

Catalytic, enantioselective, inverse electron-demand Diels–Alder reactions of 2-pyrone derivatives[#]

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Abstract. The lanthanide-catalysed, diastereo- and enantio-controlled Inverse Electron-Demand Diels–Alder cycloadditions of 3-carbomethoxy-2-pyrone derivatives with electron-rich dienophiles is shown to proceed with high levels of asymmetric induction.

The construction of carbon-carbon bonds is one of the most fundamental processes of organic chemistry. In contrast to Nature, which long ago harnessed the difficulties inherent in the formation of several carbon-carbon bonds and/or ring systems in a single step, chemists all too often construct complex natural products by the lengthy, sequential building of one covalent linkage at a time, a rather inefficient and inelegant approach.

As part of a programme aimed at the rapid and efficient synthesis of complex natural products, we recently reported a cascade process which consists of a series of pericyclic reactions.^{1, 2} This Tandem Pericyclic Reactions (TPR) methodology involves the intermolecular Diels–Alder cycloaddition of 2-pyrone **1** with an α,ω -diene **2**, followed by extrusion of CO₂ from bicyclic lactone **3** and intramolecular Diels–Alder reaction of cyclohexadiene **4** to afford the polycyclic structure **5** (Figure 1).³

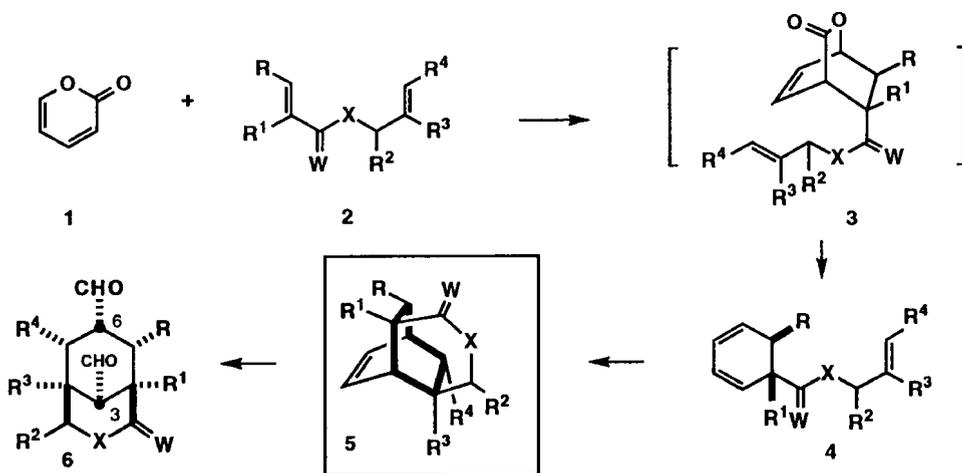


Figure 1

Further manipulation of such polycycles allows a rapid entry into a range of complex natural products.^{4, 5} For example, the combination TPR of 2-pyrone **1** followed by oxidative cleavage of the resulting tricycle **5** generates rapidly [3,1,*n*] bicycles of general structure **6** (Figure 1). These are important subunits, present in biologically active natural products, such as the gibberellins.⁶

[#] Dedicated fondly to Dr Fons De Knaep for his support and friendship

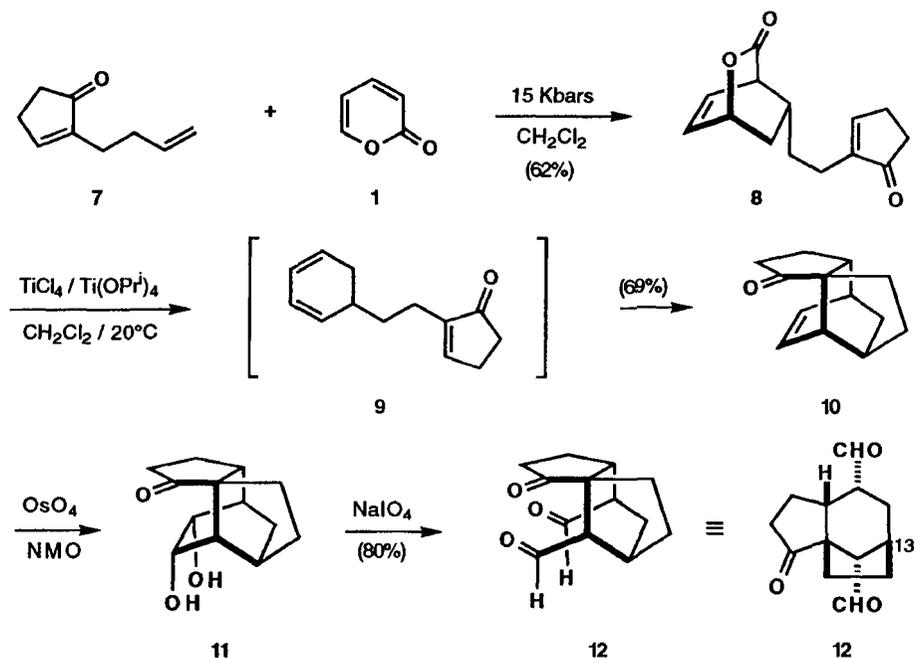


Figure 2

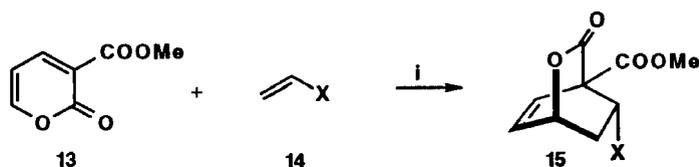
Our approach towards a model for gibberellic acid synthesis is displayed in Figure 2. The efficiency of the TPR methodology is noteworthy and is highlighted by the obtention of the CDE model system in only four steps from readily available starting materials.^{4a}

At this stage, the necessity to incorporate a tertiary hydroxyl function at C13 of 12 prompted us to study the tandem pericyclic reactions of electron-deficient 2-pyrone derivatives with electron-rich dienophiles.^{2b, 7} Impressive work in this area, using sulphur-substituted 2-pyrones had been already reported by Posner^{7a-d} while Shimo described the TPR of 5-carbomethoxy-2-pyrone with various dienophiles.^{7e} For our synthetic venture, we employed 3-carbomethoxy-2-pyrone 13 (3-CMP) and we rapidly discovered, that in contrast to a previous report,⁸ 3-CMP underwent smooth inverse electron-demand Diels-Alder (IEDDA) cycloaddition with a range of enol ethers, affording bicyclic lactones 15 in moderate to good yields (Table 1).⁹ A highly polar solvent such as nitromethane or DMSO proved to be essential to the success of this reaction. In every case studied, and in notable contrast to the lack of stereoselectivity displayed by the corresponding 5-carbomethoxy-2-pyrone (5-CMP),^{2b} and other 3-substituted-2-pyrones,⁷ complete *endo*-selectivity was observed.

Unfortunately however, even under these optimised conditions, some dienophiles refused to undergo cycloaddition. For example, while vinyl sulphides reacted sluggishly, no cycloadducts were observed with enolsilanes, even under forcing conditions.

After considerable experimentation, it was eventually discovered that certain lanthanides were highly effective catalysts.¹⁰ Moreover, they are sufficiently powerful to catalyse the IEDDA reaction between 3-CMP and several electron-rich dienophiles, but are not acidic enough to promote the extrusion of CO₂ from the bicyclic lactone 15, a reaction rapidly observed with most common Lewis acids.¹¹ As an added bonus, polymerisation of the vinyl ether/vinyl sulphide partner was rarely encountered using lanthanide catalysis. Some results illustrating the scope this methodology are collected in Table 1.

Table 1. Lanthanide Catalysed IEDDA Reactions of 3-CMP



Entry	Olefin	Thermal	Catalysed	Entry	Olefin	Thermal	Catalysed
1		95%	98%	5		-	77%
2		-	80%	6		-	88%
3		-	67%	7		95%	96%(a)
4		-	92%	8		95%	94%(b)

i = Eu(hfc)₃ ; (a) = Pr(hfc)₃ ; (b) = Yb(hfc)₃

With a simple and efficient broad-ranging method available for the preparation of a plethora of bicyclic lactones of type 15, we next turned our attention to their asymmetric synthesis and decided to employ initially the chiral auxiliary approach. Two options were possible: either appending the auxiliary on the 2-pyrone skeleton or connecting it onto the dienophile. Pioneering work by Posner¹² and Thornton¹³ demonstrated that useful levels of diastereocontrol could be attained when a chiral vinyl ether was employed as the dienophile in conjunction with either a 3-sulphonyl substituted-2-pyrone or a 3-hydroxy/acyloxy-2-pyrone respectively, in the presence of a Lewis acid.

With the belief that 3-CMP coordinates to the lanthanide catalyst by virtue of both of its carbonyl functions, forming a six-membered ring chelate, we chose to place the chiral auxiliary on the ester function of 3-CMP. Four auxiliaries ((-)-menthol, (+)-menthol, (-)-ethyl lactate and (-)-pantolactone) were selected and the corresponding 2-pyrone esters 17 were prepared in a straightforward manner, as shown in Figure 3.¹⁴

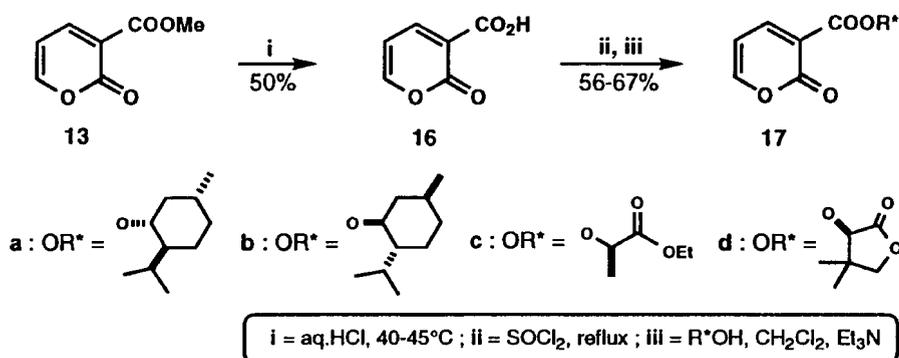
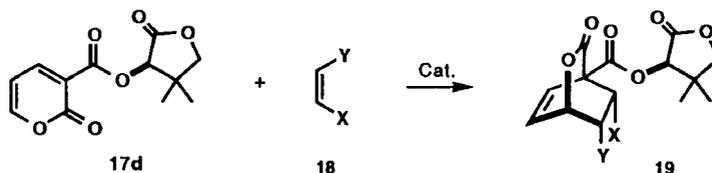


Figure 3

Table 2. Lanthanide-Catalysed Diastereoselective Diels-Alder Reaction of **17d**

Entry	Substrate	Catalyst ^(a)	Yield	d.e. ^(c)	Entry	Substrate	Catalyst ^(a)	Yield	d.e. ^(c)
1		(+)-Eu(hfc) ₃	97%	>95%	5		Eu(fod) ₃	95%	>95%
2		(-)-Eu(hfc) ₃	91%	>95%	6		(+)-Eu(hfc) ₃	87%	>95%
3		Eu(fod) ₃	94%	>95%	7		(+)-Eu(hfc) ₃	91%	75% ^(d)
4		(+)-Eu(hfc) ₃	84%	>95%	8		(+)-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 ¹³C NMR and/or ¹H NMR; (d) After one crystallisation from petrol/CCl₄, a d.e. >95% is obtained.

The pantolactone-derived 2-pyrone **17d** soon proved to be the most efficient. High levels of diastereocontrol could be obtained in its reaction with a range of enol ethers and vinyl sulphides, as summarised in Table 2.

It is noteworthy that, in this case, both (+)- and (-)-Eu(hfc)₃ afforded the same diastereoisomer **19d** with >95% *de* (Entries 1 and 2). Thus, the asymmetric inducing ability of the pantolactone auxiliary far outweighs any matching or mismatching influences of the lanthanide catalyst.^{15, 16} This useful property allowed us to employ less expensive, achiral lanthanides, such as Eu(fod)₃ and obtain the desired diastereoisomer with >95% *de* (Entry 3). It is important to mention at this stage that these IEDDA cycloadditions only employ **catalytic amounts** of the lanthanide complex in contrast to an example reported by Posner that necessitates **more than stoichiometric quantities** of the organometallic reagent.¹⁷

Apart from dihydrofuran, which gave a 1:1 mixture of two diastereomeric bicyclic lactones **19**, all the other vinyl ethers and vinyl sulphides afforded the desired CO₂ adducts with good to excellent diastereocontrol (Entries 1-7). In the case of the phenyl vinyl sulphide adduct (**19**, X=SPh, Y=H), one recrystallisation gave optically pure product.

Suitable crystals of this single diastereoisomer were grown and an X-ray diffraction analysis was performed, allowing the absolute stereochemistry of the major isomer to be unambiguously established.¹⁸ The structure is shown in Figure 4.

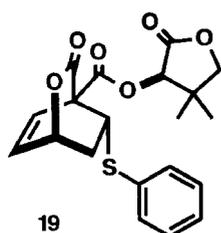
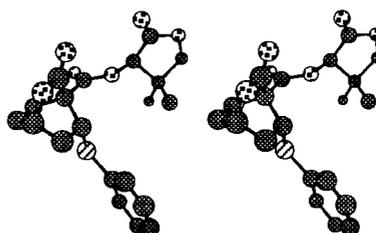
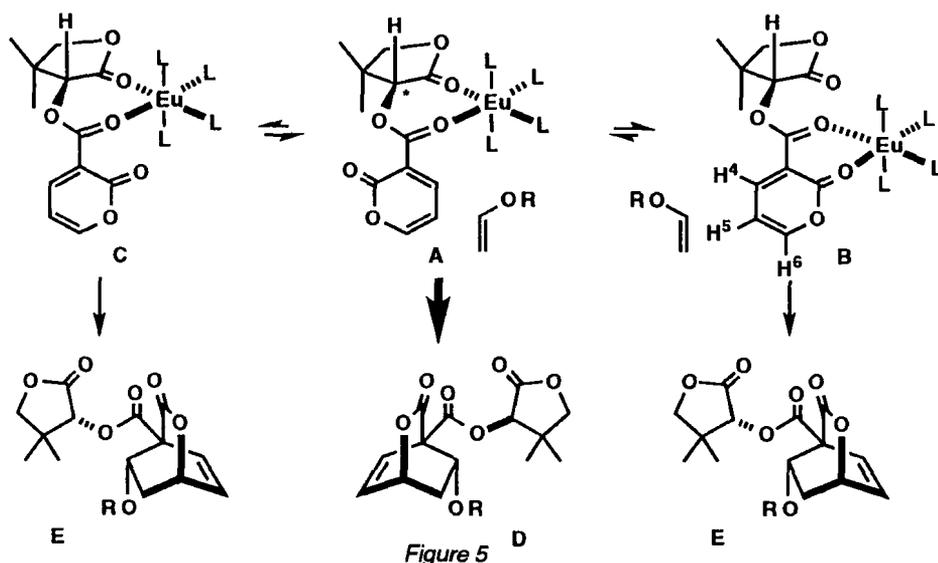


Figure 4





The preferential formation of this diastereoisomer implies that the dienophiles, while presenting their *Si* face, approach the pyrone derivative on its *3Re,6Re* face. A plausible mechanistic rationale is displayed in Figure 5.

From kinetic and spectroscopic studies,¹⁹ it is believed that the cycloaddition proceeds through chelate **A**. In this complex, the seven-membered ring renders the complex rigid and the pseudo-axial methyl substituent of the pantolactone auxiliary shields the *3Si,6Si* face of the diene. Selective attack of the dienophile at the other face, leads to the formation of the observed major diastereoisomer **D** (Figure 5).

Although high levels of diastereocontrol have already been obtained, some vinyl ethers/vinyl sulphides give poor to moderate *de*'s. We are currently optimising this method and are investigating synthetic applications of the bicyclic lactones and cyclohexadienes.

While the auxiliary-based approach was being studied, the beautiful work of Kobayashi²⁰ appeared in the literature. In this key article, a chiral ytterbium species, prepared from ytterbium triflate, binol and a tertiary amine was demonstrated to be an excellent catalyst for the enantioselective Diels-Alder cycloaddition between cyclopentadiene **21** and the oxazolidinone-derived crotonate **20** (Figure 6).

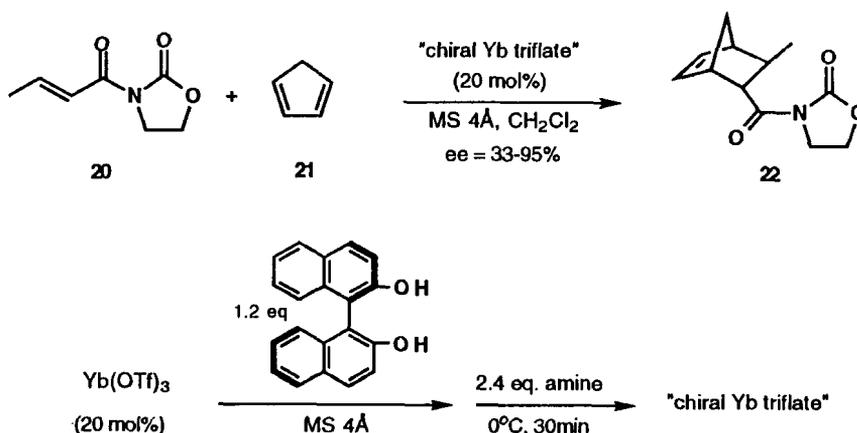


Table 3. Catalytic Enantioselective IEDDA Reactions of 3-CMP with Vinyl Ethers.

Reaction scheme: 3-CMP (13) + Vinyl ether (21) $\xrightarrow[\text{iPr}_2\text{NEt}]{\text{Yb(OTf)}_3, \text{(R)-(+)-binol}}$ Lactone (22) + Lactone (23)

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

(a) 0.2eq 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) Recrystallisation gave essentially optically pure product. Cy = cyclohexyl; Ad = adamantyl.

Based on our diastereoselective chelate model, we reasoned that the Kobayashi ytterbium complex could be a suitable catalyst for the enantioselective inverse electron-demand Diels-Alder reaction of 3-carbomethoxy-2-pyrone derivatives (Table 3).

Initial use of the combination Yb(OTf)₃/binol led to only moderate success.^{21b} For example, the IEDDA cycloaddition of 3-CMP 13 with butyl vinyl ether afforded the lactone 22/23 with an optical purity of only 31% *ee* (Table 3, Entry 3). The nature of the amine was shown by Kobayashi to be crucial to the obtention of high *ee*'s in the normal Diels-Alder cycloadditions. In our case, employing different amines resulted in no significant changes in the *ee*'s. Besides binol, several other diols, alcohols and amino-alcohols were also tested in attempts to increase the enantioselectivity of this reaction but, unfortunately, to no avail.²²

It is important to note that Yb(OTf)₃ alone does not catalyse the IEDDA reaction of 3-CMP with either vinyl ethers or vinyl sulphides. In sharp contrast, addition of an alcohol, a diol or an amino-alcohol leads to smooth cycloaddition.²³ Alas, in all the cases studied, virtually racemic material was obtained.

The reaction was then extended to other vinyl ethers and vinyl sulphides in order to delineate its scope and determine any possible trend that could allow better *ee*'s to be obtained.

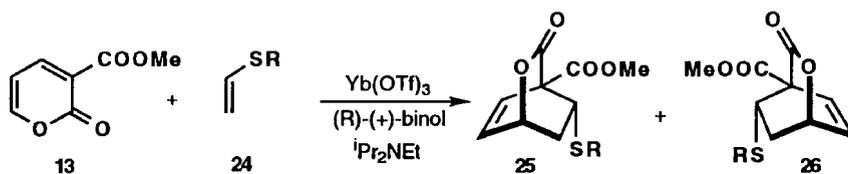
Whilst dihydrofuran gives essentially racemic cycloadduct, ethyl vinyl ether affords the desired product in a lower *ee* than the corresponding butyl vinyl ether (Table 3). Interestingly, an almost linear relationship between the size of the substituent present on the oxygen atom of the dienophile and the enantioselectivity of the reaction could be established. The best enantiomeric excess observed under these standard conditions was 85% *ee* which was obtained using the adamantyl substituent.^{21a} Cyclohexyl vinyl ether gave similar levels of enantiocontrol but the

adamantyl vinyl ether was preferred because both the vinyl ether and the cycloadduct are beautifully crystalline. In this case, careful recrystallisation produced optically pure bicyclic lactone.

Since the absolute stereochemistry of the bicyclic lactones could not easily be inferred from correlation with other compounds of known absolute stereochemistry, the lactone ring of the enantiomerically pure cyclohexyl vinyl ether/3-CMP adduct was opened with (*S*)-(-)- α -methyl benzylamine. The diastereomerically pure amide was beautifully crystalline and an X-ray diffraction analysis was successfully performed allowing the absolute stereochemistry of the adduct to be unambiguously established as 1*R*,2*R*,5*R*.²⁴

This implies that the alkene approaches the 3-CMP/ytterbium complex on the 3*Re*,6*Re* face while presenting its Si-face. The opposite stereochemistry is observed employing (*S*)-(-)-binol as the chiral adjutant.

Table 4. Catalytic Enantioselective IEDDA Reactions of 3-CMP with Vinyl Sulphides.



Entry	Substrate ^(a)	Yield ^(b)	ee ^(c)
1	SEt	96%	30%
2	SBu	70%	57%
3	SBn	93%	72%
4	SCy	88%	86%
5	SPh	91%	>95%

(a) 0.2eq 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) Recrystallisation gave essentially optically pure product. Cy = cyclohexyl.

While good levels of enantiocontrol could now be achieved with vinyl ethers, even better *ee*'s were obtained with vinyl sulphides (Table 4).^{21a} In each case, the enantioselectivity was higher for the vinyl sulphide than for the corresponding vinyl ether (Compare Tables 3 and 4). For example, while butyl vinyl ether afforded the bicyclic lactone in 36% *ee*, butyl vinyl sulphide lead to the corresponding sulphur containing adduct in 57% *ee*.

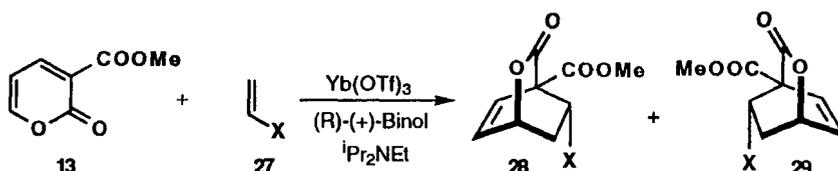
Delightfully, the same correlation between *ee* and size of the substituent on the heteroatom was also observed in the sulphur series. The gradual increase in *ee* culminated with phenyl vinyl sulphide; a single enantiomer of the bicyclic lactone product being obtained (Table 4, Entry 5).

The thiophenyl-substituted adduct was also crystalline and an X-ray analysis was performed. The absolute stereochemistry of the adduct was determined to be 1*R*,2*R*,5*R* by using the anomalous dispersion effect of the sulphur atom, in complete agreement with the oxygen series.²⁴ The reason for the increase in the enantiomeric excesses of the sulphur series compared to the oxygen one is not yet understood.

With the desire to further increase the enantioselectivity of the asymmetric IEDDA reaction of the vinyl ethers, various parameters were varied. It was soon realised that both non-polar solvents, such as toluene, and highly polar ones, such as acetonitrile or nitromethane, lead to lower enantioselectivities in the cycloaddition reaction. While it is believed that the active catalyst is not very soluble in toluene, resulting in reduced levels of enantiocontrol, solvents like nitromethane coordinate to $\text{Yb}(\text{OTf})_3$ and generate an active, yet achiral, catalyst that competitively promotes the formation of racemic material.

In an independent experiment, $\text{Yb}(\text{OTf})_3$ alone, known not to catalyse the IEDDA reaction of 3-CMP with vinyl ethers and vinyl sulphides in CH_2Cl_2 , was dissolved in nitromethane and the reactants added. Smooth formation of the [4+2] adduct rapidly ensued, strongly suggesting activation of the lanthanide catalyst by nitromethane and corroborating the above-mentioned hypothesis.

Table 5. Improved Enantioselective Catalytic IEDDA Reactions of 3-CMP



Entry	X in substrate ^(a)	Yield ^(b)	ee ^(c,d) (%)
1	OBu	82%	53 (36)
2	SBu	95%	74 (57)
3	OCy	90%	92 (82)
4	OAd	91%	93 (86)
5	SPh	91%	>95 (95)

(a) 0.2 eq of catalyst used unless otherwise indicated ; (b) All yields are for pure, isolated material ; (c) Measured by ^1H NMR; (d) numbers in parenthesis refer to previous ee's ; Cy = cyclohexyl; Ad = adamantyl

Of all the solvents tested to date, dichloromethane proved to be the best. However, the purification of this solvent is a critical parameter for the obtention of high ee's. Indeed, it was found that traces of ethanol had to be eliminated in order to achieve high enantioselectivities. Under these optimised conditions, high enantioselectivities (>90% ee) could be obtained for some vinyl ethers and vinyl sulphides and significant improvement was observed for the others (Table 5).²⁵ For example, cyclohexyl vinyl ether underwent smooth IEDDA cycloaddition to produce the corresponding bicyclic lactone in up to 92% ee (Table 5, Entry 3).

Although gratifyingly high levels of enantioselectivities can now be obtained with some dienophiles, in both the sulphur and oxygen series, the asymmetric lanthanide-catalysed IEDDA reaction of 3-CMP does not yet afford uniformly high enantiomeric excesses. The search for improved catalysts²⁶ and/or ligands as well as the study of the mechanistic intricacies of this unique reaction²⁷ is currently underway in our laboratory and the results obtained are very promising.

Finally, the access to optically active CO_2 adducts, key-intermediates in our TPR process, gives an extra dimension to the scope of this efficient methodology for the preparation of complex polycyclic compounds.

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