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Catalytic, Enantioselective, Inverse Electron-Demand Diels-Alder (IEDDA) Reactions of 3-Carbomethoxy-2-Pyrone (3-CMP).¶

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¶ Dedicated with deep respect to Professor Henri Kagan

Abstract: *Cycloaddition reactions between 3-CMP 1 and various vinyl ethers and vinyl sulphides, catalysed by the Yb(OTf)$_3$-Binol complex, afford bicyclic lactones 3 in moderate to excellent enantiomeric excesses.*

In the preceeding Communication,[1] we have described our results on the lanthanide-catalysed diastereocontrolled Inverse Electron-Demand Diels-Alder (IEDDA) cycloadditions of chiral esters derived from 3-carbomethoxy-2-pyrone (3-CMP) 1 and have demonstrated that good that excellent levels of facial selectivity were obtained using pantolactone as the chiral auxiliary. The presence of a lanthanide shift reagent, chiral or not, was a prerequisite for high d.e. Although this diastereoselective procedure is quite efficient, enantioselective catalysis is, by far, a more elegant and versatile alternative.

In this Article, we report on some of our recent results in the generation of a **lanthanide-catalysed, enantioselective**, version of the IEDDA cycloaddition of 3-CMP 1[2] with vinyl ethers and vinyl sulphides 2, leading to the preparation of bicyclic lactones 3 in good to excellent enantiomeric excesses (Figure 1).[3] These lactones, upon mild thermolysis, extrude CO_2 and generate the corresponding substituted cyclohexadienes, which are analogues of those obtained by microbial oxidation of aromatics.[4]

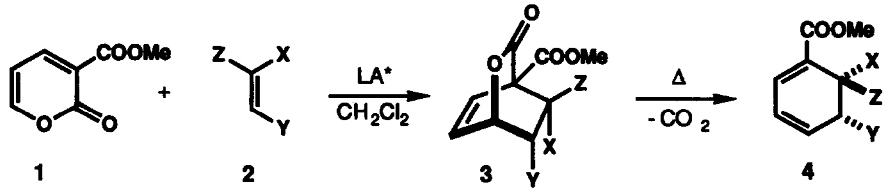
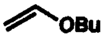
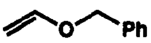
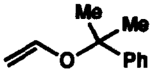
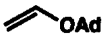


Figure 1

X = OR, SR ; Y, Z = H, alkyl

Early attempts at using chiral lanthanide shift reagents, such as (+)-Eu(hfc)$_3$,[5] to catalyse the enantioselective IEDDA reaction of 3-CMP 1 lead to disappointingly low levels of enantioselection (<5% ee). While screening a range of optically pure lanthanide catalysts,[6] we became aware of the beautiful work of Kobayashi,[7] using a chiral ytterbium triflate complex, to catalyse the enantioselective Diels-Alder reaction between cyclopentadiene and acryloyl-1,3-oxazolidin-2-one derivatives with good e.e.'s. Initial cycloaddition between 1 and butyl vinyl ether, using the Kobayashi system afforded the desired adduct 3 (X = OBu, Y = Z = H) in a modest 36% e.e., after considerable variation of the reaction conditions (Table 1, Entry 3).

Table 1. Catalytic Enantioselective IEDDA Reactions of 3-CMP with Vinyl Ethers.

Entry	Substrate(a)	Yield(b)	ee(c)
1		93%	<5%
2		90%	27%
3		95%	36%
4		95%	49%
5		93%	71%
6		91%	82%
7		97%	85%(d)

(a) 0.1eq of catalyst used unless otherwise indicated ; (b) All yields refer to pure, isolated material ; (c) Measured by ^1H NMR using (R)-(+)-Eu(hfc)$_3$; (d) One recrystallisation gave optically pure product. Cy = cyclohexyl ; Ad = adamantyl.

The presence and nature of the chiral adjuvant proved to be critical to the success of this reaction. Indeed, whereas Yb(OTf)$_3$ itself, or as a combination with an amine, does not catalyse the IEDDA reaction of 1 with butyl vinyl ether, addition of an alcohol, a diol or an amino-alcohol modifies the catalyst in such a way that cycloaddition can take place.[8] Although any chiral additive belonging to these three classes does efficiently promote the IEDDA reaction, the enantiomeric excess of the product varied considerably (Binol was found to be the best chiral ligand).[9] The presence of a base was also important but its effect on the e.e. was less pronounced.[10]

Remarkably, the enantioselectivity of this reaction is directly dependent upon the nature of the group present on the oxygen atom of the vinyl ether substrate (Table 1, Entries 2-7).[11] Thus, increasing the size of the alkyl substituent from ethyl to butyl to benzyl resulted in a gradual increase of the e.e. from 27% to 49%. Using a bulkier, tertiary substituent, such as the cumyl one, brought the enantiomeric excess, for the first time, above 50% (Table 1, Entry 5). The cyclohexyl moiety proved to be even better, affording the bicyclic lactone 3 (X = OCy, Y = Z = H) in 91 % yield and 82% e.e. (Table 1, Entry 6). Maximum enantiofacial selectivity was eventually reached in the reaction of adamantyl vinyl ether with 3-CMP, giving the cycloadduct 3 (X = OAd, Y = Z = H) in 85% e.e. (Table 1, Entry 7). Although the increase in e.e. from cyclohexyl to adamantyl is negligible, both the adamantyl vinyl ether and the derived bicyclic adduct are highly crystalline conpounds. **One recrystallisation gave essentially optically pure product.** The strong dependence of enantioselectivity upon steric bulk is also confirmed by the formation of nearly racemic bicyclic lactone when employing dihydrofuran as the dienophile (Table 1, Entry 1).

Vinyl sulphides also reacted smoothly with 3-CMP 1 in the presence of the chiral ytterbium triflate complex. Again, a linear dependence of e.e. with the steric size of the substituent on sulphur was noticed. However, the vinyl sulphides always gave higher e.e.'s than the corresponding vinyl ethers (Table 2).

Table 2. Enantioselective IEDDA Reactions of 3-CMP with Vinyl Sulphides.

Entry	Substrate[(a)]	Yield[(b)]	ee[(c)]
1		96%	30%
2		70%	57%
3		93%	72%
4		88%	86%
5		91%	>95%

(a) 0.1eq of catalyst used unless otherwise indicated ; (b) All yields refer to pure, isolated material ; (c) Measured by ^{1}H NMR using (R)-(+)-Eu(hfc)$_3$; Cy = cyclohexyl

The cyclohexyl group proved equally efficient in the sulphur series, producing bicyclic lactone 3 (X= SCy, Y = Z = H) in 86% e.e. However, the right balance between electronic and steric factors was reached using the phenyl substituent. **The desired cycloaddition product was obtained as a single enantiomer in up to 91% yield** (Table 2, Entry 5).[12] This ytterbium-catalysed reaction also displays a negative non-linear effect. Indeed, using (S)-(-)-Binol of 96% optical purity lead to the scalemic adduct 3 (X= SPh, Y = Z = H) in only 86% e.e.

In summary, we have described an efficient, catalytic, asymmetric version of the IEDDA cycloaddition of 3-CMP with vinyl ethers and vinyl sulphides that gives bicyclic lactones 3 in good to excellent e.e.'s. Further studies aimed at improving the enantioselectivity of these cycloadditions, expanding the range of substrates and understanding the mechanism of this asymmetric catalysis are being actively pursed in our laboratory. The results of these investigations will be reported in due course.

Acknowledgements

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8. We have observed previously that Lewis acids such as BF$_3$.Et$_2$O, TiCl$_4$, and Et$_2$AlCl coordinate strongly to 2-pyrone, eventually precipitating the complexed pyrylium cation (Markó, I. E.; Evans, G. R. *Unpublished Observations*). We believe that Yb(OTf)$_3$ coordinates too strongly to 3-CMP, forming the unreactive pyrylium form. By adding an alcohol and displacing one or more triflate ligands, the Lewis acidity of the lanthanide complex is tempered and IEDDA reaction then ensues.
9. (l)-(-)-menthol (<5% e.e.), (-)-ephedrine (<5% e.e.), dimethyl Taddol (<5% e.e.), phenyl Taddol (<5% e.e.).
10. Bu$_3$N (95% yield, 31% e.e.), 1,2,2,6,6,-pentamethyl-piperidine (93% yield, 31% e.e.).
11. The importance of the steric effect of the amine additive was demonstrated by Kobayashi (Ref. 7). Increase in steric effects related to increase in d.e. in double diastereocontrolled reactions of a sulphur-substituted 2-pyrone derivative was noticed earlier: Posner, G. H,; Wettlaufer, D. G. *Tetrahedron Lett.*, **1986**, *27*, 667.
12. It is noteworthy that, in contrast to the sulphur series, phenyl vinyl ether gives a lower e.e. (75% e.e.) than the cyclohexyl derivative (82% e.e.). The cycloaddition of phenyl vinyl ether also proceeds abnormaly slowly, giving only an 11% yield of Diels-Alder adduct after 24 hrs. Even more puzzling is the observation that the e.e. of the product decreases (58% e.e.; 48 hrs) with the reaction time. Study of this system might shed some light on the mechanism of the asymmetric catalysis.

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