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Silylated diaryl-2-pyrrolidinemethanols in catalysis

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Silylated diaryl-2-pyrrolidinemeth

Dr Gerald L. Larson of **Gelest** reviews recent developments in an expanding field of catalysis

The area of organic catalysis for asymmetric aldol and related reactions has been expanded to include highly effective cascade approaches to the stereoselective multi-component construction of highly functionalised ring systems. This mini-review will summarise some of the highlights of these approaches in which the readily synthesised and versatile silylated derivatives of diaryl-2-pyrrolidinemethanols are employed as the asymmetric catalysts.

Figure 1 shows representative examples of the most studied of these. In addition to the single-step creation of several new C-C and C-heteratom bonds, these transformations can simultaneously generate multiple chiral centres with extremely high stereoselectivity.

Traditionally, a multi-step organic synthesis has required a series of steps to be carried out in a logical sequence to arrive at the desired target. A simplified view of this approach is the introduction of various functional groups or synthetic units one at a time. Moreover, this can often involve the introduction and subsequent removal of a suitable protecting group.

This step-by-step protocol can, at times, be modified by not isolating certain intermediates, thereby reducing the overall number of steps and purifications. Clearly, the step-by-step introduction of single units and functionalities is one that will add cost and effort to the synthesis as a result of more time being needed, increased consumption of solvents and reagents and a loss in overall yield, due to the greater number of purification steps.

Chiral secondary amine catalysts have been applied in a number of classic transformations, including Michael additions, Henry reactions, aldol reactions, epoxidations and Diels-Alder reactions, among others. This article focuses on applications in multi-component reactions generating two or more C-C or C-heteroatom bonds.

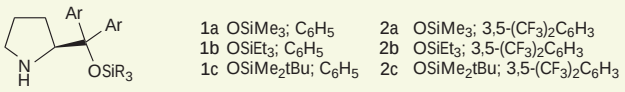
Organic secondary amine catalysts can function by two principle mechanisms, namely by the reaction of an aldehyde or ketone via the formation of an iminium ion or an enamine intermediate. Iminium ion intermediates are favoured with substrates like enals. Thus, a secondary amine may be employed in the catalysis of cascade reactions, as shown in Figure 2.

In a tandem cascade sequence, the design is to introduce a nucleophile, ideally one that also provides a reactive electrophile such as, for example, the enolate of a β-keto ester in which the enolate is the nucleophile and the ketone the electrophile.

Furthermore, the use of a chiral secondary amine catalyst creates the opportunity for the enantioselective generation of two or more stereocentres. Organic secondary amines like 1 and 2 (Figure 1) have been employed as chiral catalysts in a number of enantioselective aldol and related reactions, mainly through the work of the Jorgensen and Hayashi groups.[1]

MacMillan and coworkers reported intramolecular enantioselective cyclisations of enones and enals using a chiral imidazolidinone catalyst to exploit an iminium ion-enamine activation sequence and other examples have been reviewed.[2]

Here I will focus on the recent examples of the use of substituted pyrrolidinemethanols, in particular the diaryl-2-pyrrolidinemethanols 1 and 2 in the execution of the iminium ion-enamine-iminium ion sequence, or variations thereof, towards the efficient preparation of highly functionalised systems, in particular ring systems.



1a $OSiMe_3$; C_6H_5 2a $OSiMe_3$; 3,5-$(CF_3)_2C_6H_3$
1b $OSiEt_3$; C_6H_5 2b $OSiEt_3$; 3,5-$(CF_3)_2C_6H_3$
1c $OSiMe_2tBu$; C_6H_5 2c $OSiMe_2tBu$; 3,5-$(CF_3)_2C_6H_3$

Figure 1 - Substituted proline catalytsts

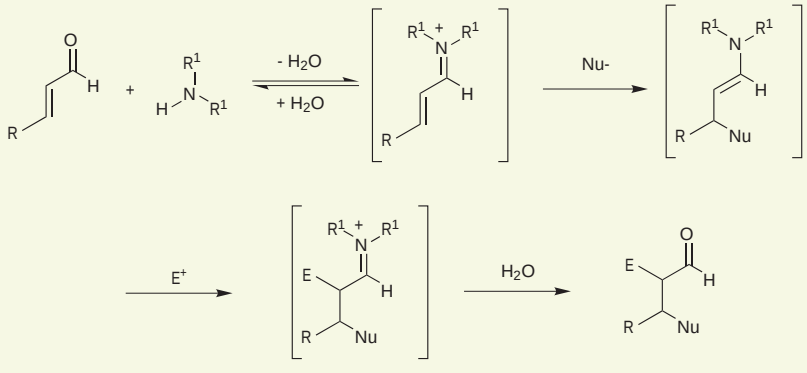


Figure 2 - General iminium ion-enamine mechanism

Asymmetric Michael addition-alkylation

Enders and coworkers have reported the cascade Michael addition alkylation of 5-iodo-1-nitropent-1-ene with various aldehydes under both basic and acidic conditions, the latter proving best (Figure 3).[3]

This reaction proceeds via the initial formation of the enamine of the aldehyde. This, upon Michael addition to the α,β-unsaturated nitroalkene forms an iminium ion that isomerises to a second enamine which is intramolecularly alkylated, forming the cyclopentane.

The use of 2-bromo dimethylmalonate as the nucleophile-electrophile pair in the cascade reaction with enals leads to an efficient synthesis of substituted cyclopropanes.[4]

Asymmetric Michael-Michael additions

A formal [3 + 3] cycloaddition of enals with α,β-unsaturated β-ketoesters (Nazarov reagents) can be used to prepare cyclic hemiacetals, which can then be oxidised to highly substituted 3,4-dihydropyranones or reduced to the corresponding pyrans, all in high ee (Figure 4a).[5]

The proposed mechanism shows the oxygen of the keto group attacking the second iminium ion formed after the initial attack of the β-keto ester enolate on the iminium ion of the enal rather than an intramolecular Morita-Baylis-Hillman reaction.

This reaction sequence offers an alternative to the asymmetric hetero-Diels-Alder reaction. In contrast, the reaction of enals with an α,β-unsaturated β-keto ester under similar conditions gives the intramolecular Morita-Baylis-Hillman after the initial Michael addition of the malonate to the iminium salt of the enal.[6]

The reaction of enals with malonate esters containing an α,β-unsaturated ester in the β-position undergoes a Michael-Michael sequence leading to stereoselective preparation of highly functionalised cyclopentanes.[7] Although the diastereomeric ratios are modest, the ee values are very high.

A Michael-Michael-aldol cascade reaction sequence can be used to prepare highly functionalised cyclohexene carbaldehydes. This involves the Michael attack of the enolate of an aldehyde on a

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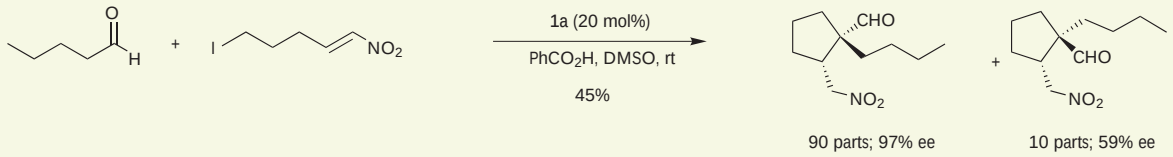

Figure 3 - Asymmetric Michael addition-alkylation

nitroalkene followed by the reaction of the resulting α-nitro carbanion on an enal and finally an intramolecular aldol condensation in an enamine-iminium-enamine sequence (Figure 4b).[8]

A very similar transformation can be accomplished with a polymer-supported prolinol derivative in which the diaryl portion of the catalyst of type **1** is bound to a polystyrene backbone.[9] The results of this study showed yields in the low to mid-80s % range, *syn* to *anti* ratios of >95:5 and ee values ranging from 89% to 99%.

A β-amido ester approach is used to prepare quinolisidone derivatives in a remarkable cascade of additions and condensations.[10] The last cyclisation is brought about by an acid-catalysed electrophilic aromatic substitution from an intermediate aminal. **2a** gave only 45% yield and 54% ee.

A β-nitro-α,β-unsaturated ester serves as the Michael acceptor in a one-pot, three-step sequence to form a key intermediate in the synthesis of (-)-oseltamivir, commonly known as Tamiflu.[11] The overall yield for the three steps including a final purification is 70%.

A β-keto-γ-phosphito ester is useful in the reaction with enals in a Michael-Knoevenagel sequence to provide highly-substituted cyclohexenones in good yields, excellent diastereomeric ratios and very high ee values (Figure 4c).[12]

The (R) enantiomer of **1a** consistently gave the opposite diastereomer in 76% yield, 95:5 diastereomeric ratio and in 98% ee. 3-Alkyl substituted enals undergo this reaction sequence in good yields, poor diastereomeric ratios and slightly lower ee than the corresponding 3-aryl enals.

β-Keto diesters and enals are shown to react to form highly functionalised cyclohexenones in what amounts to a [3 + 3] carbocycloaddition.[13] Finally, the reaction of a nitroalkene with a dialdehyde is a combination for a Michael-Henry reaction sequence to produce heavily-substituted cyclohexane carbaldehydes in good yields and 99% ee's.[14]

Michael-Michael cascade route

Ortho hydroxy cinnamaldehydes are shown to react with nitroalkenes in a Michael-Michael sequence to form highly substituted chromans in a single step and a similar reaction scheme is reported with ortho hydroxyphenyl nitroalkenes (Figure 5a).[15]

This reaction, however, does not stop at the simple chroman stage, but undergoes a second Michael-aldol sequence to the tricyclic cyclohexene carbaldehyde. This domino aldol-oxa-Michael reaction using **2b** was employed in a short synthesis of α-tocopherol.[16]

Ortho hydroxy benzaldehydes undergo an oxa-Michael-aldol sequence with enals.[17] The conversions and ee values are good to excellent, with **1b** being more effective than **1a** or **1c**. This and similar work represent a significant improvement over an earlier study on this transformation.[18] It seems that a higher catalyst load and the addition of benzoic acid is very beneficial in the success of the reaction. A mercapto version of this useful transformation has also been reported.[19]

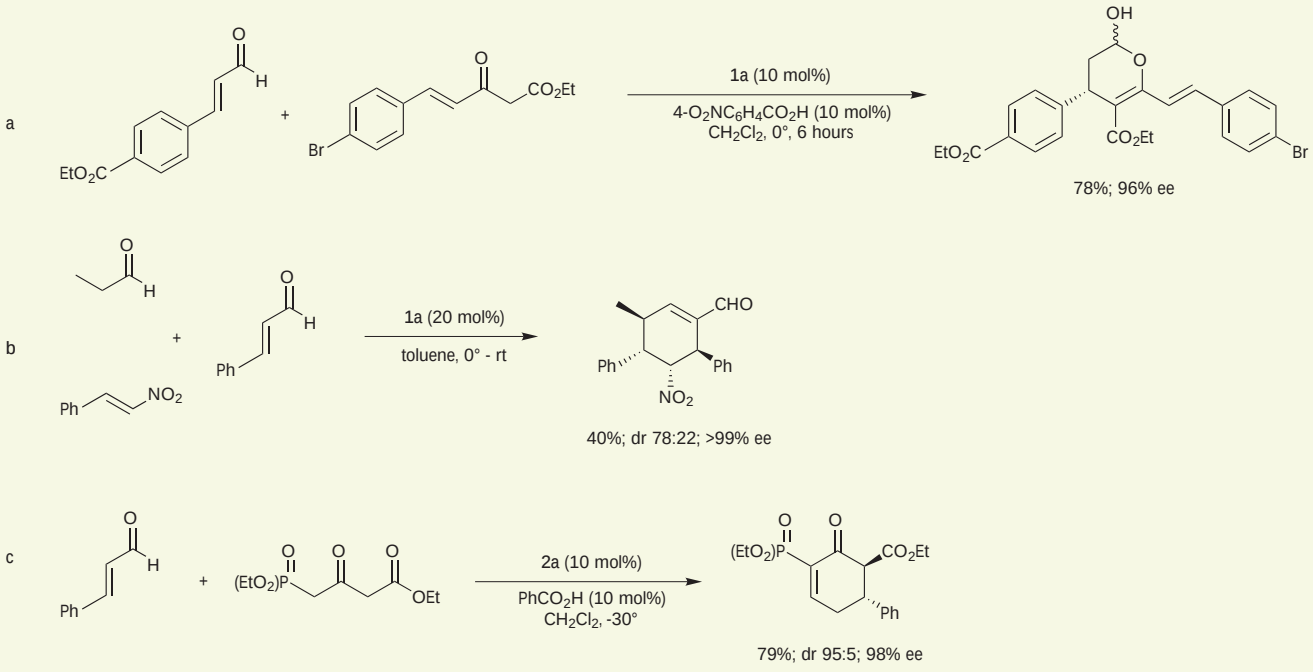

Figure 4 - Asymmetric Michael-Michael additions

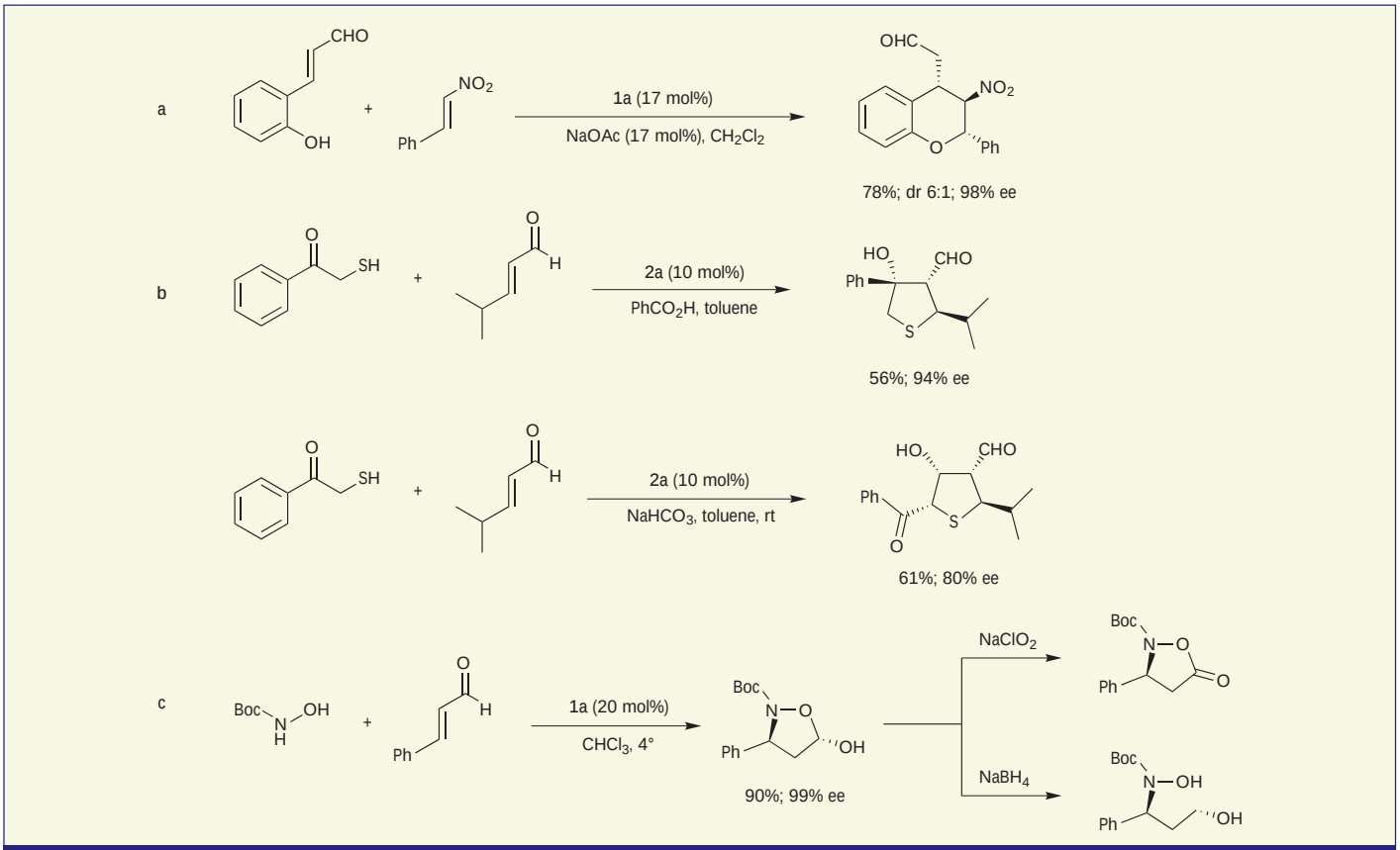

Figure 5 - Michael-Michael cascade routes to heterocycles

The reaction can be extended to the synthesis of pyranonaphthoquinones, again with high ee values, and also to dihydroquinolines. **1b** is best for the transformation; the chemical yields are high and the ee values range from 88% to 96%.[20]

The synthesis of highly functionalised tetrahydrothiophenes is possible with high ee values via a double Michael approach using a combination of an enal and a γ-mercapto-α,β-unsaturated ester or a Michael-aldol approach employing an enal and an α-mercapto ketone.[21] This reaction can take either of two pathways for the aldol step, depending on whether the additive is benzoic acid or potassium bicarbonate (Figure 5b).

N-protected hydroxylamines are shown to react with enals under the catalysis of **1a** to 5-hydroxyisoxazolidines, which are important chiral intermediates. For example, these can be oxidised to isoxazolidin-5-ones or reduced to γ-hydroxy oximes (Figure 5c). Finally, the combination of a hydroxylamine, an enal and an aldehyde can be employed in a one-pot, three-component, highly enantioselective synthesis of highly-substituted isoxolidines.[22]

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