depending on the counter anion of the achiral

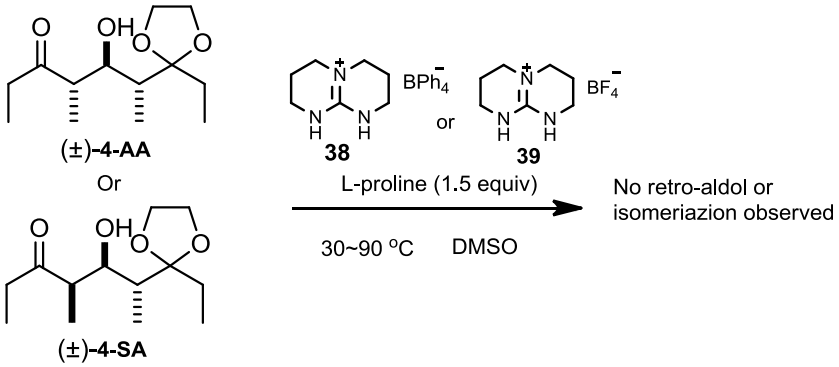
triazabicyclodecene salt, the co-catalyst and L-proline mixture could either be rendered *syn* selective or *anti* selective. Both co-catalysts were able to increase conversion without loss of ee.[46]

It was of particular interest to learn that the syn selective co-catalyst **38** with L-proline catalyzed the isomerization of ***anti*-40** to ***syn*-40**. Their study revealed that L-proline produced *anti*-products regardless of which co-catalyst was used, the apparent reversal of the *anti*-selectivity resulted from isomerization of ***anti*-40** to ***syn*-40** when **38** and L-proline were used.

Thus far, conditions for isomerization of the **4** series of aldol adducts have not been identified. An isomerization reaction is desired because it provides an alternative access to stereoisomers or increases yield of a particular isomer. The conditions that Amo and Concellon developed to epimerize **40**, seemed promising as a potential method to achieve isomerization of **4**.

The triazabicyclodecene salts **38** and **39** were prepared following the reported procedures.[46,47] Retro-aldol reactions were attempted with **38** or **39** as additive. However, no retro-aldol or isomerization reaction was observed on either **4-AA** or **4-SA** (Table 17).

Table 17. Attempted Retro-Aldol Reaction on **4-AA** and **4–SA** with Co-catalysts



Entry	Starting Material	[b] Co-catalyst	Temp (°C)	Time (hours)	[c] Yield
1	(±)-**4-AA**	**39** (1 equiv)	30	24	no reaction
2	(±)-**4-AA**	**38** (0.8 equiv)	40	48	no reaction
[a] **3**	(±)-**4-AA**	**38** (0.4 equiv)	90	15	no reaction
4	(±)-**4-SA**	**39** (0.8 equiv)	70	72	no reaction
5	(±)-**4-SA**	**38** (1 equiv)	70	72	no reaction

Reaction conditions: **4-AA** or **4-SA** (0.05 M); L-proline (0.075 M) and co-catalyst **38** or **39**, stirred in DMSO. [a] Water (0.75 M) as an additive; [b] Co-catalyst equivalents is with respect to starting material. [c] Based on ^{1}H NMR using an internal standard.

In Amo and Concellon's work, the forward aldol reaction co-catalyzed by L-proline and **38**/**39** was done without solvent in a large excess of ketone. To test if excess of ketone had a role in L-proline and co-catalyst activity, 3-pentanone was used as solvent. After 2 days at 60 °C, neither retro-aldol reaction nor isomerization occurred. A variety of solvents were tested. Starting material was fully recovered in all cases (Table 18**)**.

Table 18. Attempted Retro-Aldol Reaction on **4–SA** with Co-catalysts in Different Solvents

Entry	Starting Material	[a] Co-catalyst	Solvents	Temperature (°C)	[b] Yield
1	(±)-**4-SA**	**38** (0.5 equiv)	3-pentanone	60	no reaction
2	(±)-**4-SA**	**39** (0.8 equiv)	3-pentanone	60	no reaction
3	(±)-**4-SA**	**38** (0.5 equiv)	acetone	40	no reaction
4	(±)-**4-SA**	**39** (0.5 equiv)	acetone	40	no reaction
5	(±)-**4-SA**	**38** (0.4 equiv)	EtOH	70	no reaction
6	(±)-**4-SA**	**39** (0.5 equiv)	EtOH	70	no reaction
7	(±)-**4-SA**	**38** (0.4 equiv)	DMF	70	no reaction
8	(±)-**4-SA**	**39** (0.5 equiv)	DMF	70	no reaction

Reaction conditions: **4-SA** (0.05 M); L-proline (0.075 M) and co-catalyst **38** or **39** in the indicated solvent, heated at the indicated temperature. [a] Co-catalyst equivalents is with respect to starting material; [b] Based ^{1}H NMR using an internal standard.

It appeared that L-proline was not able to access the transition state of aldol/retro-aldol with acyclic substrates **4-AA** and **4-SA**. The ease of retro-aldol on thiopyran-based **3-AA** and **3-AS** stems from the fact that they are products from L-proline catalyzed aldol reactions; therefore, access to the relevant transition states was established. For **4-SA** and **4-AA**, the forward aldol reactions are not known to be catalyzed by L-proline. If L-proline was not able to form a productive catalytic pathway in the forward synthesis, the reverse process may not be feasible.

CONCLUSION

Central to the research in the Ward Group is the stereoselective aldol couplings of thiopyran based reactants to construct polypropionate chains. Enantioselective aldol reactions that proceed with (dynamic) kinetic resolution are a prominent feature of this strategy and allow the use of racemic reactants. However, the enantioselective preparations of two essential building blocks of this approach, **3-AA** and **3-SA**, requires the use of enantiopure aldehyde. Because the preparation of this aldehyde is not scalable, synthetic applications of these building blocks are limited. As a result, it was imperative to develop a new approach to access enantiopure **3-AA** and **3-SA**. The goal of this M.Sc project was to develop a simple and scalable method starting from racemic substrates.

The research project was inspired by a previous report that enantioenriched **3-AA** was a minor product in the organocatalyzed enantioselective aldol reaction of **1** with **2** to give **3-AS** (>99% ee). Therefore, considering the principle of microscopic reversibility, an L-proline catalyzed enantioselective retro-aldol reaction of **3-AA** was hypothesized.

Preliminary studies suggested the feasibility of promoting enantioselective retro-aldol reaction on **3-AA**. More in-depth studies revealed a thermodynamic equilibrium between **3-SA** and **3-AA**, occurred in parallel with the retro-aldol process. These studies also indicated that **3-AA** was much more reactive than **3-SA** in the retro-aldol reaction, and that the enantiomeric excess of **3-SA** originates from isomerization of enantioenriched **3-AA**. In accordance with those conclusions, addition of imidazole was shown to increase the rate of the overall retro-aldol due to its ability to catalyze the isomerization. A variety of reaction

parameters were optimized. The major product of the forward reaction, **3-AS**, was also subjected to the retro-aldol reaction, the opposite enantiomer, compared to the forward synthesis, was enriched. Unfortunately, enantioselective retro-aldol reaction of the acyclic **4-AS** and **4-SS** were not achieved, despite extensive experimentations.

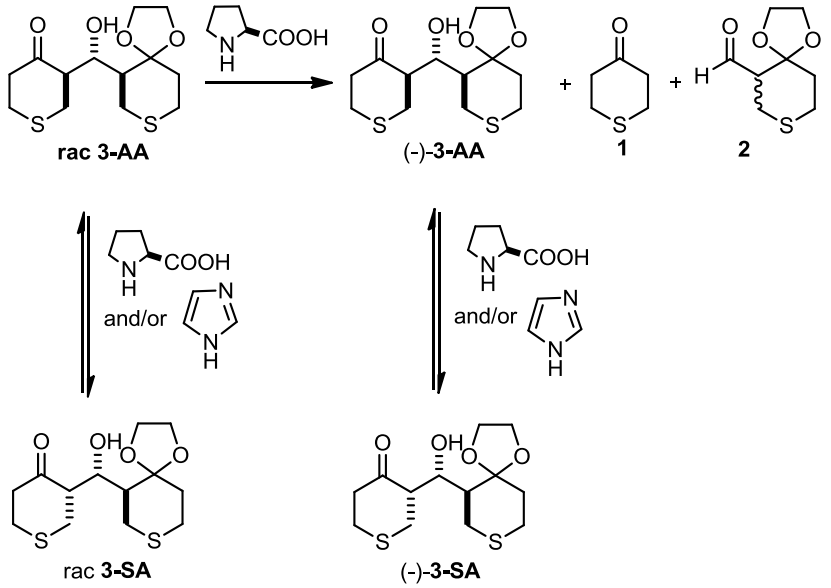


Figure 27. Enantioselective Retro-aldol and Isomerization Reactions of **3-SA** and **3-AA**

In summary, an L-proline-catalyzed retro-aldol reaction that provides an alternative access to highly enantiomerically enriched (-)-**3-AA** (ca. 95% ee) and (-)-**3-SA** (ca. 95% ee) in moderate yield (ca. 30%) was achieved. Similar results but opposite enantioenrichment is expected if D-proline is used as catalyst in the enantioselective retro-aldol reaction, therefore making all four enantiomers of **3-AA** and **3-SA** available in good purity via this approach. This method was demonstrated to be a robust, simple and readily scalable shortcut to prepare two essential building blocks of the Ward Group's synthetic strategy for polypropionate. Due to the parallel isomerization and retro-aldol processes, any mixtures of **3-AA** and **3-SA** with

any ee can be subjected to this methodology to produce high ee materials in one step. Moreover, L-proline is without question the most readily available, cost efficient and widely used organocatalyst for asymmetric aldol reactions. To the best my knowledge, this is the first report on L-proline catalyzed enantioselective retro-aldol reaction.

This novel L-proline-catalyzed enantioselective retro-aldol reaction raises a valuable concept that may guide the development of many practical enantioselective syntheses. In circumstances when the target compound is: 1) produced as a minor isomer in an enantioselective reaction; 2) the catalyst for the forward reaction has been established; and 3) the racemic form of the target compound is readily available, then the reverse process promoted by the forward catalyst could provide access to high enantioenriched material. Alternatively, the product(s) of catalytic enantioselective reactions with moderate enantioselectivity might be enantioenriched by the reverse process with the enantiomeric catalyst. Although, only moderate yields may be achieved using this concept due to the nature of kinetic resolution, rapid catalyst selection (e.g. catalysts screening and optimization may not be necessary) can justify its use in many occasions.

EXPERIMENTAL

4.1 General Methods

Anhydrous solvents were distilled under an argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; CH_2Cl_2, from CaH_2; MeOH from $Mg(OMe)_2$·DMF and DMSO were distilled from CaH_2 under reduced pressure (ca. 1 Torr) and stored over 4Å molecular sieves. All experiments involving air and/or moisture sensitive compounds were conducted in oven dried glassware capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). High temperature oil baths were maintained by a thermostated hot plate. Low temperature baths were: ice/water (0 °C) and CO_2(s)/acetone (–78 °C). Reaction temperatures refer to those of the baths.

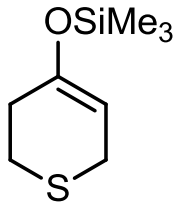
Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F254. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v) followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[48] with silica gel 60 (40-63 μm). All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR.

Spectra: Unless otherwise noted, ^{1}H NMR spectra were measured in $CDCl_3$ solution at 500 MHz. The proton signal of residual $CHCl_3$(7.26 δ_H) served as the internal standard. The

^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Enantiomeric excesses (ee's) for **3-AA** and **3-SA** were determined using a Chiralpak AS-H 5 μm 2.1×150 mm chiral column (10% isopropanol in hexanes, 1.0 mL/min, 25 °C) on an Agilent Technologies 1200 series HPLC. Enantiomeric excess (ee's) for **3-AS** was determined using a Chiralpak IC 2.1×150 mm column (8% isopropanol in hexanes, 1.0 mL/min, 25 °C) on an Agilent Technologies 1200 series HPLC.

Materials: The following compounds were prepared as described previously: **1**[10]; **2**[10]; (±)-**3-AS**[14], **38**[47], **39**[46]. All other reagents were commercially available and unless otherwise noted, were used as received.

3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyran (1-TMS)



1-TMS

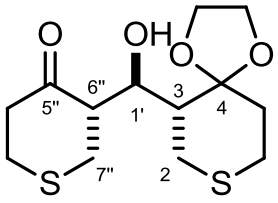
1-TMS was prepared according to the procedure by Ward et al.[11] Et_3N (24.0 mL, 17.4 g, 0.172 mol) and Me_3SiCl (16.6 mL, 14.2 g, 0.131 mol) were added in sequence to a stirred solution of **1** (obtained from Dieckmann cyclization of dimethyl 3,3'-thiobispropanoate followed by decarboxylation[11]) (10.0 g, 0.086 mol) in $CHCl_3$ (100 mL) under argon. The mixture was stirred in the dark at room temperature in a stoppered flask that was wrapped with aluminum foil. The reaction was monitored by ^{1}H NMR (a small aliquot of the reaction mixture worked up as described below). When the reaction was complete (6 days), the mixture was directly concentrated, diluted with hexanes (160 mL), and filtered through

Celite® washing with hexane. The combined filtrate and hexane washings were concentrated to give **1-TMS** (15.1 g, 94%) as a yellow oil that was homogeneous by ^{1}H NMR.

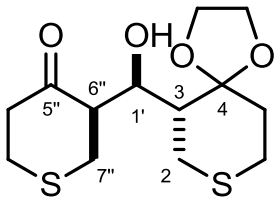
(1'*R,3*S**,6"*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (3-AA)**

and

(1'*R,3*R**,6"*R**)-3-[(1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl)-hydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (3-SA)**



(±)-3-AA

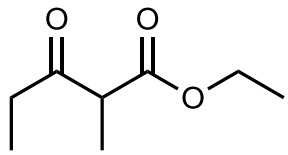


(±)-3-SA

According to the procedure by Ward et al,[9] $MgBr_2$·OEt (9.6 g, 37.5 mmol) was added to a stirred solution of **2** (4 steps from dimethyl 3,3'-thiobispropanoate[9]) (2.4 g, 13 mmol) in CH_2Cl_2 (57 mL) at room temperature under argon,. After 2 min, the resulting creamy, off-white suspension was placed in an ice bath and after 15 min, a solution of **1-TMS** (4.7 g, 25 mmol) in CH_2Cl_2 (2.2 mL) was added dropwise via syringe over 3 min. After 1 h at 0 °C, the reaction mixture was poured onto ice-cold phosphate buffer (pH 7, 100 mL) with vigorous stirring. The mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to give an orange oil that by ^{1}H NMR analysis contained a ca. 3:1 mixture of **3-SA** and **3-AA** respectively, along with **1**. This orange oil was diluted with CH_2Cl_2, washed by hot water (3×) (to remove remaining **1)**, and brine, dried over Na_2SO_4 and concentrated to give the crude product. Recrystallization

from hot methanol afforded **3-SA** (1.9 g, 49%). A 2nd cycle of recrystallization afforded another sample of **3-SA** (0.21g, 5.4%) as off-white crystal. Fractionation of the concentrated mother liquor by FCC (50% ethyl acetate in hexanes) gave **3-AA** (0.79 g, 20%) as white crystal and **3-SA** (0.14g, 3.6%) as white crystal.

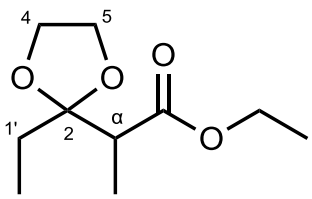
Ethyl-2-methyl-2-propionylacetate (31)



31

31 was prepared using the procedure of Brown[49] with minor modification. Under Ar atmosphere, KH (13.7 g KH suspended in mineral oil, 30% w/w, 0.102 mol) was washed with hexane to remove the oil. Dry THF (75 mL) was added to this KH to make a suspension, to which ethyl propionate (**30**) (11.7 mL, 10.3 g, 0.101 mmol) was added at 0 °C under Ar. After 2 hours, the reaction mixture was allowed to warm up to room temperature. When the reaction was complete by TLC analysis, the reaction was quenched by addition of glacial acetic acid (6.5 mL, 6.1 g, 0.11 mol) at 0 °C. This mixture was filtered through a sintered glass funnel with the aid of CH_2Cl_2, dried over Na_2SO_4 and concentrated to give the known **31** (6.48 g, 81%).

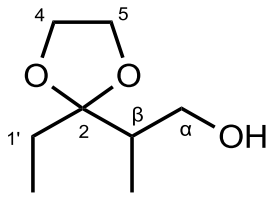
Ethyl 2-Ethyl-α-methyl-1,3-dioxolane-2-acetate (32).



32

32 was prepared adapting the procedure of Dignaut and Eliel.[50] PTSA (0.34g, 1.8 mmol) and 1,2-ethanediol (2.6 mL, 2.9 g, 46 mmol) were added sequentially to a stirred solution of **31** (5.5 g, 35 mmol) in benzene (44 mL). This solution was heated under reflux with a Dean-Stark trap fitted for removal of water. After 24 hours, the reaction was allowed cool to room temperature, concentrated, diluted with ethyl acetate, washed by saturated aqueous $NaHCO_3$ (3×) solution , water, brine, dried over Na_2SO_4 and concentrated to give **32** (6.4 g, 91%) as a colorless oil.

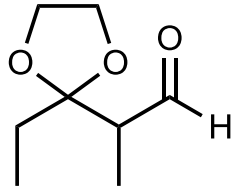
2-Ethyl-β-methyl-1,3-dioxolane-2-ethanol



33

According to the procedure by Ward et al.,[11] a solution of **32** (10.3 g, 50.9 mmol) in dry THF was added dropwise to a stirred suspension of $LiAlH_4$ (1.99 g, 52.4 mmol) in THF (150 mL) at 0 °C under Ar. The mixture was allowed to warm to room temperature and stirred for 2 hours then quenched by addition of water (1.5 mL). The THF was removed by rotary evaporation and the residual was taken up in Et_2O (160 mL). With vigorous stirring, aqueous NaOH (15% w/v, 1.5 mL) and water (4.5 mL) were added sequentially to the above mixture resulting in a milky white suspension. This suspension was filtered through a short column of Celite® and Na_2SO_4 washing with ethyl acetate. The combined filtrate and washings were concentrated to give **33** as a colorless oil (6.4 g, 78%).

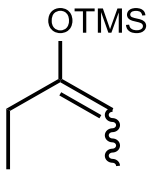
2-Ethyl-α-methyl-1,3-dioxolane-2-acetaldehyde (±)-34



34

According to the procedure of Ward et al,[11] a solution of oxalyl chloride (2.1 mL, 3.1 g, 24 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe to a stirred solution of DMSO (2.2 mL, 2.4 g, 31 mmol) in CH_2Cl_2 (50 mL) at -78 °C, under Ar. After 15 min, a solution of **33** (3.0 g, 20 mmol) in CH_2Cl_2 (20 mL) was added dropwise via syringe to the above mixture. After 15 min, Et_3N (2.3 mL, 4.5 g, 44 mmol) was added, and the reaction mixture was allowed to warm to rt. The mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give the crude product. Fractionation of the crude product by FCC (10% ethyl acetate in hexanes) afforded **34** as a yellow oil (2.47 g, 83%).

Trimethyl-(2-penten-3-yloxy)-silane

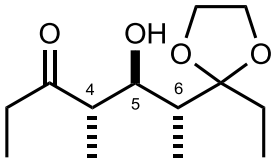


35

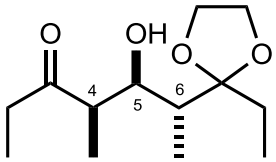
Adapting procedure of Ahamad, Khan, and Iqbal,[51] TMS-Cl (23.6 mL, 20.2 g, 0.186 mol) was added dropwise to a stirred solution of NaBr (19.1 g, 0.186 mol) in dry DMF (200 mL) at room temperature under Ar. The resulting white milky solution was stirred for 20 min and then 3-pentanone (12.3 mL, 10.0 g, 0.116 mol) and Et_3N were added (25.8 mL, 18.8 g, 0.186 mol). After 18 h, the reaction mixture was transferred to a separatory funnel with the aid of

n-pentane. The organic layer was washed with saturated aqueous $NaHCO_3$ (2×). The combined aqueous layers were back extracted with n-pentane (4×). The combined organic layers were dried over Na_2SO_4, and fractionally distilled (60 – 140 °C) to obtain **35** (8.5 g, 46%) as a light yellow oil.

(4*S*,5*R*,6*R*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methyl-3-heptanone (±)-4-AA) and (4*R*,5*R*,6*R*)-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methyl-3-heptanone ((±)-4-SA)



(±)-4-AA



(±)-4-SA

According to an unpublished procedure developed in the Ward Group (M. Biniaz and A. Karagiannis), $MgBr_2 \cdot OEt_2$ (32.17 g, 0.1264 mol) was added to a stirred solution of **34** (9.83 g, 0.0632 mol) and **35** (11 g, 0.070 mol) in CH_2Cl_2 (500 mL) at 0 °C. After 2 hours at 0 ^oC, the suspension was cooled to -15 ^oC and the reaction was quenched by addition of cold (0 ^oC) phosphate buffer (pH=7, 250 mL) with vigorous stirring. The mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, passed through a plug of Na_2SO_4 and concentrated to give the crude product. Fractionation of the crude product by FCC (20% ethyl acetate in hexane) gave **4-AA** (6.38 g, 41%) and a 10:1 mixture of **4-SA** and **4-AS** as colorless oils (5.98 g, 39%).

4.2 General Procedures

Table 4 (Section 2.1)

A representative procedure is shown. Entry 1: **3-AA** was dried by concentration from toluene prior to use. **3-AA** (0.126 g, 0.414 mmol) and L-proline (0.046 g, 0.40 mmol) were weighed into a vial followed by addition of DMSO (2 mL). The vial was capped and stirred at room temperature for 22 hours at which time a portion of the reaction mixture was removed via a syringe (0.3 mL) and quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR spectroscopy of the crude product indicated the absense of aldehyde **2**.

Figure 18 (Section 2.1)

3-AA was dried by concentration from toluene prior to use. **3-AA** (21 mg, 0.070 mmol) and L-proline (7.2 mg, 0.063 mmol) were weighed into a vial followed by addition of DMSO (0.6 mL). The vial was capped and stirred at room temperature for 24 hours at which time a portion of the reaction mixture was removed via a syringe (0.2 mL) and quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR spectroscopy of the crude reaction mixture with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0087 mmol; 36%) and **3-SA** (0.0071, 29%). Analysis of the crude product with chiral phase HPLC (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) indicated enantioenrichment of **3-AA** (43% ee).

Figure 19 (Section 2.1)

3-AA (15.6 mg, 0.0513 mmol) and L-proline (17.7 mg, 0.154 mmol) were weighed into a vial followed by addition of DMSO (1.0 mL). The vial was capped and stirred at 60 °C for 24 hours. The reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine 3 times to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR of the crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0147 mmol; 28%) and **3-SA** (0.0240 mmol, 47%). Fractionation of a portion of the crude product by PTLC (60% ethyl acetate in hexane) gave a mixture of **3-SA** and **3-AA**. Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of the above mixture indicated enantioenrichment of **3-AA** (62% ee) and **3-SA (**28% ee**)**.

Table 5 (Section 2.2)

A representative procedure is shown. Entry 6: **3-SA** (30 mg, 0.10 mmol) and L-proline (34 mg, 0.30 mmol) were weighed into a vial followed by addition of DMSO (2 mL) and water (28 µL, 1.6 mmol). The vial was capped and stirred at 60 °C. After 10 days, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR of the crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.010 mmol; 10%) and **3-SA** (0.021 mmol, 21%) in crude product. Fractionation of this crude

product by FCC (50% ethyl acetate in hexanes) gave a 2:1 mixture of **3-SA** and **3-AA**, respectively (10 mg, 33%). Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (96% ee) and **3-SA (**79% ee**)**.

Table 6 (Section 2.2)

A representative procedure is shown. Entry 1: **3-AA** (20 mg, 0.065 mmol, 94% ee) and L-proline (22 mg, 0.19 mmol) were weighed into a vial followed by addition of DMSO (2.0 mL) and water (20 µL, 1.1 mmol). The vial was capped and stirred at 60 °C. After 24 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR of the crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.025 mmol; 38%) and **3-SA** (0.027 mmol, 42%). Fractionation of the crude product by FCC (50% ethyl acetate in hexanes) gave a 1:1 mixture of **3-SA** and **3-AA**, respectively (16 mg, 81%). Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (>99% ee) and **3-SA** (95% ee).

Table 7 (Section 2.31)

A representative procedure is shown. Entry 5: **3-AA** (20.8 mg, 0.0684 mmol) and L-proline (23.6 mg, 0.205 mmol) were weighed into a vial followed by addition of DMSO (0.7 mL), EtOH (0.7 mL) and water (4 µL, 0.2 mmol). The vial was capped and stirred at

70 °C. After 70 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0037 mmol; 5.3%) and **3-SA** (0.0047 mmol, 6.7%) in crude product. Fractionation of a portion of the crude product by PTLC (80% ethyl acetate in hexanes) gave a mixture of **3-SA** and **3-AA**. Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (95% ee) and **3-SA** (84% ee).

Table 8 (Section 2.32)

A representative procedure is shown. Entry 4: **3-SA** (31.0 mg, 0.102 mmol), L-proline (11.5 mg, 0.0989 mmol), **2** (18.9mg, 0.112 mmol) and **1** (12.4 mg, 0.106 mmol) were weighed into a vial followed by addition of DMSO (2 mL) and water (9 µL, 0.5 mmol). The vial was capped and stirred at 70 °C. After 48 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR with trichloroethylene as a quantitative internal standard suggested full recovery of starting material.

Table 9 (Section 2.32)

A representative procedure is shown. Entry 9: **3-AA** (30 mg, 0.10 mmol) and L-proline

(34 mg, 0.29 mmol) were weighed into a vial followed by addition of DMSO (2 mL) and water (28 µL, 1.6 mmol). The vial was capped and stirred at 70 °C. After 64 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. Fractionation of the crude product by FCC (50% ethyl acetate in hexanes) gave a 1.6:1 mixture of **3-SA** and **3-AA**, respectively (12 mg, 39%). Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (93% ee) and **3-SA** (87% ee).

Table 10 (Section 2.32)

A representative procedure is shown. Entry 1: 3:1 mixture of **3-SA** and **3-AA** (20.4 mg, 0.0671 mmol) and L-proline (12.6 mg, 0.110 mmol) were weighed into a vial followed by addition of DMSO (1.3 mL), EtOH (1.3 mL) and water (9 µL, 0.5 mmol). The vial was capped and stirred at 70 °C. The mixture appeared clear during the course of the reaction. After 15 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^1H NMR analysis of crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0154 mmol; 23%) and **3-SA** (0.0354 mmol, 53%).

Table 11 (Section 2.33)

A representative procedure is shown. Entry 5: **3-AA** (21.1 mg, 0.0694 mmol) and

L-proline (22.1 mg, 0.192 mmol) were weighed into a vial followed by addition of DMSO (1.4 mL) and water (18 μL, 0.10 mmol). The vial was capped and the mixture was stirred at 100 °C. After 7 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR analysis of the this crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.00840 mmol; 12%) and **3-SA** (0.0132 mmol, 19%) in crude product. Fractionation by PTLC (70% ethyl acetate in hexanes) on a portion of the crude product gave a mixture of **3-AA** and **3-SA**. Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (81% ee) and **3-SA** (77% ee).

Table 12 (Section 2.34)

A representative procedure is shown. Entry 6: 3:1 mixture of **3-SA** and **3-AA** (30 mg, 0.0987 mmol), L-proline (34.1 mg, 0.296 mmol) and imidazole (33.9 mg, 0.498 mmol) were weighed into a vial followed by addition of DMSO (2.0 mL) and water (26 μL, 1.4 mmol). The vial was capped and stirred at 70 °C. After 70 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR analysis of the crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0126 mmol; 13%) and **3-SA** (0.0227 mmol, 23%). Fractionation by PTLC (70%

ethyl acetate in hexanes) on a portion of the crude product gave a mixture of **3-AA** and **3-SA**. Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (89% ee) and **3-SA** (90% ee).

Table 13 (Section 2.34)

A representative procedure is shown. Entry 2: 3:1 mixture of **3-SA** and **3-AA** (30 mg, 0.0987 mmol), L-proline (34.0 mg, 0.296 mmol) and imidazole (16.5 mg, 0.243 mmol) were weighed into a vial followed by addition of DMSO (1.0 mL) and water (27 µL, 1.5 mmol). The vial was capped and stirred at 70 °C. After 72 hours, the reaction mixture was quenched by addition to aqueous citric acid solution (0.1 M). The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR analysis of this crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.0109 mmol; 11%) and **3-SA** (0.0227 mmol, 23%). Fractionation by PTLC (70% ethyl acetate in hexanes) on a portion of the crude product gave a mixture of **3-AA** and **3-SA**. Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AA** (78% ee) and **3-SA** (72% ee).

Table 14 (Section 2.41)

A 3:1 mixture of **3-SA** and **3-AA** (1.50 g, 4.95 mmol), L-proline (1.71 g, 14.9 mmol) and imidazole (0.841 g, 12.4 mmol) were weighed into a flask followed by addition of

DMSO (50 mL) and water (1.35 mL, 75.0 mmol). The flask was stoppered and stirred at 70 °C. After 72 hours, the reaction mixture was quenched by addition to aqueous citric acid (0.1 M). The mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed sequentially by hot water (3×) to remove **1**, brine, dried over $NaSO_4$ and concentrated. The residual was eluted through a short column of SiO_2 (to remove polar impurities) washing with ethyl acetate and combined filtrate and washings were concentrated to give the crude product. ^{1}H NMR analysis of this crude product with trichloroethylene as a quantitative internal standard suggested the presence of **3-AA** (0.535 mmol), **3-SA** (1.12 mmol), **1** alone with the elimination product **3-elim** (0.214 mmol) and other minor impurities. Fractionation by FCC (50% ethyl acetate in hexane) gave a 2:1 mixture of **3-SA** and **3-AA**, respectively (493 mg). This mixture was subjected to 2 cycles of crystallization from methanol to give **3-SA** (285 mg, 19%). The mother liquor was concentrated and fractionated by FCC (25%-50% ethyl acetate in hexane) to afford **3-AA** (153 mg, 10%) and **3-SA** (39 mg, 2.6%). Chiral phase HPLC analysis (Chiralpack AS-H, 10% isopropanol in hexanes, 1.0 mL/min, 25 °C) on the isolated samples indicated enantioenrichment of **3-AA** (93%) and **3-SA** (92%). Copies of HPLC traces can be found in Section **3.3**.

Table 15 (Section 2.42)

A representative procedure is shown. Entry 2: **3-AS** (19.6 mg, 0.0645 mmol) and L-proline (22.8 mg, 0.198 mmol) were weighed into a vial followed by addition of DMSO (1.3 mL) and water (18 µL, 1.0 mmol). The vial was capped and stirred at 60 °C. After 24 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The

mixture was extracted with ethyl acetate (3×) and the combined organic layers were washed with brine (3×) to remove residual DMSO, dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR with trichloroethylene as a quantitative internal standard suggested the presence of **3-AS** (0.0226 mmol; 35%) and **3-SS** (0.0121 mmol, 19%). Fractionation by PTLC (60% ethyl acetate in hexanes) on a portion of the crude gave a mixture of **3-AS** and **3-SS**. Chiral phase HPLC analysis (Chiralpack IC, 8% isopropanol in hexanes, 1.0 mL/min, 25 °C) of this mixture indicated enantioenrichment of **3-AS** (83% ee) and **3-SS** (50% ee)

Table 16 (Section 2.43)

A representative procedure is shown. Entry 3: **4-AA** (20.3 mg, 0.0831 mmol) and L-valine (17.8 mg, 0.152 mmol) were weighed into a vial followed by addition of DMSO (1.7 mL) and water (11 μL, 0.61 mmol). The vial was capped and stirred at 60 °C. After 62 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. ^{1}H NMR of the crude product with trichloroethylene as internal standard suggested quantitative recovery of starting material.

Table 17 (Section 2.43)

A representative procedure is shown. Entry 1: **4-AA** (19.6 mg, 0.0802 mmol), L-proline (13.8 mg, 0.120 mmol) and **38** (36.8 mg, 0.0802) were weighed into a vial followed by addition of DMSO (1.6 mL). The vial was capped and stirred at 30 °C. After 24 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was

extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. The concentrated sample was eluted by ethyl acetate through a plug of SiO_2 to remove residual **38** and afford the crude product. ^{1}H NMR analysis of the crude product with trichloroethylene as a quantitative internal standard suggested quantitative recovery of starting material.

Table 18 (Section 2.43)

A representative procedure is shown. Entry 1: **4-SA** (19.5 mg, 0.0798 mmol), L-proline (13.5 mg, 0.0893 mmol) and **38** (16.5 mg, 0. 0359) were weighed into a vial followed by addition of 3-pentanone (1.6 mL). The vial was capped and stirred at 60 °C. After 45 hours, the reaction mixture was quenched by addition to saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3×) and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. The concentrated sample was eluted by ethyl acetate through a plug of SiO_2 to remove residual salt **38** and afford the crude product. ^{1}H NMR analysis of this crude product with trichloroethylene as a quantitative internal standard suggested the recovery of starting material.

[1] An inseparable mixture of **4-SA** and **4-AS** at about 10:1 ratio

4.3 Typical HPLC Analyses

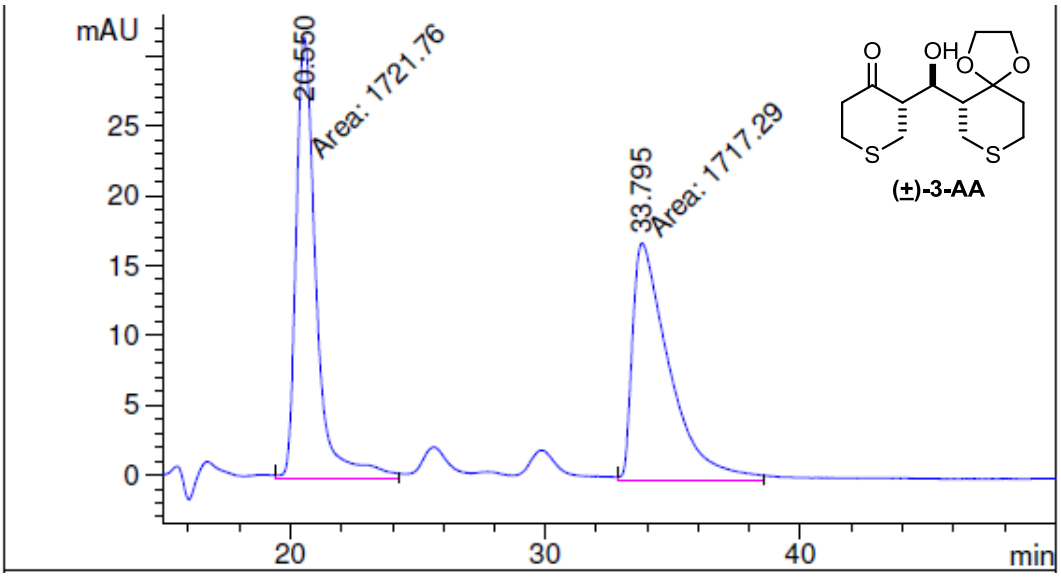
Column: DAICEL CHIRALPAK® AS-H 5 µm; 2.1x 150 mm

Solvent: 10% 2-PrOH in hexane

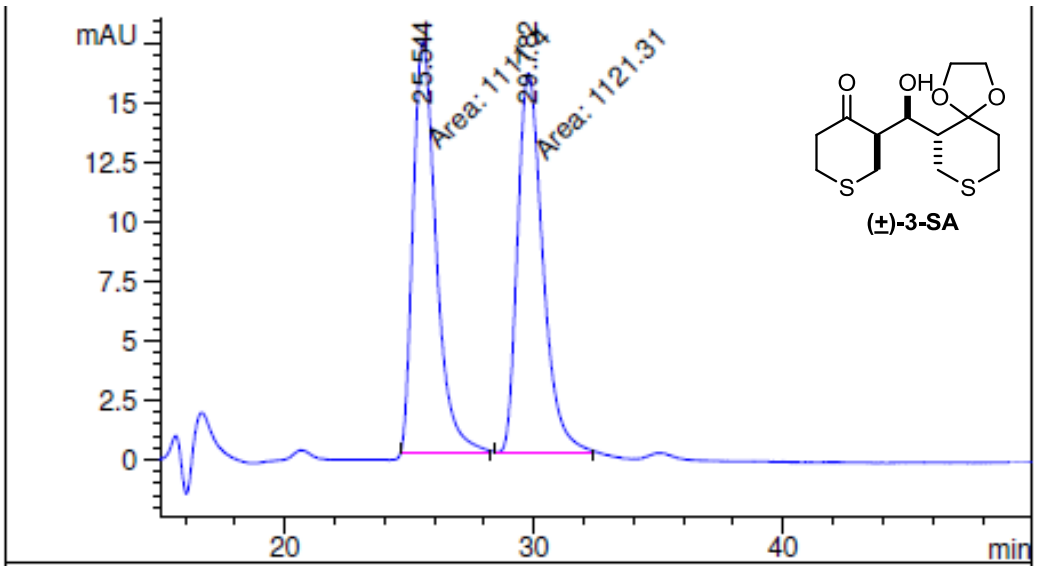
Flow Condition: 0.1 mL/min; 25 °C

Detector: UV, 254 nm

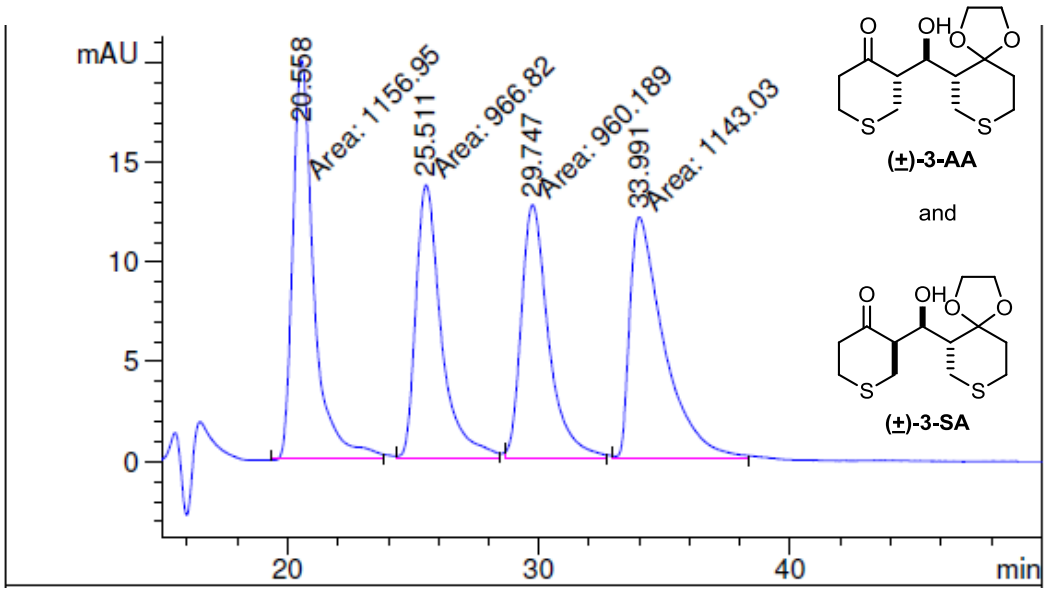
1) (±)-3-AA



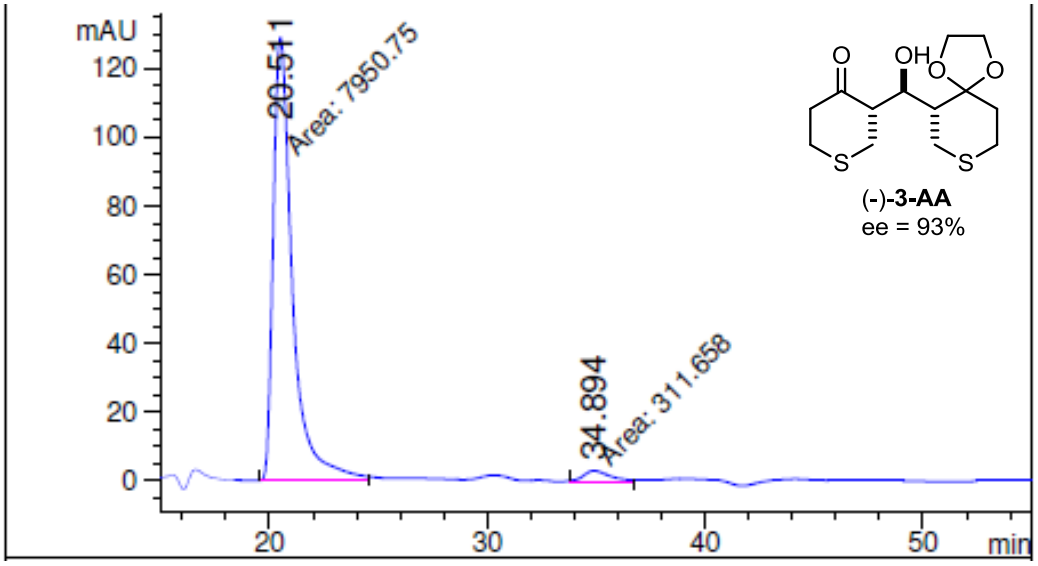
2) (±)-3-SA



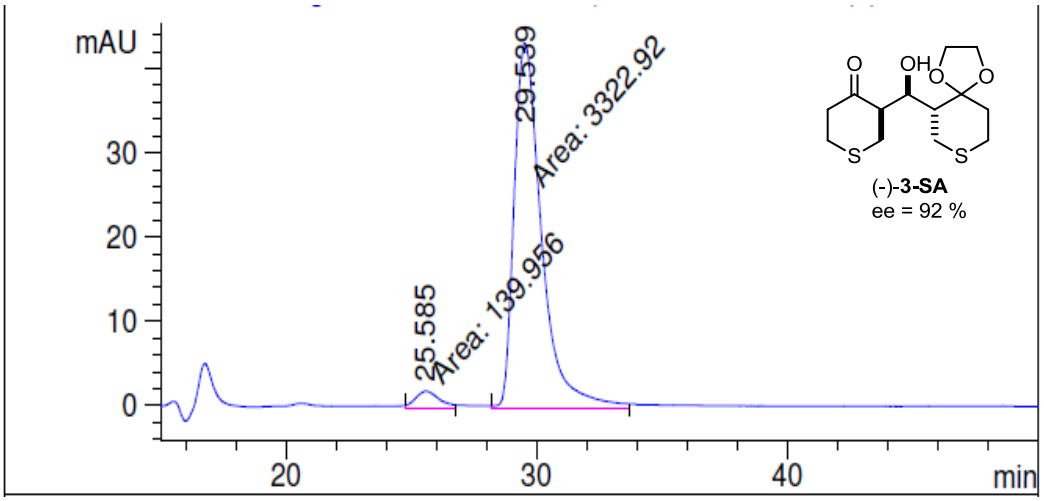
3) (±)-3-AA and (±)-3-SA mixed sample



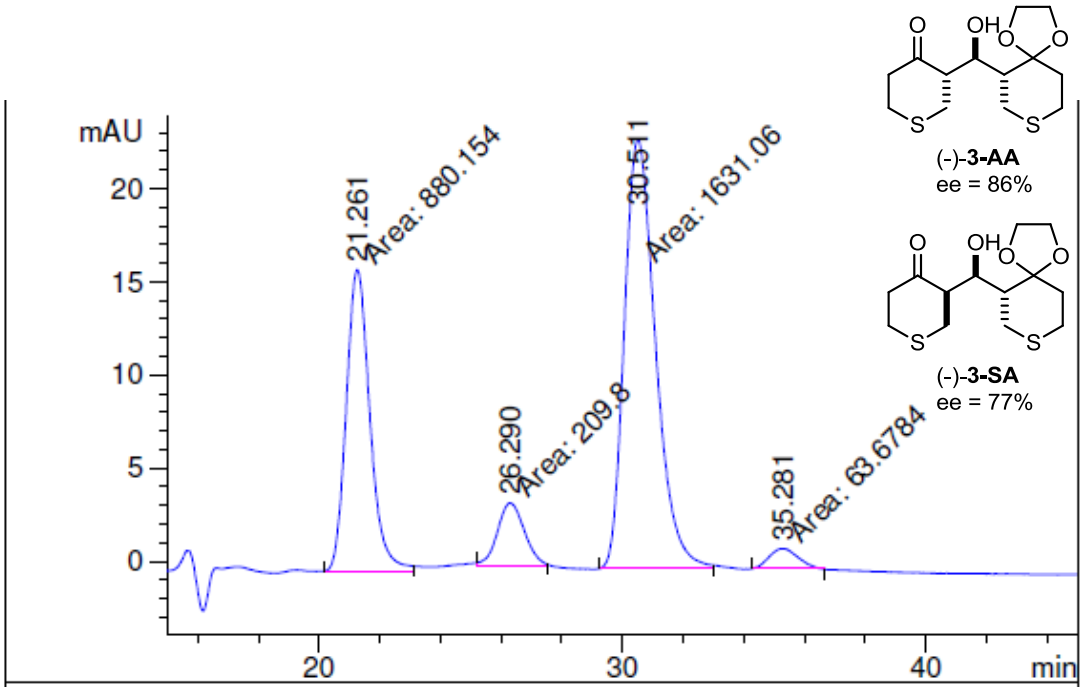
4) (-)-3-AA (isolated product of Table 14, Entry 3)



5) (-)-3-SA (isolated product of Table 14, Entry 3)



6) Enantioenriched 3-AA and 3-SA mixed sample



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