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Diastereoselective, Lanthanide-Catalysed, Inverse Electron-Demand Diels-Alder (IEDDA) Reactions of 3-Carbomethoxy-2-Pyrone (3-CMP) Derivatives.¶

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¶ Dedicated with deep respect to Professor Gunter Helmchen

Abstract: *Cycloaddition reactions between the chiral 2-pyrone derivatives 3 and various dienophiles, catalysed by lanthanide shift reagents, afford bicyclic lactones 8 in high diastereomeric excesses.*

Tandem and cascade processes are important synthetic reactions which allow the regio- and stereo-controlled formation of several carbon-carbon bonds and/or ring systems in a single operation.[1] We have recently described a novel cascade process: the Tandem Pericyclic Reaction (TPR),[2] which involves thermal, sequential, Diels-Alder cycloadditions of 2-pyrone derivatives,[3] such as 1 with suitable α,ω-dienes, affording polycyclic structures in good yields. Optimisation of this process naturally lead us to investigate the use of Lewis acids[4] and it was rapidly discovered that usual Lewis acids (e.g. $BF_3.Et_2O$) promptly decarboxylate the bicyclic lactones.[5] Stimulated by the pioneering work of Danishefsky,[6] we successfully used lanthanides, including chiral shift reagents, to catalyse the IEDDA cycloaddition of 3-CMP 1 with a range of alkyl- and silyl-enol ethers **without subsequent decarboxylation of the [4+2] adducts.**[7]

In this letter, we report on the **catalytic, highly diastereoselective,** IEDDA cycloadditions of the chiral 3-CMP derivative **3d**. While this work was in progress, Posner and Co-workers, reported an example of this type of reaction.[8]

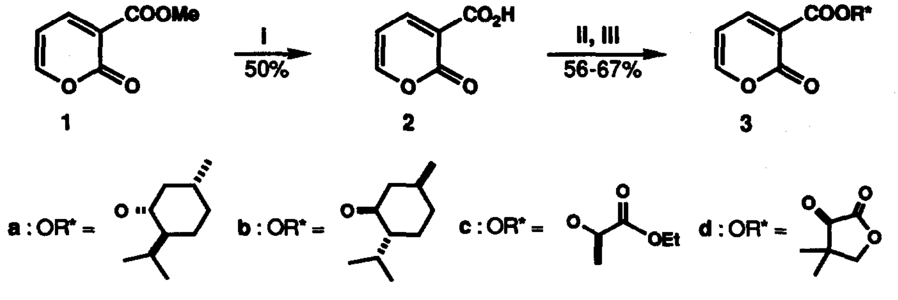
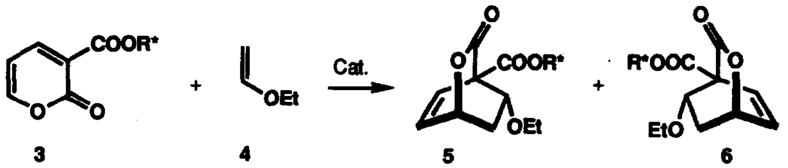


Figure 1

I = aq.HCl, 40-45°C ; II = $SOCl_2$, reflux ; III = R*OH, CH_2Cl_2, Et_3N

The starting 2-pyrones **3a** - **3d** were easily prepared by acid-mediated hydrolysis[9] of 3-CMP **1** followed by esterification of acid **2** using a variety of homochiral alcohols (Figure 1). The diastereoselectivity of the inverse electron-demand Diels-Alder reaction was then investigated using ethyl vinyl ether **4** as the dienophile and readily available Europium shift reagents. The results are summarised in Table 1.

Table 1. Diastereoselective Reaction of 3 with Ethyl Vinyl Ether



Entry	Pyrone	Catalyst[a]	Yield[b]	d.e.[c]
1	1	(+)-Eu(hfc)$_3$	88%	<5%[d]
2	3a	(+)-Eu(hfc)$_3$	83%	28%
3	3b	(+)-Eu(hfc)$_3$	85%	8%
4	3c	(+)-Eu(hfc)$_3$	82%	61%
5	3d	(+)-Eu(hfc)$_3$	97%	>95%
6	3d	(-)-Eu(hfc)$_3$	91%	>95%
7	3d	Eu(fod)$_3$	94%	>95%

(a) 0.1 eq of catalyst, 20°C, CH_2Cl_2 ; (b) All yields refer to pure, isolated material ; (c) Measured by ^{13}C NMR and/or ^{1}H NMR ; (d) Enantiomeric excess.

Initial cycloaddition of 3-CMP **1**, employing 10 mol% of (+)-Eu(hfc)$_3$, produced the adduct **5** in good yield but with negligible enantiocontrol (Table 1, Entry 1). In contrast, the homochiral 3-CMP derivative **3a**, possessing a (-)-menthol ester, afforded the bicyclic lactones **5a** and **6a** in a 64:36 ratio (Table 1, Entry 2). The increase in diastereoisomeric excess reflects the matching of the two reaction partners.[10] Indeed, replacing the (-)-menthol ester by the (+)-enantiomer resulted in a substantial lowering of the d.e. due to the mismatching of the chiralities of the pyrone **3b** and the lanthanide catalyst (Table 1, Entry 3).

The significant increase in diastereocontrol, observed with the lactate-containing 3-CMP **3c** (Table 1, Entry 4), provided the first indication that two carbonyls were required for attaining efficient facial selectivities.[11] **When employing pantolactone[12] as the chiral auxiliary, essentially complete diastereocontrol was finally realised, at room temperature and under catalytic conditions** (Table 1, Entry 5). In contrast to the results obtained with the menthol- and lactate-containing reagents **3a-c**, the powerful directing effect of the pantolactone auxiliary completely overrides the facial preference of the lanthanide catalyst, giving rise to the formation of the same diastereoisomer **5d** in >95% d.e. (Table 1, Entry 7). **Remarkably, equally high levels of diastereofacial preference are obtained using the achiral shift reagent: Eu(fod)$_3$** (Table 1, Entry 7).[13] Although the sense of asymmetric induction is dictated by the chiral auxiliary, the lanthanide catalyst is crucial to the obtention of high diastereomeric excesses. Other examples of this catalytic, diastereoselective IEDDA reaction are collected in Table 2.

Table 2. Lanthanide-Catalysed Diastereoselective Diels-Alder Reaction of **3d**

Entry	Substrate	Catalyst$^{(a)}$	Yield$^{(b)}$	d.e.$^{(c)}$
1		Eu(fod)$_3$	95%	>95%
2		(+)-Eu(hfc)$_3$	84%	>95%
3		(+)-Eu(hfc)$_3$	87%	>95%
4		(+)-Eu(hfc)$_3$	91%	75%$^{(d)}$
5		(+)-Eu(hfc)$_3$	96%	~5%

(a) 0.1eq of catalyst used unless otherwise indicated ; (b) All yields refer to pure, isolated material ; (c) Measured by ^{13}C NMR and/or ^{1}H NMR ; (d) After one crystalisation from petrol/CCl$_4$, a d.e. >95% is obtained.

Aside from dihydrofuran, that gave a negligible d.e.,[14] all the other substrates reacted with **3d** with good to excellent diastereoselectivity. The facial selectivity observed in these cycloadditions can be rationalised by invoking the chelated structure **B** (Figure 2). Attack of the dienophile from the Re-face of this complex leads to the observed stereochemistry of the final product.[15] The absolute chirality at carbon (•) dictates which one of the two possible seven-membered ring chelates could be produced upon coordination to the lanthanide. The rigidity of this chelate then ensures efficient steric blocking of the Si-face by the α-methyl substituent. This model also rationalises the observation that achiral $Eu(fod)_3$ leads to the same levels of diastereocontrol than optically active $Eu(hfc)_3$. Chelate **A** is disfavoured by dipole-dipole interactions.

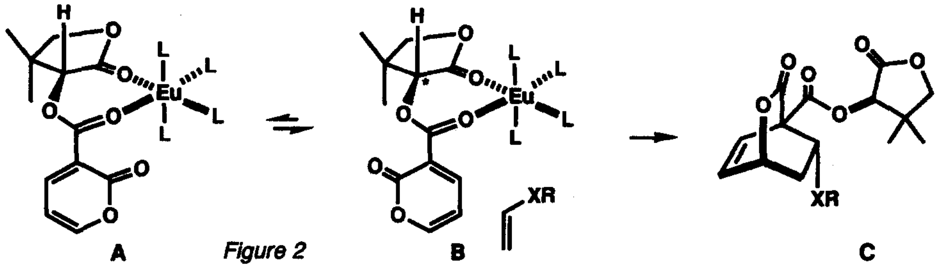


Figure 2

In summary, a highly diastereoselective, lanthanide-catalysed IEDDA cycloaddition of 3-CMP **3d** has been described. Further studies aimed at extending the scope of this methodology are being actively pursued in our laboratory and the results will be reported in due course.

Acknowledgements
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13. This results contrasts with the one reported by Posner and highlights again the increased facial selectivity provided by the pantolactone auxiliary over the lactate one. Indeed, using the lactate derived 2-pyrone, a significant fall in diastereocontrol is observed when an achiral lanthanide is used or when mismatching with the enantiomeric praseodymium complex occurs.
14. This poor d.e. might be due to the reversibility of this reaction. We are grateful to Professor G. Helmchen for this suggestion
15. The relative and absolute stereochemistry of the major diastereoisomer was established by X-ray crystallographic analysis.

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