Enantioselective catalysis of the Henry reaction by a chiral macrocyclic ytterbium complex in aqueous media†

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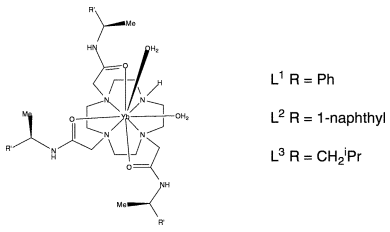
A chiral macrocyclic ytterbium cationic complex catalyses the nitro-aldol reaction between α-ketocarboxylates and nitromethane under ambient aqueous conditions, leading to the formation of for example, methyl-2-hydroxy-2-methyl-3-nitropropanoate in 96% yield and 59% enantiomeric purity. Monitoring of the paramagnetically shifted intermediate Yb species by ^{1}H NMR allows several different species on the catalytic cycle to be identified and is consistent with the intermediacy of stereoisomeric chelated pyruvates of differing reactivity towards the nucleophile, as well as product inhibition of turnover.

Introduction and background

The Henry condensation reaction may be catalysed by Lewis acids or by base and affords an efficient route to substituted β-nitroalcohols from readily available carbonyl and nitroalkane precursors.[1] It is, therefore, not surprising that catalytic asymmetric variants have been sought for this carbon–carbon bond-forming reaction.[2] The most successful of these operate under chiral base catalysis, typically at low temperatures in non-aqueous media,[3] and with rare exceptions[3a] are most effective for reactions of aldehydes.[4] The reactions in neat nitromethane with α-keto esters, catalysed by chiral bisoxazoline–copper(II) complexes,[4a,5] are particularly useful and the use of *Cinchona* alkaloids[3a] as catalytic chiral bases (CH_2Cl_2, −20 °C) has been shown to give rise to products of high enantiomeric purity.

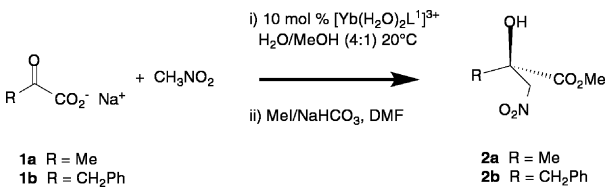
Recently, a diverse array of chiral lanthanide complexes has begun to be studied and catalysis of a variety of reduction or carbon–carbon bond forming reactions is being examined for the synthesis of small molecules.[3c,6,7] The overwhelming majority of these studies has been undertaken in non-aqueous media, as a consequence of the hydrolytic instability of many lanthanide salts and their simple complexes. However, there is a strong impetus to study the development of catalytic reactions in water under aqueous conditions for economic and environmental reasons.[8] Hydrolytically stable diaqua–lanthanide complexes of chiral ligands have been devised over the past few years, mostly as a consequence of their function as selective anion receptors or as NMR shift and relaxation agents.[9,10,11] Recently, the reduction of certain α-keto acids by sodium borohydride in aqueous solution has been shown to be catalysed by diaqua–ytterbium(III) complexes, such as (*RRR*)-[$Yb(H_2O)_2L^1$](CF_3SO_3)$_3$, giving substituted (*R*)-lactates in up to 49% ee.[12a] Preferential formation of a *si*-bound chelated pyruvate intermediate was suggested, and the X-ray structure of the chelated lactate product has been isolated.[10a,12b]



(RRR)- [$Yb(H_2O)_2L$]$^{3+}$

Results and discussion

With this background in mind, we set out to examine the utility of (*RRR*)-[$Yb(H_2O)_2L^1$](CF_3SO_3)$_3$ and related lanthanide complexes as catalysts for the Henry reaction between simple pyruvate salts and nitromethane in aqueous media. The reaction proceeds at room temperature in H_2O–MeOH (4 : 1) to give a single major product. Solubility constraints preclude the use of a system operating either in pure water or pure methanol. The use of the sodium salt of the pyruvate was found to be essential; the Li salt was slow to react under these conditions and curiously the Cs salt reacted only reacted very sluggishly (Scheme 1).



Scheme 1

Crude reaction products were converted directly into the corresponding methyl esters (MeI–$NaHCO_3$ in DMF), in order to allow ^{1}H NMR analysis of their enantiomeric purity, following addition of the chiral shift reagent Eu(hfc)$_3$ in $CDCl_3$. Data obtained for reaction of methyl and benzyl pyruvate catalysed by (*RRR*)-[$Yb(H_2O)_2L^1$](CF_3SO_3)$_3$ (Table 1) revealed good conversion and

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† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR spectra are available of racemic and enantiomerically enriched **2a** and **2b** in the absence and presence of Eu(hfc)$_3$ in $CDCl_3$. ^{1}H NMR spectra of the monitoring of the reaction using (*RRR*)-[$Yb(H_2O)_2L^1$](CF_3SO_3)$_3$ as a catalyst for the reaction between phenylpyruvate and nitromethane in aqueous media at room temperature is also provided. See DOI: 10.1039/b712470h

Table 1 Reaction of pyruvate salts[a] with nitromethane under [LnL^1] catalysis

Entry	R	Mole % catalyst	Time/h	% Yield	% ee[b]
1	Me	0	24	27	0
2	Me	0	48	44	0
3[a,c]	Me	10	48	98	58
4	Me	5	48	60	52
5[d]	Me	10	48	96	59
6[e]	Me	10	48	59	34
7[f]	CH_2Ph	0	24	25	0
8	CH_2Ph	10	48	96	41
9[e]	Ph	10	48	50	5
10[g]	$CH_2CH_2CO_2^-$	10	48	8	26

[a] In each case, the solvent used was 4 : 1 H_2O–MeOH (required for homogeneity); under these conditions the Li pyruvate salt did not react and the Cs salt gave only a 20% yield under the conditions for entry 3. [b] The (*RRR*)-[Yb$(H_2O)_2$L^1] catalyst was used as its triflate salt (use of the chloride salt gave identical behaviour) unless indicated and gives the *R* product, as shown by comparison of the shifted NMR spectrum for a sample of authentic **2a**, prepared as defined in reference 3*a*. [c] For the acid itself, no reaction was observed. [d] Reaction at 0 °C. [e] Using the Tb complex (for the Nd and Ho analogues, % ee values (% yields) were: 11 (52) and 17 (62) respectively). [f] When the reaction time was 48 h, the isolated yield was 49%, (% ee = 0). [g] No reaction was observed in the absence of added Yb complex.

moderate product enantiomeric purities, in the range 41 to 59%. The use of phenylpyruvate under the same conditions gave product with a lower yield and enantiomeric purity.

Consideration of the results summarised in Table 1 suggests that there is a competition between an uncatalysed and non-selective reaction and a lanthanide complex catalysed reaction (entries 1 and 2 *versus* 3). The most active system required the use of an Yb complex; the use of Nd, Tb and Ho analogues gave products of lower yield and enantiomeric purity. Given the well-known lanthanide contraction that determines ionic radii across the f block series, the observed reactivity and selectivity profile may be reasonably linked to the higher charge density and greater steric demand around the Yb(III) centre.

In additional work, Yb complexes of other chiral macrocyclic ligands were also examined. Thus, systems with different pendant arms, [Yb$(H_2O)_2$L^2]$^{3+}$ and [Yb$(H_2O)_2$L^3]$^{3+}$ were examined; the ligand L^2 is the tris(1-naphthyl) analogue of L^1. The complexes with L^2 gave similar behaviour to those based on L^1, whereas those derived from L^3 were inferior in reactivity and selectivity and were not studied in detail.

Mechanistic studies using ^{1}H NMR spectroscopy

In seeking to understand the mechanism of this reaction, some ^{1}H NMR studies have been undertaken. The speciation of ytterbium complexes in solution may be deduced by analysis of their paramagnetically shifted ^{1}H NMR spectra, examining in particular the shifted resonances of the chiral macrocyclic ligand. Detailed studies with a wide range of organic substrates (α-hydroxy acids, simple carboxylates, amino-acids, many phospho-anions)[10,11] have provided a wealth of spectral information that allows secure comparisons to be made.[13] Indeed, for many of these adducts (acetate, glycinate/serinate/alaninate, lactate, citrate) X-ray structural data have been obtained to corroborate solution NMR structural information. Thus, the spectral form of the ^{1}H NMR spectra of a wide range of such Yb species allows a direct correlation with solution speciation.

The (*RRR*)-[Yb$(H_2O)_2$L^1]$^{3+}$ complex (triflate salt) exists in aqueous media as one major species (Λ-δδδδ, characterised in the X-ray structure[10a]), in which there is fast exchange on the NMR timescale between three other higher energy stereoisomers, either *via* concerted arm rotation or cooperative δ/λ conformational exchange, involving the four macrocyclic five-ring chelates.[10a] For this aqua complex, the most shifted (axial) macrocyclic ring protons appear as four singlets (mean chemical shift is +77 ppm) in the range +49 to +114 ppm.

When sodium pyruvate (10-fold excess) was added to [Yb$(D_2O)_2$L^1]$(CF_3SO_3)_3$ (D_2O–CD_3OD; 500 MHz, 20 °C), two major new species could be discerned by examining the most shifted of the four 'axial' ring proton resonances, (Fig. 1). Following addition of CH_3NO_2 (10-fold excess/Yb), the relative intensity of these two species diminished rapidly, and a new major species began to appear (δ_H +62, +78, +81, +116 ppm; δ H_{ax}^{mean} = +84 ppm) whose intensity grew with time, until after about 24 h it was the only significant species present, (Fig. 1 and 2). In the period between 1 h and 6 h, an intermediate species appeared (mean shift +61 ppm; most shifted axial ring protons observed at δ_H = +94, +60, +52 and +39 ppm), grew in relative intensity and then reduced in intensity as the proportion of the product-derived complex increased.

Taken together, this behaviour is consistent with the initial formation of a chelated pyruvate adduct, in which there is modest selectivity for the formation of a given diastereomeric complex, *i.e. si- vs. re*-bound pyruvate, presumably with a preference for the (*RRR*)-Λ-δδδδ square antiprismatic set of isomers. In recent studies in solution and with related crystallographic work,[10,11] the isomeric Λ-λλλλ/Λ-δδδδ *twisted* square antiprismatic complexes have not been observed. The observed 'intermediate species' could be a chelated carboxylate, (Scheme 2 right) in which each of the carboxylate oxygens is bound. The chemical shift properties of this species are very similar to those published for the chelation of acetate to this Yb complex; the structure of the acetate complex has been established crystallographically, (δ H_{ax}^{mean} = +68 ppm in D_2O).[10a]

The origin of the observed enantioselectivity may be traced to the differing reactivity towards the nitromethane anion of the *si*- and *re*-bound equilibrating species. The final observed species (Fig. 2; also see ESI† for an analogous spectrum obtained using phenylpyruvate as substrate) was shown in a separate NMR experiment to be the chelated product, by adding an authentic sample of MeC(OH)[CO_2^-]CH_2NO_2 to the Yb complex in D_2O. Confirmation of this hypothesis was provided by positive ion electrospray mass spectrometry, as the chelated "product" adduct [YbL^{1}MeC(OH)$CO_2(CH_2NO_2)$]$^{2+}$ in the reaction mixture could be observed as the mono-triflate salt at *m/z* 1126 D.

A tentative mechanistic cycle may be formulated to account for these observations (Scheme 2). The absence of preferential formation of a preferred, *reactive* chelated intermediate at equilibrium is evidently a significant factor in limiting the product enantiomeric purity. In addition, the observation of the product as a chelated adduct with the Yb catalyst that is in slow exchange with the complex precursor on the NMR timescale (298 K, 500 MHz) is consistent with the possibility of product inhibition of catalysis, in agreement with the relatively slow turnover observed.

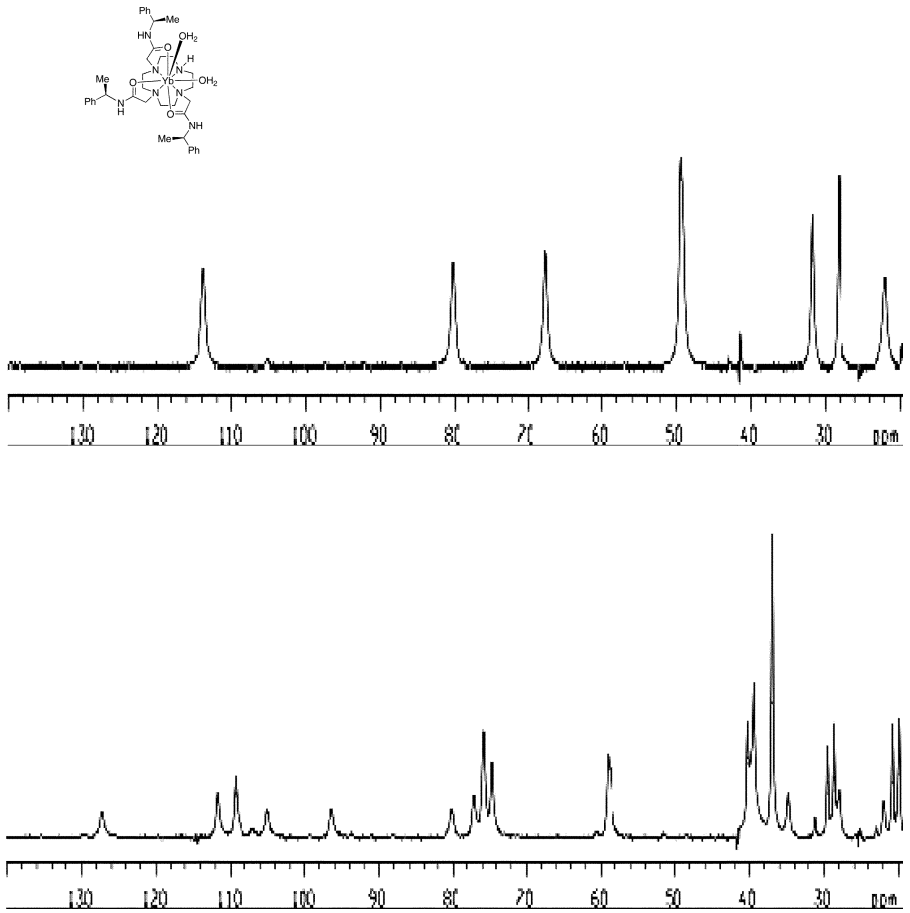
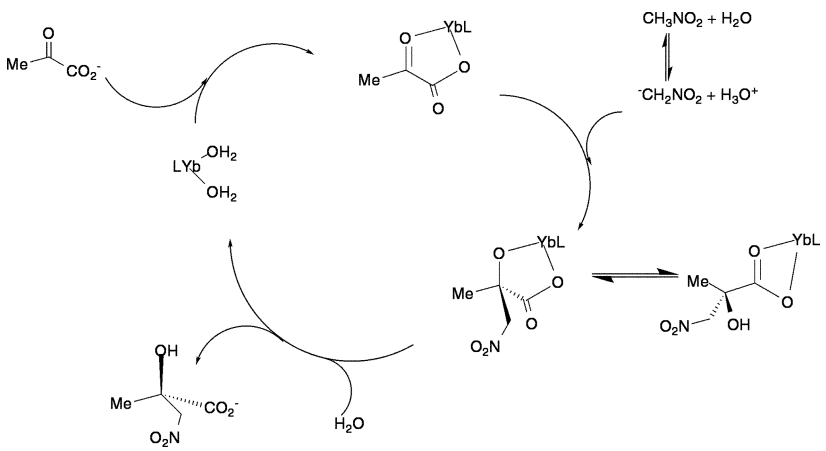


Fig. 1 Paramagnetically shifted partial ^{1}H NMR spectra (295 K, 500 MHz) for: (*upper*) the $[Yb(D_2O)_2L^1]^{3+}$ complex showing the axial ring hydrogens at +49, +67, +80 and +114 ppm (1 mmol complex, CD_3OD–D_2O, pD 5.6); (*lower*) following addition of 10 equivalents of sodium pyruvate (pD 6).



Scheme 2

Summary and conclusions

In summary, the addition of nitromethane to sodium alkylpyruvates at ambient temperature in an aqueous medium is catalysed by a cationic, chiral Yb macrocyclic complex. Although the catalytic efficiency and observed selectivity may only be considered to be moderately good, this does represent the first example of such catalysis under ambient aqueous conditions. The ^{1}H NMR studies have provided detailed information about putative catalytic intermediates and suggest that future studies require a more conformationally rigid Yb complex, in which the reactivity of one of the diastereoisomeric chelated adducts towards attack by the nitromethane anion is enhanced.

Experimental

All starting materials and reagents are commercially available and were used as received; ytterbium complexes were prepared

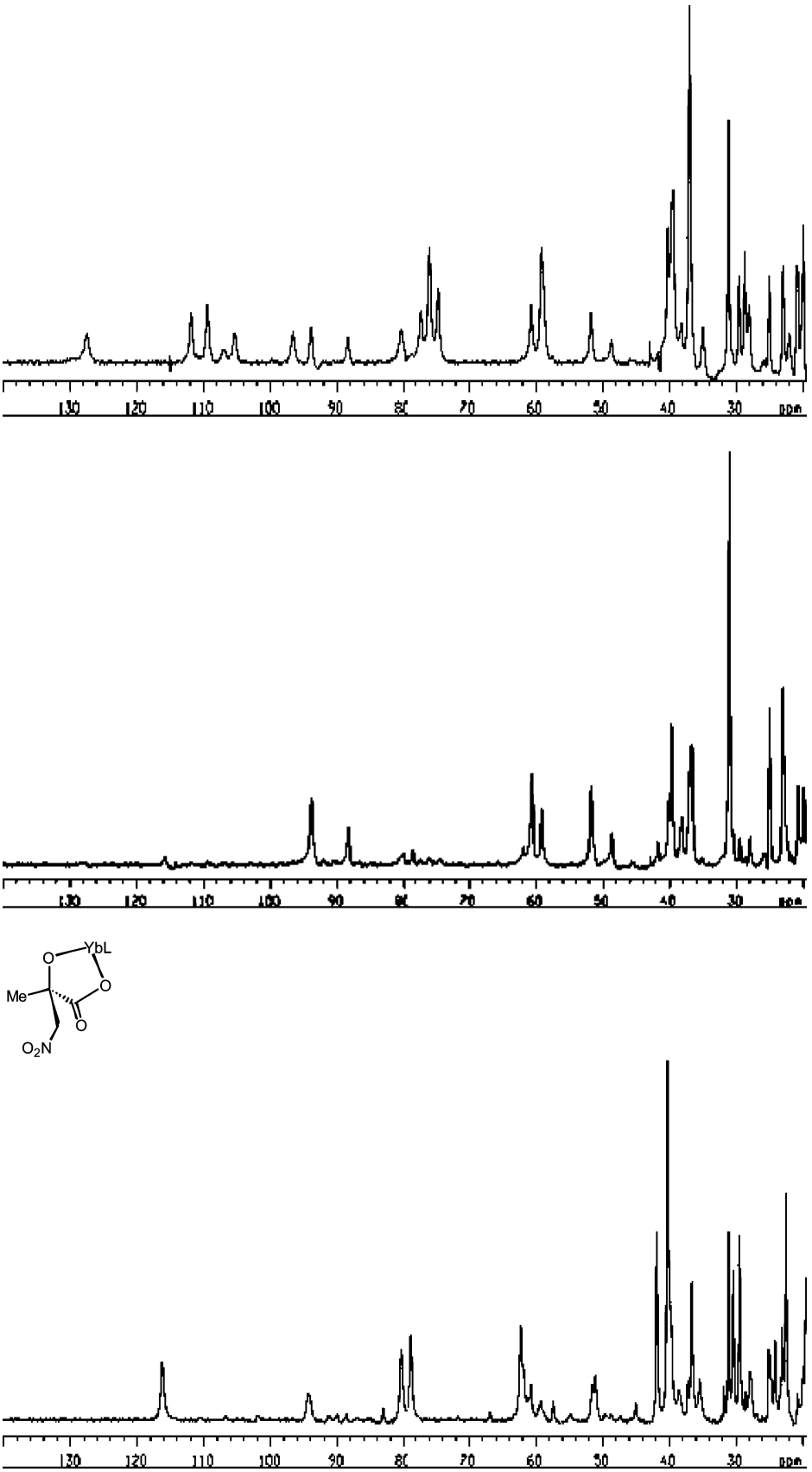


Fig. 2 Paramagnetically shifted partial ^{1}H NMR spectra (295 K, 500 MHz) of Yb complex species following addition of 10 equivalents of sodium pyruvate and 10 equivalents of nitromethane after (top to bottom): (a) 30 min; (b) 3 h; (c) 24 h. In the lower spectrum of the bound product, resonances at +62, +78, +81 and +116 ppm refer to the most shifted set of 4 ring 'axial' protons.

as described in the literature.[10] ^{1}H NMR spectra were recorded on Varian Mercury or Inova instruments at 400 or 500 MHz respectively, and ESMS spectra were obtained using a Fisons Platform-II ES spectrometer. The product enantiomeric purity was assessed following addition of 1 to 2 mol% of Eu(hfc)$_3$ to solutions of the appropriate methyl esters of the nitro-aldol products, **2a** or **2b**.

A typical reaction procedure is as follows: to a solution of $[Yb(H_2O)_2L^1](CF_3SO_3)_3$ (13.1 mg, 10 μmol) in water (1 mL) was added sodium pyruvate (11 mg, 0.1 mmol) and the mixture was stirred for 5 minutes at room temperature. A solution of nitromethane (26.9 μL, 0.5 mmol) in methanol (0.2 mL) was added and the mixture stirred at 20 °C for 48 h. After removal of solvents under reduced pressure, the crude product was dissolved in DMF (1 mL), treated with sodium hydrogen carbonate (8 mg, 10 μmol) and methyl iodide (320 μL, 1 mmol) and the mixture was heated for 2 h at 50 °C. After removal of solvent, the product was purified by chromatography (SiO_2, CH_2Cl_2) to yield the desired methyl ester, **2a**, which gave spectroscopic data in accord with literature data[3a] (see also ESI† for ^{1}H NMR spectra). Isolated yields refer to the purified methyl ester product.

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