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Imidazolidin-2-ones as Practical, Efficient Chiral Auxiliaries in Diels-Alder Reactions

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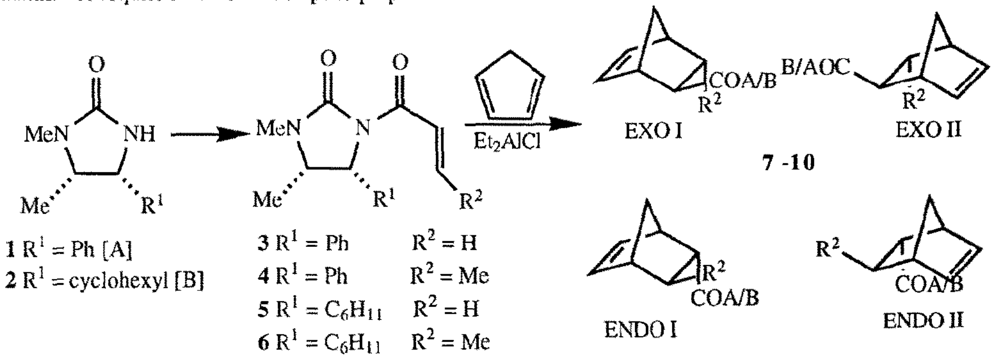
Abstract: The readily prepared (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one and its 4-cyclohexyl analogue proved to be very powerful face-selective auxiliaries in catalysed Diels-Alder cycloadditions of their α,β-unsaturated N-acyl dienophile derivatives.

In recent years, tremendous strides have been made in asymmetric reaction design in Diels-Alder cycloadditions[1]. High stereochemical control has been achieved via the use of chiral dienophiles[2], chiral dienes[3], or chiral catalysts[4]. The first of these approaches has been the most widely studied, and we here describe some of our recent findings in this area.

We have reported the efficiency of the title compounds 1[5] and 2 as auxiliaries in boron mediated aldol condensations with diverse aldehydes[6]. Because of various positive practical features of these auxiliaries (viz: low cost, effective preparation from directly accessible starting materials, ease of N-functionalisation, high degree of crystallinity imparted to derivatives), a natural extension was to investigate whether their efficiency would extend to other diastereoselective processes. Due in part to its high ranking amongst synthetic processes, the Diels-Alder cycloaddition was chosen[7]. It is worthy of note that, although a number of elegant diastereoselective studies have been successfully carried out in this area[1], in most instances the chiral auxiliaries require a number of steps to prepare.



SCHEME 1 : Diels-Alder Reactions of N-Acyl Imidazolidin-2-ones

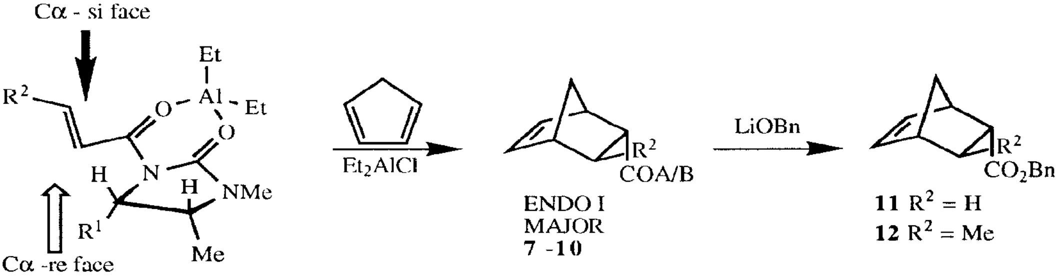
The required α,β-unsaturated N-acyl derivatives **3-6** were readily prepared in essentially quantitative yield by treatment of **1** and **2** with the corresponding acyl chlorides under appropriate mild conditions (dimethylaniline catalysis). For this primary study of the stereoface differentiation efficiency, these were then subjected to low temperature Lewis acid (Et_2AlCl, -78°C, 10-60 min, 70-90% yield) catalysed cycloaddition with the reactive cyclopentadiene (SCHEME 1). The diastereomer ratios were determined by GC-MS and are reported in TABLE 1. In order to confirm the assignment of these product ratios, authentic samples were prepared for comparison via the analogous thermal cycloaddition, separation, and coupling to the auxiliaries.

As is clear from the results, the cyclohexyl derivative **2** is a superior diastereofacial director and this is probably due to a simple increase in steric requirements. This is in stark contrast to the observation of Evans *et al*[2(b)] who report a drop in the selectivity when the related 4-benzyl-oxazolidin-2-one auxiliary is converted to its methylcyclohexyl analogue. Whilst this was rationalised in terms of electronic charge-transfer interactions (π-stacking), it is clearly not paralleled in our system which lacks the additional mobility conferred by the extra methylene present in the Evans system. The cycloaddition mixture **7** and **8** readily afforded highly diastereomerically enriched products by simple recrystallisation. The ultimate sense of stereoselection in the major products was confirmed as Endo $C\alpha$-si by conversion to the known[2(b)] benzyl esters **11** and **12** (SCHEME 2).

TABLE 1 Reaction of Dienophiles 3-6 with Cyclopentadiene

Dienophile	**Product**[a]	Σ**endo**:Σ**exo**	**Endo d.s.**
3	**7**	>6:1	6:1 (22:1)[b]
4	**8**	15:1	9:1 (98:1)[b]
5	**9**	>100:1	>100:1
6	**10**	99:1	>100:1

[a] All new compounds gave satisfactory analytical and spectral data consistent with the structures shown.
[b] The values in parentheses reflect material after a single recrystallisation



SCHEME 2 : Face Selectivity of the Diels-Alder Reaction

Whilst the above results are comparable with those obtained with the analogous oxazolidinone[2(b)] and other systems [2(d)], we believe that there are sufficient additional practical advantages to warrant the use of these systems as alternatives.

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7. Evans[2(b)] has pointed out the potential structural homology between the enolates and dienophiles derived from his related oxazolidinone systems.