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Direct one step mono-functionalisation of symmetrical 1,2-diols

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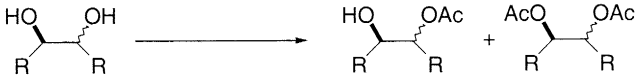
Abstract

The mono-functionalisation of *meso*- and C_2-symmetric diols has been achieved via the use of a new lanthanide(III) chloride catalysed acylation reaction.

Keywords: acylation; lanthanides; diols; desymmetrisation.

The mono-functionalisation of diols is an important challenge in organic synthesis. While sterically or electronically different hydroxyls may be selectively modified, methods for the mono-functionalisation of similar hydroxyl groups are virtually unknown. The problem is that both hydroxyl groups react at a similar, if not the same, rate and thus even with one equivalent of reagent, a statistical mixture of starting diol and mono-/bis-functionalised products are formed (Scheme 1). This problem, to date, is still very much unsolved.



Scheme 1.

Traditionally, the acylation of hydroxyl groups has been carried out using either an acyl halide or anhydride in the presence of a base and a nucleophilic activating agent. A fundamentally different approach is the use of a Lewis acid to activate the acylating agent towards nucleophilic attack by the hydroxyl group. In these systems the simple alcohols reported are acylated in good to high yields,[1] but when molecules containing several hydroxyl functions are employed, multiple acylations occur.[2] We are unaware of any procedure to date that can selectivity acylate one of two similar hydroxyl groups.

We now wish to report that lanthanide(III) chlorides can be used in conjunction with carboxylic acid anhydrides to mono-acylate *meso*- and C_2-symmetric 1,2-diols with very high levels of selectivity. While it is not surprising that lanthanide salts catalyse acylation reactions,[3,4] it is surprising that they do so with such high levels of mono-selectivity. Our preliminary investigations to find the optimum conditions

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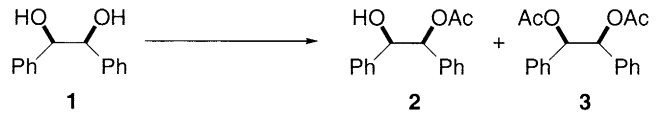
focused on the mono-acylation of *meso*-hydrobenzoin. As can be seen from Table 1, the optimum conditions (entry 4) involved the use of 10 mol% $CeCl_3$ and 10 equiv. Ac_2O. A slight improvement in the selectivity was seen if the reaction was initially run at a lower temperature. The concentration of the reaction can be seen to be important (entries 3, 6 and 7) with the reaction proceeding sluggishly in the absence of THF and at concentrations other than 0.366 M. It is also important to note the remarkable acceleration induced by $CeCl_3$: in the absence of $CeCl_3$ the reaction is only 16% complete after 44 h (entry 1).

Table 1



1 **2** **3**

Entry	Conc. THF (M)	Time (Hr.)	Ratio[a] (*1/2/3*)	Mass balance
1[b]	0.366	44	84/14/02	100
2[c]	0.366	20	21/77/2	100
3	No THF	48	42/42/16	100
4	0.366	23	5/90/5	100
5[d]	0.366	23	5/95/0	100
6[d]	0.732	23	50/50/0	100
7[d]	0.183	23	30/60/7	100

a) Product ratios as determined by 300 MHz ^{1}H NMR.
b) No $CeCl_3$ was added to this reaction. All other reactions were run with 10 mol% $CeCl_3$.
c) Ac_2O (1 eq.) was added. All other reactions were run with Ac_2O (10 eq.)
d) Reaction was run at 0^{o}C for 7 hrs then warmed to room temp and stirred for a further 16 hrs.

With conditions in hand for the selective mono-functionalisation of *meso*-hydrobenzoin, we decided to see if this methodology could be extended to other symmetrical 1,2 diol systems. We selected 3 diols for our initial study, *meso*-hydrobenzoin, 1,2-*cis*-cyclohexanediol (**4**) and *meso*-2,3 butanediol (**5**). In the case of (**4**) we found that the reaction was very slow, and in the case of (**5**) it did not proceed at all over a useful period of time. We discovered, however, that by changing the lanthanide from Ce to one of a higher atomic number (Dy or Yb) the rate of the reaction increased. The best results were obtained using $YbCl_3$ as the catalyst and are summarised in Table 2.

Table 2

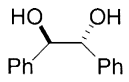
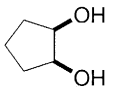
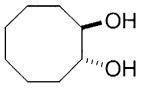
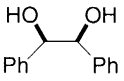
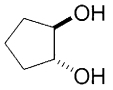
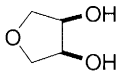
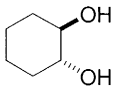
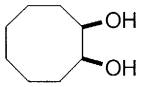
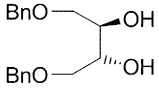
Catalyst	**1**[a]	**4**[a]	**5**[a]
$CeCl_3$	5/90/5 at 23 hr	56/44/0 at 24 hr	no reaction
$DyCl_3$	0/89/11 at 16 hr	26/70/4 at 24 hr	0/87/13 at 48 hrs
$YbCl_3$	0/95/5 at 4 hr	16/84/0 at 24 hr	b

a) Ratio of starting material/mono-acylated/*bis*-acylated products as determined by 300 MHz ^{1}H NMR.
b) Irreproducible results due to isolation problems.

Armed with these conditions we expanded our investigation to include a more varied selection of 1,2-diols. A summary of this study appears in Table 3. As can be seen from Tables 2 and 3, both *meso*- and C_2-symmetric diols can be mono-functionalised by use of this procedure. In general C_2-

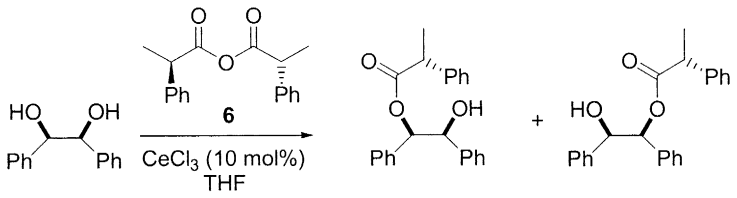
symmetrical diols were acylated at a faster rate than the *meso*-diols. It is possible that this has to do with the preferred conformational/steric requirements for the coordination of the diol to the lanthanide salt, although we do not have sufficient data to draw firm mechanistic conclusions at this time. Cyclic diols of various ring sizes all react to give good to excellent yields of the mono-acylated product. Acyclic diols are also mono-acylated in excellent yields. Diols with heteroatoms on adjacent carbons undergo the reaction selectively and at an enhanced rate. We have also extended this reaction to include the use of other carboxylic acid anhydrides (10 equiv.) further enhancing the utility of the process. In these cases **1** was functionalised to yield 91% of the mono-propionate and 45% of the mono-benzoate (at 45% conversion). 1,4-Anhydroerythritol was converted exclusively to the mono-benzoate (100%) and 1,2-*trans*-cyclopentanediol provided the mono-benzoate with 80% selectivity.

Table 3

Diol	Yield of mono acylated product	Diol	Yield of mono acylated product	Diol	Yield of mono acylated product
	100		92		86
	95		64[a]		95
	93		78		90

All reactions run with $YbCl_3$ (10 mol%), Ac_2O (10 eq.) in THF (0.366M).
a) 26% of the *bis*-acylated product was also formed.

While the two hydroxyl groups of a C_2-symmetric diol are homotopic, those of a *meso*-diol are enantiotopic. The procedure at present does not discriminate between two enantiotopic sites, it thus generates a racemic product. We decided to investigate the use of this methodology in the desymmeterisation of *meso*-1,2-diols (i.e. the formation of a non-racemic product). To date we have two examples of this process from our laboratories, which encourages further investigation. Chiral anhydride **6** was prepared from its commercially available parent acid and acid chloride in toluene with an equivalent of pyridine. *meso*-Hydrobenzoin was treated with **6** under our standard reaction conditions and produced a 3:1 ratio of diastereomeric products (Scheme 2). Racemic hydrobenzoin was also acylated under these conditions with **6** (2 equiv.) and this provided two diastereomeric products in a 3:1 ratio. The configurations of the major products in either of these reactions were not determined. When the major diastereomer was resubmitted to the reaction conditions in the absence of carboxylic acid anhydride no loss of diastereomeric purity was observed, i.e. there was no acyl transfer between hydroxyl groups.



Scheme 2.

While the levels of diastereoselection are only modest, we believe that this is an important proof of concept and it encourages further investigation. A more efficient process, however, would be the use of a chiral lanthanide(III) complex to desymmeterise *meso*- or resolve racemic systems. Investigations into this possibility are currently underway.

Acknowledgements

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