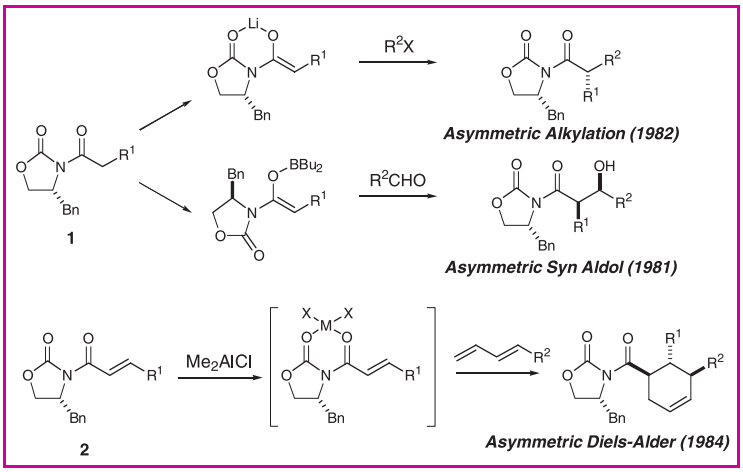
Recent advances in asymmetric synthesis with chiral imide auxiliaries

David A. Evans and Jared T. Shaw

Résumé **Progrès en synthèse asymétrique : utilisation d'imides comme auxiliaires chiraux**
Les oxazolidinones chirales et leur dérivés sont des auxiliaires efficaces en synthèse asymétrique. De nouvelles méthodologies ont été développées, notamment des alkylations de composés glycoliques et des réactions d'aldol utilisant une quantité catalytique de métal, produisant les diastéréoisomères anti. Quelques exemples récents et innovateurs d'utilisations de ce type d'auxiliaires en synthèse totale sont aussi abordés.

Mots-clés **Auxiliaires chiraux, oxazolidinones, thiazolinethiones, synthèse totale, diastéréosélectivité.**
Key-words **Chiral auxiliaries, oxazolidinones, thiazolinethiones, total synthesis, diastereoselectivity.**



Scheme 1 - Initial reports of asymmetric induction from chiral imides.

The use of chiral *N*-acyloxazolidinone auxiliaries to control absolute stereoinduction has found wide application in a variety of reactions over the last two decades [1]. Despite extensive development by our group and complementary studies by others, new reactions continue to evolve from this useful family of chiral controllers. The most widely employed reactions of these ester surrogates are the asymmetric alkylation, aldol and Diels-Alder reactions (*scheme 1*). This review covers significant contributions to these areas of development during the last five-year period.

The majority of our work with chiral imides has employed the basic structural elements of oxazolidinone **1** with few exceptions over the last 20 years. Subsequent to our initial reports, many structural variants of **1** have appeared (*figure 1*). These modified imides have been developed to exhibit different cleavage reactivity or complimentary diastereoselectivity compared to **1**. The most notable imide analog is the thiazolidine thione developed by Nagao and Fujita, then later used by Crimmins and our group [2]. This auxiliary, unlike many others that have been developed, reacts through different modes of metal binding and thus affords a useful complement to imide **1** (*vide infra*).

Stereoselective glycolate alkylation

The alkylation of lithium, sodium, and potassium enolates derived from *N*-acyloxazolidinones have proven useful for the preparation of many chiral building blocks. The reaction is generally limited to reactive alkylating agents such as allyl and benzyl halides. The Crimmins group has recently extended the alkylations reaction for use with glycolic acid equivalents such as **3** in the preparation of chiral substrates for a ring-closing metathesis approach to macrocyclic ethers from *Laurencia Sp* (*scheme 2*) [3].

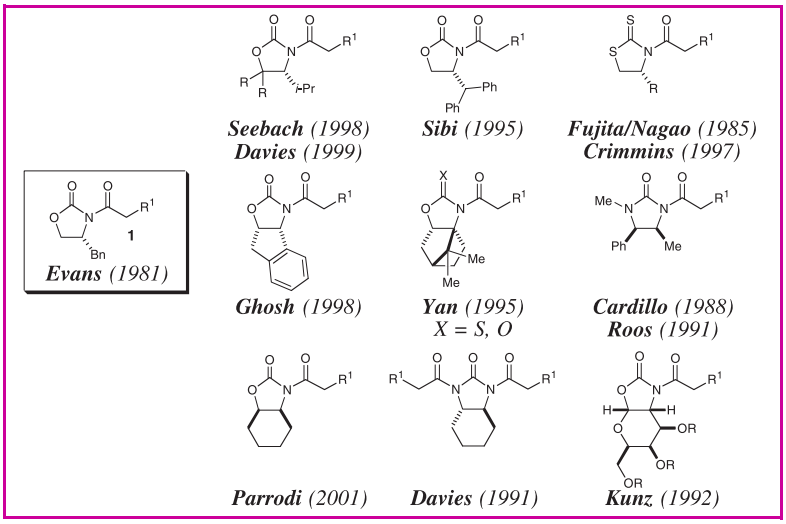
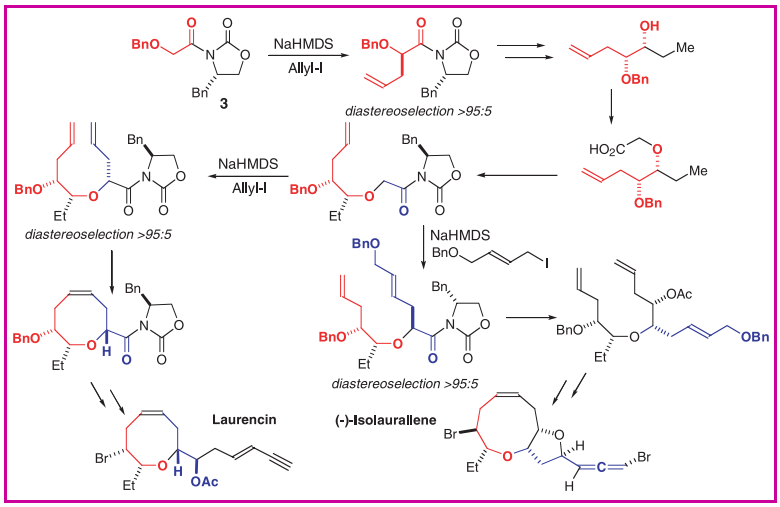
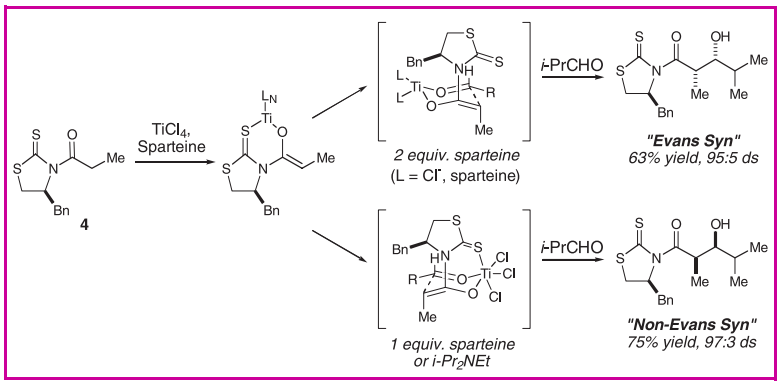


Figure 1 - Selected structural variants of chiral imide **1**.



Scheme 2 - Crimmins' use of asymmetric alkylation of glycolate synthons in recent syntheses of laurencin (1999) and isolaurallene (2001).



Scheme 3 - Crimmins' stereodivergent syn aldol reactions (1997).

New stereo-complementary syn and anti aldol reactions

Our original reports of the asymmetric aldol reactions mediated by boron and titanium produced the « Evans Syn » aldol product in very high diastereoselectivity (*scheme 1*). A recent report from the Crimmins group has shown that aldol reactions of thiazolidine thiones form each of the two syn diastereomers depending on the amount of base employed (*scheme 3*). Use of two equivalents of sparteine produces the « Evans Syn » isomer, while use of one equivalent of sparteine gives the opposite isomer with respect to the auxiliary, or the « Non-Evans Syn » isomer. When less base is employed, the thiocarbonyl of the auxiliary coordinates to the titanium center and exposes the transition state of the reaction to a different diastereoface of the auxiliary (*scheme 3*) [4].

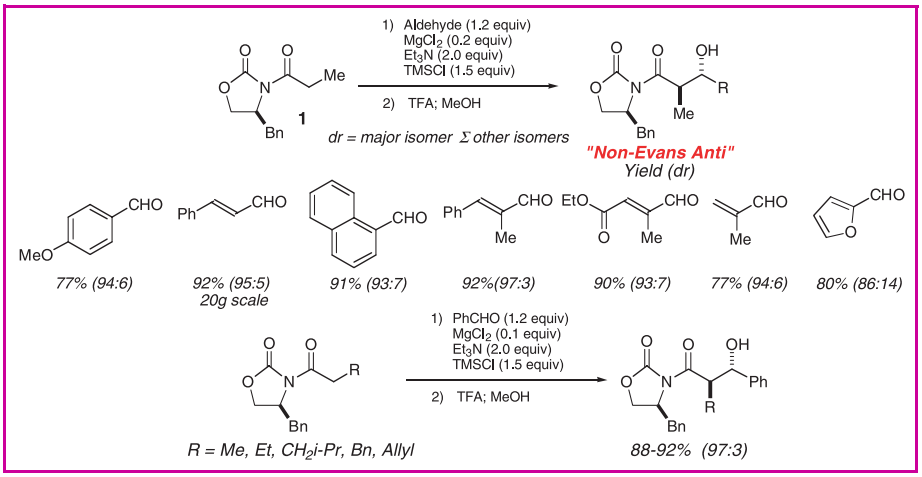
Recent studies in the Evans group have generated the first oxazolidinone aldol reactions that are catalytic in metal (*scheme 4*). In addition, the reaction produces anti aldol products, which were previously difficult to access from aldol reactions of this family of substrates. The reaction is limited to non-enolizable aldehydes, since self-condensation of the aldehydes in those cases competes with the desired aldol process [5]. Mechanistic studies have revealed that the aldol reaction of oxazolidinone **1** is reversible, but can be driven to completion by the addition of chlorotrimethylsilane and triethylamine. Control experiments indicate that the aldolate intermediate is silylated and thus the metal source ($MgCl_2$ in this case) is released and can proceed on to catalyze further reaction cycles (*scheme 5*). The « Non-Evans Anti » stereochemistry of the product is likely the result of boat-like transition state **A**.

By employing the thiazolidine thione auxiliary, magnesium halide-catalyzed aldol reactions produce the opposite aldol diastereomer with respect to the auxiliary (*scheme 6*) [6].

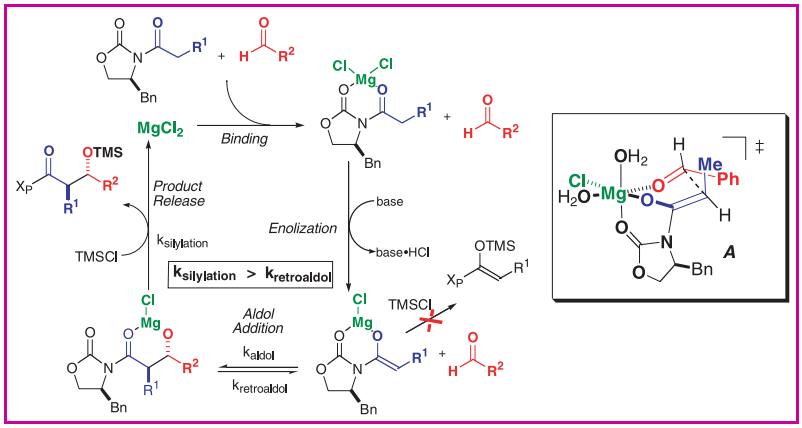
In this case $MgBr_2$ was found to be a superior catalyst. The scope of the reaction is quite similar to that of the oxazolidinone, though the selectivities are slightly lower. The extreme cost effectiveness and easy scale-up of these two new anti aldol reactions make them superb candidates for the preparation of chiral building blocks and medicinal compounds. In addition, these new magnesium halide-catalyzed aldol reactions allow selective formation of all four diastereomers of product from a *single* isomer of auxiliary.

Two important Reformatsky reactions have been developed that employ oxazolidinone auxiliaries. Fukuzawa has developed a samarium iodide-mediated reaction that affords acetate aldol products (*scheme 7*) [7]. This reaction is of interest since, unlike the propionate analogs, acetate aldol reactions of *N*-acyloxazolidinones typically exhibit low diastereoselectivity.

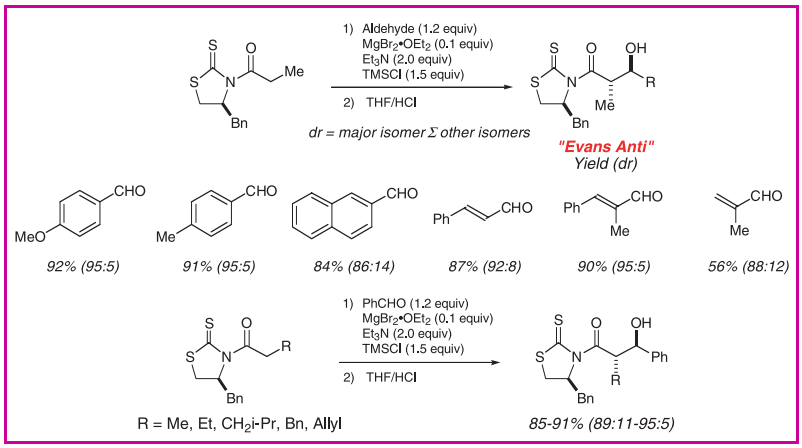
Wesjohann has also developed a Reformatsky process that affords anti aldol products [8]. Previous to our work with the magnesium halide-catalyzed process, Wesjohann's report was one of very few reactions producing anti aldol products with an oxazolidinone auxiliary. The anti diastereoselection delivered by this reaction could well be related to the anti-selective aldol reactions of magnesium enolates (*scheme 4*) that are proceeding through an octahedrally coordinated metal-based pericyclic transition state (*scheme 5*).



Scheme 4 - Evans' $MgCl_2$-catalyzed anti aldol reaction (2002).



Scheme 5 - Proposed catalytic cycle for the magnesium halide-catalyzed aldol reaction.



Scheme 6 - Evans' aldol reactions of thiazolidine thiones provide the « Evans Anti » aldol product (2002).

New asymmetric Diels-Alder reactions

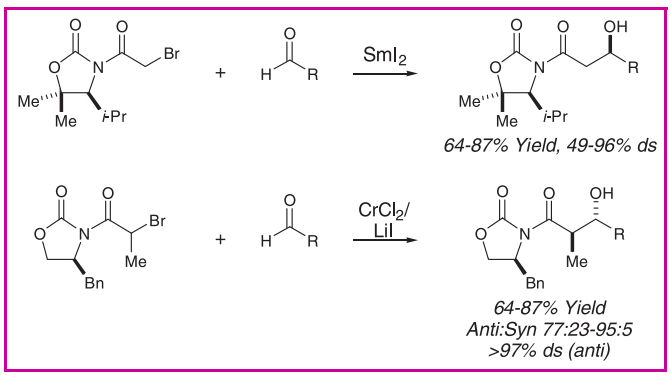
Recent approaches to stereoselective Diels-Alder reactions have focused on assembling complex starting materials through auxiliary-controlled aldol processes. Thus, the auxiliary indirectly dictates the outcome of the Diels-Alder process. Evans has recently reported a new cleavage process for oxazolidinone auxiliaries that greatly expands their scope of synthetic application and allows for new applications to Diels-Alder reactions of complex substrates [9]. Conversion of an acyl imide to a thioester allows for subsequent decarboxylation (*scheme 8*). As such, the oxazolidinone does not serve merely as an ester synthon, but as a chiral ketone-equivalent for the bi-directional assembly of polypropionates. In addition, an acylation/Diels-Alder process is possible in which the chiral influence of the auxiliary is relayed though the methyl center of the dicarbonyl moiety. This strategy has been demonstrated in a short synthesis of himachalene which features an intramolecular Diels-Alder reaction followed by decarboxylative removal of the auxiliary.

An application of this aldol-Diels-Alder reaction process has been employed by Fukuyama in his efficient synthesis of CP-263,114 (Phomoidride). In this synthesis, a « Type-2 » Diels-Alder reaction is executed with a high level of stereocontrol (*scheme 9*). The auxiliary carbonyl in this case is left intact and carried on to the maleic anhydride residue present in the natural product [10].

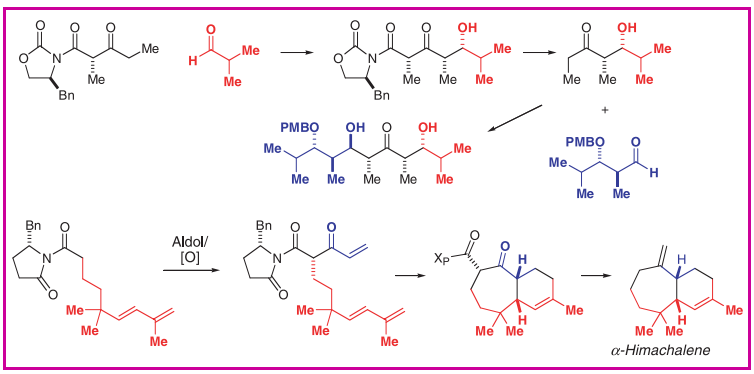
In the recent synthesis of FR-182877 by Evans, all stereochemical relationships in the target structure were obtained from the illustrated oxazolidinone auxiliary [11]. As in the syntheses of himachalene and CP-263,114, asymmetric aldol processes were employed to construct the two principal subunits which were united via a Suzuki cross coupling reaction. Upon macrocyclization and oxidation, a selective Diels-Alder–Hetero-Diels-Alder cascade was employed to produce the hexacyclic FR-182877 structure. A related strategy to this natural products target has been reported by Sorensen [12].

Conclusion

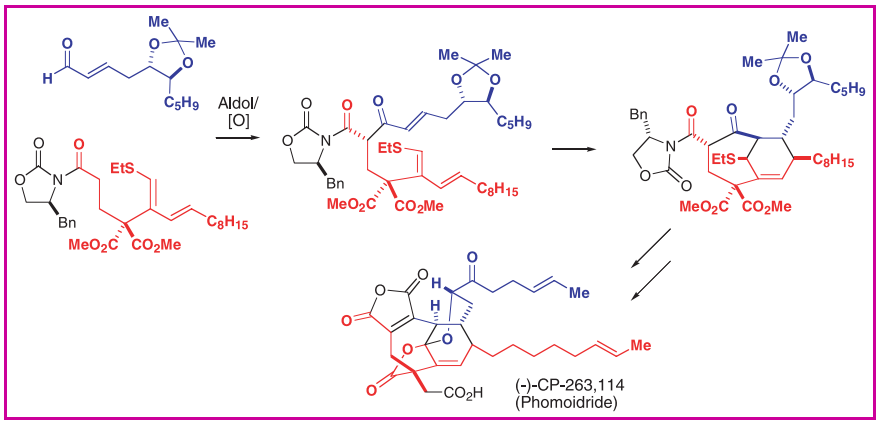
Asymmetric reactions of acyloxazolidinones have experienced an amazing level of evolution over the past two decades. Recent results from our group, as well as others, demonstrate that auxiliary-controlled processes are still essential tools in the construction of complex molecular targets. The ready availability of the starting materials, ease of cleavage, and application to a wide variety of stereoselective reactions allows oxazolidinone auxiliaries to endure as ideal intermediates for asymmetric synthesis.



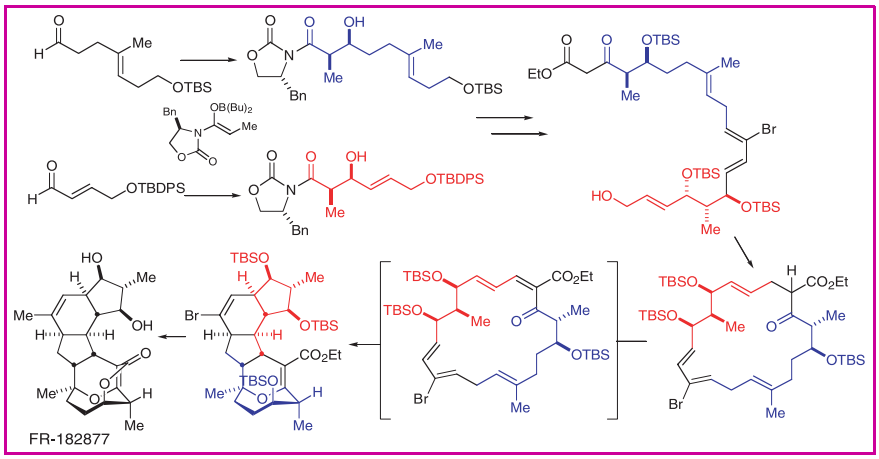
Scheme 7 - Fukuzawa's SmI_2 (1998) and Wesjohann's $CrCl_2$ (1997) Reformatsky reactions.



Scheme 8 - Evans decarboxylative auxilliary removal in the synthesis of a complex polypropionate synthon and α-Himachalene.



Scheme 9 - Fukuyama's Auxilliary-controlled Diels-Alder approach to CP-263,114.



Scheme 10 - Evans' Synthesis of FR-182877 by auxilliary controlled aldol reactions followed by a Diels-Alder cascade process.

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