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Samarium(II)-Mediated 4-*exo* trig Ketyl-Olefin Cyclisation of Unsaturated Aldehydes. A General, Stereoselective Synthesis of Functionalised Cyclobutanols

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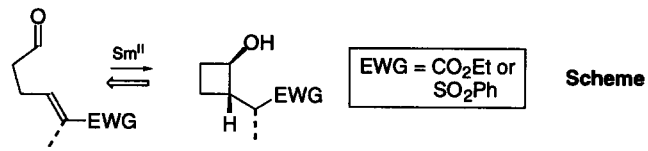
Abstract: γ,δ-Unsaturated aldehydes having a quaternary centre in either the α or β-position, have been prepared from substituted γ-butyrolactones and undergo efficient 4-*exo*-trig ketyl-olefin cyclisation on treatment with samarium(II) iodide to give functionalised cyclobutanols. In all cases cyclisation occurs with complete diastereocontrol to give *anti*-cyclobutanol products. In the cyclisation of substrate **4ab**, significant stereochemical control is achieved at three contiguous chiral centres. Both unsaturated esters and vinyl sulfones have been employed as substrates in the reaction.

keywords: radicals and radical reactions; cyclobutanes; samarium and compounds; stereocontrol

Samarium(II) iodide continues to prove an incredibly versatile reagent in organic synthesis.[1] In particular, the reductive, ketyl-olefin coupling of unsaturated aldehydes or ketones allows a variety of cyclic alcohols, or bicyclic lactones, of varying ring-size to be assembled under mild conditions with moderate diastereoselectivity.[2] Our interest in organolanthanide mediated transformations led us to consider new routes to small ring systems and in particular, to cyclobutanols, using radical ketyl-olefin cyclisations mediated by samarium(II) iodide (**Scheme 1**).



Scheme 1

To the best of our knowledge, only a single example of a samarium(II) mediated 4-*exo*-trig ketyl-olefin cyclisation has been reported.[3,4] Although the previous report contained only a single cyclisation reaction using substrate **9** and relatively harsh conditions, we believed the reaction might have considerable potential as a general route to cyclobutanols and that the inherent nature of this radical reaction would lead to good diastereoselectivity. We report here the preliminary results of our studies into a general, stereoselective approach to functionalised cyclobutanols utilising an unusual 4-*exo*-trig ketyl-olefin cyclisation mediated by samarium(II) iodide.

Cyclobutanone and cyclobutanol derivatives are important building blocks in organic synthesis and constitute a structural motif that is found extensively in natural products,[5] and non-natural, biologically active molecules.[6] Cyclobutanes are most often prepared using photochemical [2+2] cycloaddition processes.[7] Although these reactions are useful in synthesis, alternative processes which would allow more substituted cyclobutanes, and in particular cyclobutanols, to be prepared with good stereoselectivity, would be very useful. We believed that a samarium(II)-mediated 4-*exo*-trig approach to cyclobutanols would follow a well-defined stereochemical course, very different to those involved in conventional cyclobutane ring-forming reactions.

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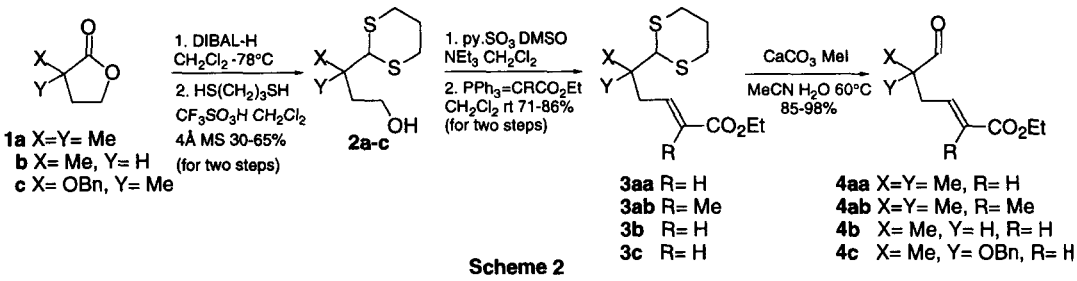
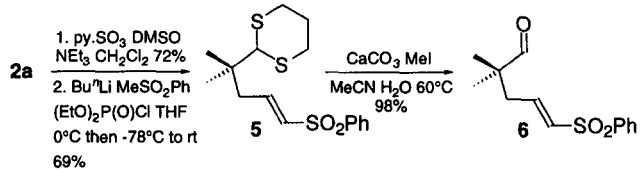


Scheme 2

Cyclisation substrates were prepared from γ-butyrolactone or α-benzyloxy-γ-butyrolactone by mono or dimethylation, lactol formation and ring-opening with 1,3-propane dithiol. Swern oxidation of dithioacetal products **2a-c**, subsequent Wittig reaction, and final deprotection, gave the required series of unsaturated ester substrates **4aa**, **4ab**, **4b**, and **4c** in good overall yield (**Scheme 2**).[8] Vinyl sulfone substrate **6a** was prepared from alcohol **2a** by Swern oxidation and subsequent stereoselective Wittig-Horner reaction with α-phosphorylated-α-lithio methyl phenyl sulfone (**Scheme 3**).[9]



Scheme 3

Enantiomerically pure aldehyde substrate **9** was prepared *via* key aldehyde **8** from (*R*)-(-)-pantolactone **7** by adaptation of a literature route.[3] Enantiomerically pure sulfone substrate **10** was prepared from **8** in a similar fashion to that discussed for **6** (**Scheme 4**).

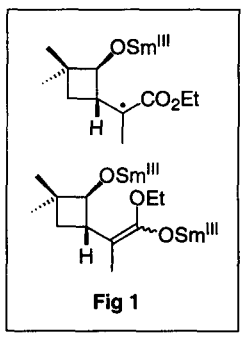
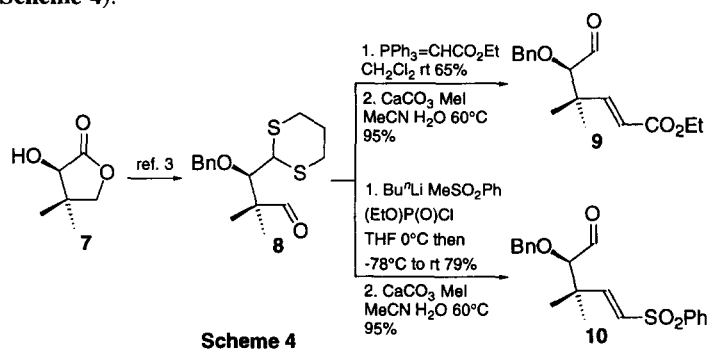


Fig 1



Scheme 4

Treatment of cyclisation substrate **4aa** with samarium(II) iodide in THF, and samarium(II) iodide in THF with HMPA gave none of the desired cyclobutanol product, however, when MeOH was used as the co-solvent in place of HMPA, the reaction proceeded effciently to give the desired cyclobutanol product in good yield and with complete *anti*-selectivity[10,11] (**Table 1, entry 1**).

Attempted cyclisation of **4b** under these conditions (**Table 1, entry 2**) failed to give any of the desired cyclobutanol product giving instead 6-hydroxy-5-methyl hexanoic acid ethyl ester as the major product. This clearly illustrates the importance of *gem*-disubstitution in the cyclisation process.[12] Cyclisation of **4ab**, however, proceeded efficiently with significant stereochemical control at all three new chiral centres to give a 5:1 mixture of diastereoisomers at the centre α- to the ester group (**Table 1, entry 3**). Interestingly, the use of ethanol, or *tert*-butanol in the cyclisation gave only traces of cyclobutanol product. Labelling experiments using CH_3OD clearly

showed that the cyclisation proceeded as expected *via* the samarium(III) enolate (**Fig 1**) and that the methanol was acting as a proton source (**Table 1, entry 4**). The specific requirement for methanol in the cyclisation appears to suggest a further role for the alcohol co-solvent possibly in activating the samarium(II) reductant by complexation.[13] The origin of the stereoselectivity α- to the carbonyl group is currently under investigation.[14]

In an attempt to probe the longevity of the α-carboethoxy radical formed initially upon cyclisation (**Fig 1**), allyl ester **11** was prepared by transesterification of **3ab** with allyl alcohol[15] and subsequent removal of the thioacetal group. It was believed that the α-carboethoxy radical formed initially upon cyclisation might be trapped by the pendent allyl group in a sequential 4-*exo*-trig, 5-*exo*-trig cyclisation, however, only products arising from the first cyclisation were obtained, clearly illustrating the ease with which the initial α-carboethoxy radical is reduced further with samarium(II) iodide (**Table 1, entry 5**).

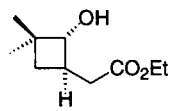
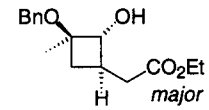
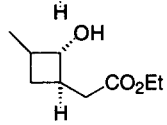
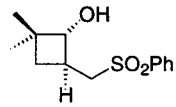
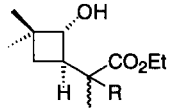
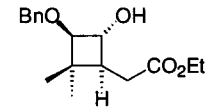
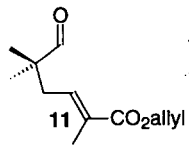
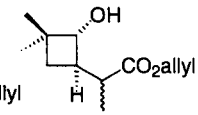
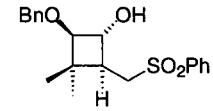
Entry	Substrate	Product (Isolated Yield %)[a]	Entry	Substrate	Product (Isolated Yield %)[a]
1	**4aa**	 (65)	6	**4c**	 (57)[c,f]
2	**4b**	 (0)[b]	7	**6**	 (21)[g]
3 4	**4ab** **4ab**	 R= H[c] (66) R= D[c,d] (66)	8	**9**	 (70)[h]
5		 (65)[e]	9	**10**	 (60)[i]

Table 1 [a] Reaction Conditions - as for typical procedure (unless otherwise stated) [b] 6-hydroxy-5-methyl hexanoic acid ethyl ester was the major product (31%) [c] 5:1 mixture of diastereoisomers [d] CH_3OD used as cosolvent [e] 1:1 mixture of diastereoisomers [f] Reaction conditions: substrate in THF (0.25M) with Bu^{t}OH (1.2eq), added to SmI_2 in THF (1.0M , 2eq), HMPA (8eq) at 0°C [g] 5-phenylsulfonyl-pent-4 *E*-ene-2-dimethyl-1-ol was the major product (35%) [h] *cf.* ref. 3 [i] 5-phenylsulfonyl-pent-4 *E*-ene-3-dimethyl-1-al (26%) was also obtained

Treatment of **4c** with samarium(II) iodide and methanol co-solvent gave aldehyde **4b** resulting from loss of the α-benzyloxy group. However, by employing HMPA as the co-solvent, with a single equivalent of *tert*-butanol, cyclisation could be affected to give the desired *anti*-cyclobutanol in reasonable yield as a 5:1 mixture of diastereoisomers[11] (**Table 1, entry 6**).

In general, the cyclisation of vinyl sulfones was far less efficient than that of the analogous esters. Treatment of vinyl sulfone **6** under our standard conditions gave only a small amount of the desired cyclobutanol (**Table 1, entry 7**).

Employing our mild cyclisation conditions, enantiomerically pure ester substrate **9** gave the *anti, anti*-diastereoisomer[11] as the only product in good yield (**table 1, entry 8**).[3] Similarly, analogous sulfone **10** gave the corresponding *anti, anti*-cyclobutanol[11] product accompanied by uncyclised aldehyde having lost the α-benzyloxy group (**Table 1, entry 9**).

In summary, we have described a general method for the assembly of functionalised cyclobutanols from simple acyclic substrates in a stereoselective manner. The samarium(II)-mediated 4-*exo*-trig cyclisation of γ,δ-unsaturated aldehydes gives *anti*-cyclobutanols as the sole cyclic products and in one example, stereochemical control at three newly formed stereocentres is observed. Further investigations into this reaction and its application in the synthesis of biologically active molecules are currently underway in our laboratories and will be reported in due course.

Typical Procedure To a solution of SmI_2 in THF (0.1 M, 10.1ml, 1.01mmol) and MeOH (2.5ml) at 0°C under Nitrogen, was added aldehyde **4ab** (100mg, 0.50mmol) in THF (2ml). The reaction mixture was then stirred for 2h at 0°C before the addition of aqueous saturated NaCl (2ml) and citric acid (128mg, 0.61mmol). The aqueous layer was then extracted with EtOAc, and the combined organic extracts dried (Na_2SO_4) before concentration *in vacuo*. Purification by column chromatography (silica gel, 30% EtOAc/Hexane) gave **4ab** (67mg, 0.34mmol, 66%) as a colourless oil (5:1 mixture of diastereoisomers).

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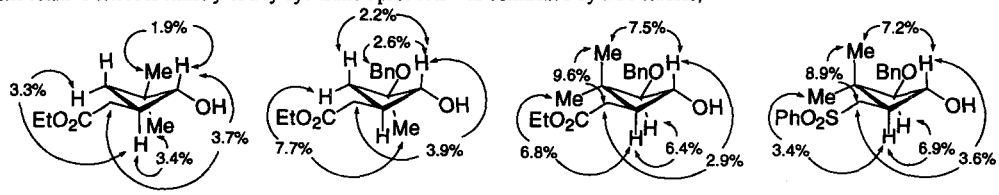

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