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Diels-Alder Reaction on Solid Supports Using Polymer-Bound Oxazolidinones

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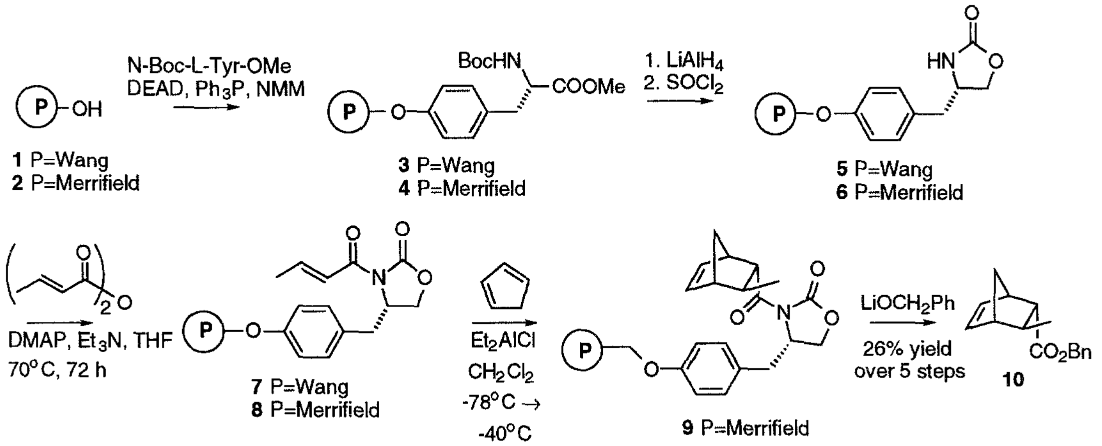
Abstract: Hydroxymethyl resin-bound oxazolidone crotonates undergo Diels-Alder reactions with yields and stereoselectivities comparable to those observed in solution. The stability of the resin to the Lewis acid (Et_2AlCl) employed is critical to the success of these cycloadditions.

Keywords: *Diels-Alder reactions; oxazolidinones; solid-phase synthesis*

The widespread use of combinatorial chemistry as a means to generate libraries of small organic molecules in the process of drug discovery has necessitated expansion of the techniques of solid-phase organic synthesis.[2] Polymer-bound chiral auxiliaries are of particular importance as they can lead to asymmetric reactions with facile recycling of the auxiliary by simple filtration. The Evans oxazolidinone is one of the most versatile and successful chiral auxiliary systems currently available for asymmetric acyl group-based transformations, including the aldol reaction[3] and the Diels-Alder cycloaddition.[4] The attachment of the Evans oxazolidinone to solid supports and the utility of such systems for asymmetric alkylation has been reported.[5] We describe herein a novel approach to the preparation of the polymer-bound Evans auxiliaries **5** and **6** and the the first application of this system to the Diels-Alder cycloaddition reaction with overall yields and stereoselectivities that are comparable to those observed for the analogous reactions in solution.



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While the polymer-bound N-propionylated oxazolidinone has been prepared via direct coupling of an N-propionylated oxazolidinone to various resins in loading yields of 30-60%,[5b] we reasoned that acylation of the polymer-bound oxazolidinones **5** and **6**, derived from Wang and hydroxymethyl Merrifield resin, respectively, would provide a more general and higher yielding solution to the preparation of polymer-bound unsaturated N-acyl oxazolidinones. Mitsunobu reaction of either Wang **1** or hydroxymethyl Merrifield resin **2** with *tert*-(butyloxycarbonyl)-L-tyrosine methylester[6] according to the method of Richter and Gadek[7] gave **3** and **4**, respectively, which on reduction (LAH, THF) and reaction with thionyl chloride gave the oxazolidinones **5** and **6**, respectively [IR (KBr): ν_{max} 3423, 1737 cm^{-1} (Wang); ν_{max} 3424, 1756, cm^{-1} (Merrifield)], in consistently greater than 80% loading yields for both resins.

Acylation of the resin-bound oxazolidinones **5** and **6** could be achieved under mild conditions by preforming *trans*-crotonic anhydride *in situ* at -20°C, adding the resin, triethylamine and DMAP, then heating to reflux for 72 hours to give **7** and **8** [IR (KBr): ν_{max} 1720, 1654 cm^{-1} (Wang);ν_{max} 1779, 1686, 1638 cm^{-1} (Merrifield)].[8] Attempted Lewis acid catalysed Diels-Alder reactions between cyclopentadiene and Wang resin-bound N-crotonyl oxazolidinone **7** did not lead to any desired reaction with 1.4-2.8 equivalents of diethylaluminium chloride (Et_2AlCl) within the temperature range -78 °C to 25 °C, either in dichloromethane or neat cyclopentadiene in a sealed tube, as the Wang resin was not stable to Et_2AlCl.

The Merrifield resin-derived dienophile **8** proved to be more robust to the Lewis acidic reaction conditions. Et_2AlCl catalyzed Diels-Alder reaction of **8** and cyclopentadiene gave **9**, which on exposure to lithium benzyloxide gave the Diels-Alder adduct **10**[4] in 26% overall yield (an average of 76% for each of the five steps in the reaction sequence).[9] The 21:1 *endo/exo* ratio and 86% ee of **10** compares favorably with the >20:1 ratio and 88% ee that we observe for the analogous reactions in solution (**10** could be obtained in 42% overall yield for the same sequence of five reactions in solution starting from *tert*-(butyloxycarbonyl)-*O*-benzyl-L-tyrosine methyl ester).[10]

These results establish that Lewis acid-catalyzed Diels Alder reactions can be realized on solid supports by judicious choice of resin. Further studies on Diels-Alder reactions on solid supports are currently underway in our laboratory and our results will be reported in due course.

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9. IR analysis of the polymer recovered from the cleavage reaction shows the carbonyl absorbance of the oxazolidinone (1756 cm^{-1}) so that it should be possible to recycle the resin.
10. The *endo*:*exo* ratios were measured using 500 MHz ^1H NMR of the crude reaction mixtures and the ee of the *endo* product was established by the addition of 20 mol% of $Eu(hfc)_3$ and integrating the methyl doublets.

Note Added in Proof: A complementary procedure for the preparation of **5** and **6** and the application of these materials to aldol and conjugate addition reactions has recently appeared. Similar results regarding the Lewis acid sensitivity of the solid supports are described (Lee, C.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655-2658).