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Remarkable Effect of Basic Ligands in the Lanthanide-Catalysed Enantioselective Cycloadditions of 3-Carbomethoxy-2-Pyrone (3-CMP)

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Abstract: The key-role of basic ligands in attaining high enantiomeric excess in the lanthanide catalysed asymmetric cycloadditions of 3-CMP is reported. A model, rationalising all our previous observations is discussed. © 1997 Elsevier Science Ltd.

We have recently reported the first examples of the catalytic enantioselective Inverse-Electron Demand Diels-Alder (IEDDA) reactions of 3-carbomethoxy-2-pyrone (3-CMP) **1** with various electron-rich dienophiles **2**, affording optically active bicyclic lactones **3** with modest to good enantioselectivities (Figure 1).[1]

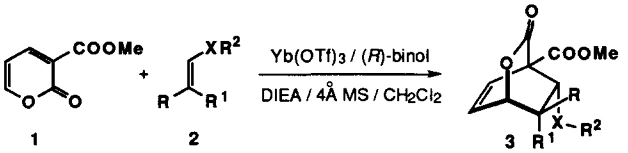


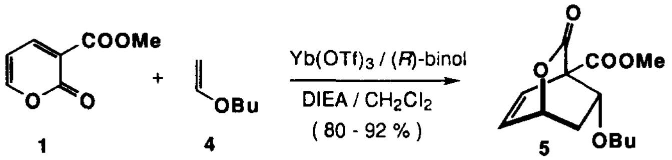
Figure 1 X = O,S ; R, R^1, R^2 = alkyl, aryl, H ; ee ~ 30 to > 95 %

During studies aimed at extending the scope of these reactions, it was discovered that the use of "old" $Yb(OTf)_3$ - *i.e.* stored for several weeks in a dessicator - consistently afforded higher enantioselectivities than the freshly prepared and dried catalyst. To understand the origin of this discrepancy, a series of control experiments were performed in which the reaction parameters were varied systematically. Butyl vinyl ether **4** was selected as the test-dienophile since lanthanide-catalysed IEDDA cycloadditions of this vinyl ether proceeded with modest asymmetric induction and would thus be more responsive to experimental variations.

Some salient features of this study are collected in Table 1. Whereas most reaction parameters had a negligible effect on the ee of lactone **5** (entries 1 and 2), we were quite surprised to find that small amounts of water, present in slightly greater concentration in the "old" $Yb(OTf)_3$ were responsible for the variation of enantioselectivity.[2] This was even more surprising since activated molecular sieves was employed to rigorously exclude moisture from the reaction medium. To verify the hypothesis that water was accountable for the observed increase in ee, the molecular sieve was omitted and freshly prepared $Yb(OTf)_3$ used as the catalyst. A similar though small enhancement in enantioselectivity was again realised (entry 3). Finally, **addition of H_2O to the reaction mixture containing fresh catalyst and molecular sieves led to a remarkable increase in the optical purity of lactone 5, more than doubling the previously observed ee's** (entry 4).[3,4]

Replacement of water by ${}^tBuOH$ and omission of the 4 Å sieves resulted in a similar improvement in ee's (entry 5). Moreover, we found that an alcohol function was not a prerequisite for increased enantioselectivity. Indeed, when THF was added to a CH_2Cl_2 solution containing the chiral ytterbium catalyst, 3-CMP and butyl vinyl ether, the optically active bicyclic lactone **5** was obtained in up to 65% ee (Table 1, Entry 6). It would thus appear that H_2O, ^tBuOH and THF act as ligands to the ytterbium catalyst and somehow modify its environment (*vide infra*).[5] The optimised conditions described in entry 6 were next applied to the IEDDA cycloadditions of some selected dienophiles with 3-CMP (Table 2).

Table 1. Effect of basic ligands on the enantioselectivity of 3-CMP cycloadditions



Entry	Catalyst	4Å MS	Additives	ee[(a)(b)]
1	Fresh	Yes	No	30 %
2	Old	Yes	No	40 %
3	Fresh	No	No	36 %
4	**Fresh**	**Yes**	**10 eq H_2O[(c)]**	**69 %**
5	**Fresh**	**No**	**1.5 eq ^tBuOH[(c)]**	**61 %**
6	**Fresh**	**No**	**5 eqs THF[(c)]**	**65 %**

(a) All yields are for isolated, pure products. **(b)** The ee's were measured by ^1H NMR spectroscopy using $Eu(hfc)_3$ and by chiral HPLC. **(c)** Per Yb.

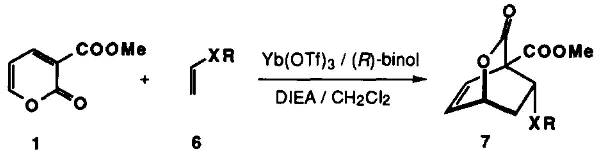
Pleasingly, in all cases tested so far, the addition of THF (5-10 eq. per $Yb(OTf)_3$)[6] to a solution of 3-CMP **1**, vinyl ether or vinyl sulfide **6** and the chiral lanthanide catalyst, **in the absence of 4 Å MS**, led to a dramatic increase in the enantiomeric excesses of the bicyclic lactones **7**. In several cases, essentially optically pure adducts were obtained (Table 2, entries 3-5).

It can also be seen from the data in Table 2 that the ee's of adducts **7** rise as the size of the substituent on the dienophiles increases.[7] To rationalise these observations, we propose that the asymmetric IEDDA cycloadditions of 3-CMP proceed *via* the monomeric square antiprismatic complexes **8** and **9** (Figures 2a/2b).

Initial spectroscopic analysis by Kobayashi *et al.*[8] suggested a trigonal bipyramid structure for the $Yb(OTf)_3$.binol.$(DIEA)_2$ complex with partial H-bonding between the binol OH protons and the two amine nitrogens. Kinetic studies performed in our laboratory[9] revealed that after addition of 3-CMP, a new complex (1:1:1 ratio of Yb:binol:3-CMP) was generated. The absence of a non-linear effect further supported the presence of a monomeric active species. NMR spectroscopy of the parent scandium complex revealed a dynamic equilibrium between coordinated and non-coordinated 3-CMP, hence establishing a pathway for rapid interconversion between **8** and **9**.[10]

Examination of these complexes reveals destabilising steric interactions between the 3-CMP methyl ester substituent and one of the binaphtol aromatic ring in derivative **8**. These repulsions are absent in **9** and cycloadditions should preferentially proceed through the intermediacy of **9**.

Table 2. Improved Enantioselectivity in the Presence of THF



Entry	Dienophile	THF	Yield[a]	ee[b][c]
1	BuO	5 eq	81 %	65 % (30)
2	BuS	10 eq	85 %	74 % (42)
3	CyO	10 eq	90 %	96 % (80)
4	CyS	10 eq	67 %	> 95 % (92)
5	PhS	5 eq	92 %	> 95 % (88)

(a) All yields are for pure, isolated products. (b) The ee's were measured by ^1H NMR spectroscopy using $Eu(hfc)_3$ and by chiral HPLC. (c) The numbers in parentheses refer to ee's obtained without added THF (Ref 1)

The key-roles played by the H-bonded amines in the facial discrimination become apparent upon inspection of models **8** and **9**. By shielding one of the two faces of the coordinated 3-CMP (the top face in Figures 2a/2b), they force the dienophile to approach from the other side of the 2-pyrone (underneath in Figures 2a/2b).[11] Moreover, we believe that the presence of the H-bonded amines help to lower the energy of the transition state of the IEDDA cycloadditions by Coulombic stabilisation between the fractional positive charge on the nitrogen atom and the developing negative charge on the pyrone nucleus during these highly asynchronous reactions.

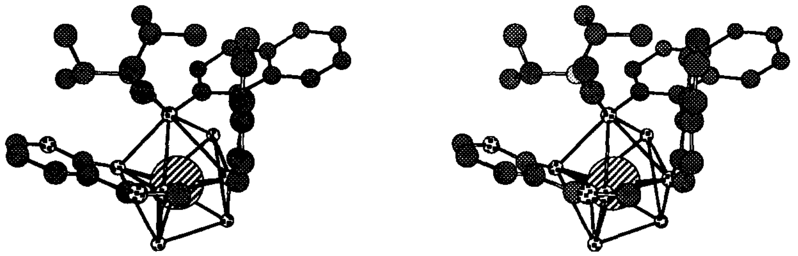


Figure 2a. Cross-eyed stereoview of disfavoured complex **8**. The second amine and the hydrogen atoms have been removed from the structure. The triflates and THF ligands are represented only by their coordinated oxygen atom for clarity.

With regard to the role of the basic adjuvants, we believe that they not only expand the coordination sphere of the Yb catalyst but that they also displace one or more triflate ligands, generating the corresponding cationic ytterbium complexes.[5] These cationic organometallics will be more contracted than the neutral catalysts **8** and **9**. The steric and electronic effects disfavouring the IEDDA reactions *via* **8** will be further exacerbated. At the same time, the cationic nature of these complexes will alter the electronics of the coordinated 3-CMP, making them more reactive catalysts and leading to bicylic lactones **7** of high enantiopurity.

In summary, we have observed that some basic ligands provide a remarkable enhancement of the enantioselectivity of the lanthanide-catalysed cycloadditions of 3-CMP with various dienophiles. Although the proposed model rationalises some of our observations, it is still tentative and the correct structure of the active catalyst has to be unambiguously demonstrated.

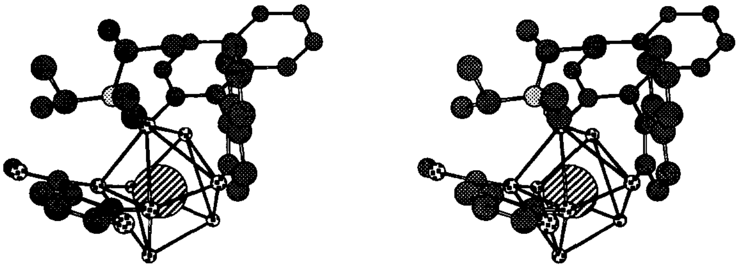


Figure 2b. Cross-eyed stereoview of favoured complex **9**. The second amine and the hydrogen atoms have been removed from the structure. The triflates and THF ligands are represented only by their coordinated oxygen atom for clarity.

Acknowledgements

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References and Notes

1. (a) Markó, I.E.; Evans, G.R. *Tetrahedron Lett.*, **1994**, *35*, 2771; (b) Markó, I.E.; Evans, G.R.; Declercq, J.-P. *Tetrahedron Special Issue,* **1994**, *50*, 4557; (c) Markó, I.E.; Evans, G.R.; Declercq, J.-P.; Feneau-Dupont, J.; Tinant, B. *Bull. Soc. Chim. Belg.*, **1994**, *103*, 295; (d) Markó, I.E.; Evans, G.R.; Declercq, J.-P.; Tinant, B.; Feneau-Dupont, J., *Proceedings of the Chiral Synthesis Symposium and Workshop, Nice, France,* **1994**, 21; (e) Markó, I.E.; Evans, G.R.; Declercq, J.-P.; Tinant, B.; Feneau-Dupont, J., *Acros Organics Acta,* **1995**, *1*, 63; (f) Markó, I.E.; Evans, G.R.; Seres, P.; Chellé, I.; Janousek, Z., *Pure & Appl. Chem.* **1996**, *68*, 113. For the use of titanium complexes, in more than stoichiometric amounts, to promote some of these IEDDA reactions, see: (a) Posner, G.H.; Carry J.-C.; Lee, J.K.; Bull, D.S.; Dai, H. *Tetrahedron Lett.*, **1994**, *35*, 1321; (b) Posner, G.H.; Eydoux, F.; Lee, J.K.; Bull, D.S. *Tetrahedron Lett.*, **1994**, *35*, 7541.
2. It is interesting to note that anhydrous Yb(OTf)$_3$ contains one residual water molecule. Water is also present in Shibasaki's catalyst (Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.*, **1993**, *115*, 10372).
3. The influence of water on the enantioselectivity of the titanium-promoted cycloaddition of 3-CMP with two vinyl ethers was recently reported: Posner, G.H.; Dai, H.; Bull, D.S.; Lee, J.K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr, S. *J. Org. Chem.*, **1996**, *61*, 671. According to the authors, the moisture modifies the surface of the sieves and allows more complete formation of the chiral titanium mediator. In our case, the sieves can be totally omitted and the water clearly plays a very different role.
4. Addition of more than 0.1 eq of H_2O per ytterbium in CH_2Cl_2 did not improve the ee's (41%). This is due to the low solubility of H_2O in CH_2Cl_2. The role of the sieves thus appears to be that of a "water reservoir", adsorbing a large amount of water and gradually releasing it to the ytterbium complex.
5. For the replacement of triflate ligands on lanthanide complexes by water and THF, see: (a) Kobayashi, S. *Synlett*, **1994**, 689; (b) Hachiya, I.; Kobayashi, S. *J. Org. Chem.*, **1993**, *58*, 6958.
6. Performing the ytterbium-catalysed reaction in neat THF resulted in the formation of racemic adduct **5**. We believe that THF not only displaces the triflate substituents but also exchanges the binol ligand, generating an active though achiral complex that leads to racemic product **5**.
7. We are currently studying the origin and scope of this peculiar effect.
8. (a) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.*, **1994**, *35*, 6325; (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron*, **1994**, *50*, 11623.
9. Leroy, B., Mémoire, Université catholique de Louvain, September 1994.
10. This interconversion is faster than the subsequent IEDDA cycloadditions which can be easily monitored by ^{1}H NMR spectroscopy. The dynamic nature of this equilibrium is also evident from the titration curve of the Yb complex with 3-CMP, which shows no saturation kinetics.
11. This explanation is also consistent with the negligible variation in ee's observed when altering the structure of the amines. The steric size of the nitrogen bases is particularly important in the ytterbium-catalysed Diels-Alder reactions of cyclopentadiene (ref. 8).

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