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TETRAHEDRON: *ASYMMETRY*

Enhanced reactivity of tuned imidazolidin-2-one chiral auxiliaries in Diels–Alder reactions

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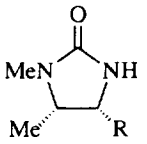
Abstract

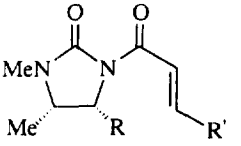
Readily accessible alkyl 1-*N*-benzoyl-2-oxoimidazolidin-4-carboxylates display enhanced reactivity as efficient chiral auxiliaries in the Diels–Alder reaction of their 3-*N*-enoyl derivatives.

Asymmetric variants of the powerful Diels–Alder reaction have continued to attract attention in recent times.[1] Although various groups have shown that the reaction may be amenable to spectacular chiral catalysis,[2] there remains a fundamental need to provide efficient chiral auxiliaries which have an unrestricted range of application. In addition, the beneficial physical properties which an auxiliary (e.g., diastereomer crystallinity) may bring to particular examples, further motivates the requirement for continued efforts in this area.

Earlier, we[3] and others[4,5] communicated the fundamental efficiency of the ephedrine-derived (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one **1** and its 4-cyclohexyl analogue **2** in this role. However, when we tried to extend these applications to dienes beyond the highly reactive cyclic variants (e.g., cyclopentadiene), it became clear that the 3-*N*-enoyl derivatives **3** of these readily accessible imidazolidin-2-ones lacked sufficient reactivity, irrespective of reaction conditions employed.



1 R = Ph
2 R = cycloC_6H_{11}



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This was in stark contrast with the observations of the Evans' group in their elegant exploitation of the closely related oxazolidin-2-one systems.[6] It therefore appeared that the problem was 'electronic' in

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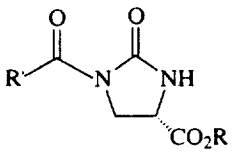
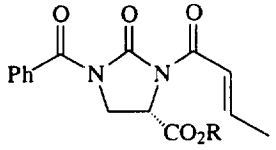
nature and was most likely attributable to the donor properties of the ring 1-*N*-methyl. Since we wished to retain the intrinsically good crystallinity that the imidazolidin-2-one skeleton conferred on our systems, we sought to tune these auxiliaries via modification of the offending 1-*N*-substituent.

In connection with another programme,[7] we had developed easy access to what appeared to be suitably tuned imidazolidin-2-ones **4** derived from a commercially available asparagine derivative.[8] This would then allow the electronic effect of the ring 1-*N*-methyl to be reversed via the corresponding *N*-acyl derivatives **4a**. However, since subsequent functionalisation of the 3-*NH* requires basic conditions, the 3-*N*-benzoyl derivatives **4b** were chosen ahead of the acetyl variants **4b** so as to obviate any possible competitive enolisation. In addition, this selection also provided the auxiliary with a suitable phenyl chromophoric handle to simplify any required chromatographic monitoring.

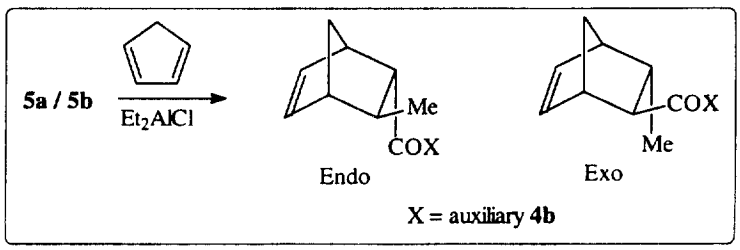


4 R = Me or *t*Bu
a R' = Me
b R' = Ph



5 a R = Me
b R = *t*Bu

With these imidazolidin-2-ones in hand, it was necessary to test not only any enhanced reactivity, but also whether the single ester at the stereogenic C4-centre would retain the desired levels of facial discrimination necessary for synthetically useful asymmetric induction. In order to evaluate these proposals, the corresponding 3-*N*-crotonyl dienophiles **5** were prepared. It was our view that, based on our earlier observations of the corresponding crotonyl derivatives of auxiliaries **1** and **2**,[3] the additional steric element provided by the β-methyl substituent would provide a reasonable test of the reaction limits. The dienophiles **5** were initially subjected to cycloaddition (Et_2AlCl, −78°C) with cyclopentadiene (Scheme 1) to evaluate the endo/exo and face selectivities in comparison with that achieved earlier with auxiliaries **1** and **2**.[3] As shown in Scheme 1, good to excellent endo preference was obtained through variation of the steric demand of the ester. The absolute sense of the stereoselection in the major products was confirmed as endo Cα-*si*, arising from attack of the diene on the dienophile in the preferred *S-cis* conformation, by auxiliary cleavage to the known benzyl ester.[6]



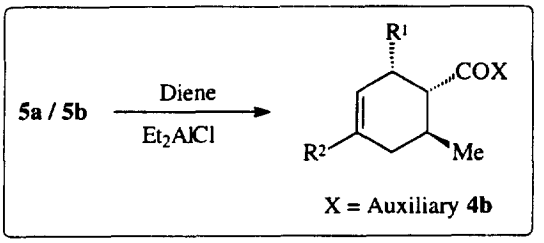
Dienophile	Yield	Endo:Exo	Endo d.r.[a]	Exo d.r.[a]
5a	72	90:10	>100:1	>100:1
5b	78	98:2	>100:1	>100:1

[a] As measured by HPLC versus authentic samples of all four diastereomers.[10]

Scheme 1. Reaction of dienophiles **5** with cyclopentadiene[9,10]

With continued high facial discrimination confirmed, the reactivity of the dienophiles **5** were then tested with the less reactive acyclic isoprene and piperylene dienes (Scheme 2). The results of these

studies show that, even with the steric demand of the β-substituted *N*-crotonyl systems, the presence of the electron-withdrawing 1-*N*-benzoyl raises the dienophile reactivity profile to permit cycloaddition to proceed with relatively unreactive dienes.[11] These reactions did, however, require that the temperature be raised to 0°C in order to achieve complete consumption of the dienophile. Whilst these results, probably due to the higher reaction temperature required, show lower levels of stereoselectivity than the corresponding oxazolidinones,[6] the greater crystallinity of the comparatively much higher melting products, allows facile purification of the major isomer by simple recrystallisation.[12]



Dienophile	Diene	d.r.[a,b]	Isolated yield of pure major	m.p. °C
5a	isoprene	69:31	68 (R^1 = Me,R^2 = H)	140
5b	isoprene	83:17	61 (R^1 = Me, R^2 = H)	127
5b	piperylene	72:28	50 (R^1 = H, R^2 = Me)	121

[a] As determined by HPLC.[13] [b] The purity of each major diastereomer was raised to >99:1 after a single recrystallisation

Scheme 2. Reaction of dienophiles **5** with acyclic dienes[9,13]

Acknowledgements

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9. All new compounds gave satisfactory analytical and spectral data consistent with the structures shown.
10. Silica gel column with CH_2Cl_2:EtOAc:hexane eluant (1:5:94). Retention times: endo II 9.1; exo I 9.6; exo II 10.0; endo I 10.7 min.

11. Initial results of this work were presented at the Royal Australian Chemical Institute Organic Chemical Congress, Rockhampton, July 1996.
12. The absolute configuration of the major isoprene adduct was determined via auxiliary cleavage to the benzyl ester (45%). This gave benzyl (4*S*,5*S*)-1,5-dimethylcyclohexene-4-carboxylate with $[\alpha]_D$ +51, (lit:[6] +54). The absolute configuration of the major piperylene adduct was inferred by analogy with the corresponding literature.[6]
13. Silica gel column with CH_2Cl_2:EtOAc:hexane eluant (1:5:94). Retention times of isoprene adduct: major 18.4; minor 19.1 min. Piperylene adduct: major 13.6; minor 12.3 min.