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Diastereoselective SmI_2-mediated cyclisation of δ-oxo-α,β-unsaturated esters to cyclopropanols

Hélène Villar and François Guibé*

Institut de Chimie Moléculaire et des Matériaux d'Orsay, Laboratoire de Catalyse Moléculaire, ESA-8075 Bât. 420, Université Paris-Sud, 91405 Orsay, France

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Abstract—In the presence of samarium diiodide and a proton source, δ-oxo-γ,γ-disubstituted-α,β-unsaturated esters readily cyclise with complete diastereocontrol to give *anti*-cyclopropanol products.

We recently reported that δ-iodo and δ-bromo-α,β-unsaturated esters readily cyclise to cyclopropane compounds in the presence of samarium diiodide and a proton source.[1] We present here an extension of this cyclisation reaction to the obtention of cyclopropanols starting from γ,γ-disubstituted δ-oxo α,β-unsaturated esters (Fig. 1).

Unsaturated aldehydes **1a** and **1b** were prepared in four steps (Scheme 1) that included the preparation of morpholino-enamines **4a**,**b** from isobutyraldehyde[2] or cyclohexane–carboxaldehyde, their condensation with 2-chloro-1,3-dithiane,[3] Horner–Emmons olefination with benzyl diethoxyphosphonoacetate and unmasking of the aldehyde by cleavage of the thioacetal function through acid catalysed hydrolysis[4] or treatment with methyl iodide/collidine in acetone/water.[5] Unsaturated aldehyde **2** with *Z*-configuration of the double bond was prepared in a similar manner except that the olefination reaction was conducted with benzyl ditrifluoroethoxy–phosphonoacetate.[6] Unsaturated methylketone **3** was prepared from tiglic aldehyde **7** (Scheme 2) via Horner–Emmons olefination, monoepoxidation of diene-ester **8**, ring opening of unsaturated epoxide **9** with trimethylaluminum[7] and alcohol oxidation with pyridinium dichromate.

The cyclisation reactions were carried out in THF at 0°C with 2 equiv. of SmI_2 and 3 equiv. of *t*-BuOH as the proton source. Our results are summarized in Table 1. The relative stereochemistry of the cyclopropanols was determined by ^1H NMR and deduced from values of coupling constants and from NOE studies.[8,9]

All reactions, which were repeated several times, proceed efficiently and with complete *anti*-selectivity, irrespective of the *E* or *Z* configuration of the double bond in starting olefins (entries 1, 2 and 3). Some alcohol resulting from direct reduction of the carbonyl group without cyclisation was also sometimes observed. Attempts to separate them from the cyclised adducts by chromatography were unsuccessful.

At the present time, we have no clear-cut explanation for the observed stereoselectivity. We tentatively propose the following one. A likely mechanism for the present cyclisation, akin to that already proposed for

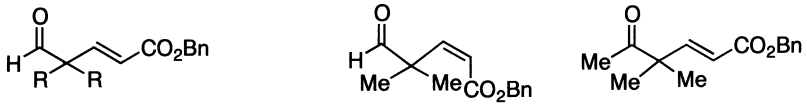

Figure 1.

Keywords: samarium and compounds; radical reactions; cyclisation; cyclopropanols.

* Corresponding author. Tel.: +33-01-69-15-52-59; fax: +33-01-69-15-46-80; e-mail: fraguibe@icmo.u-psud.fr

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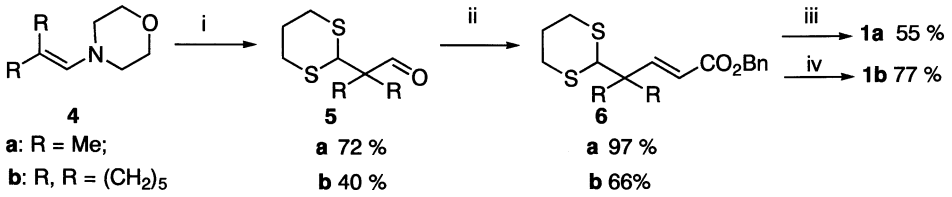
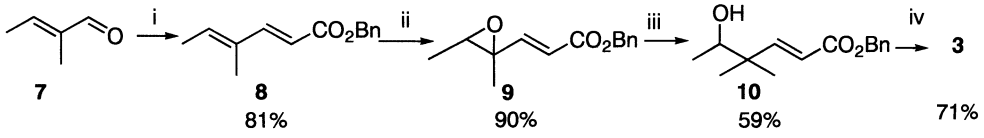
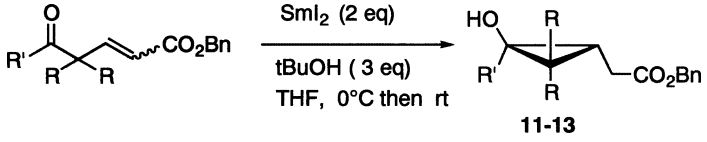


Scheme 1. *Reagents and conditions*: (i) 2-chloro-1,3-dithiane, 0°C, Et_2O/THF; (ii) $(EtO)_2P(O)CH_2CO_2Bn$, NaH, THF, 0°C, then reflux 5 h; (iii) HgO, BF_3OEt_2, 15% aqueous THF; (iv) s-collidine, MeI, acetone/H_2O (v/v 4:1).



Scheme 2. *Reagents and conditions*: (i) $(EtO)_2P(O)CH_2CO_2Bn$, NaH, THF, 0°C, then reflux 5 h; MCPBA 1.5 equiv., $CHCl_3$, rt; (iii) Me_3Al/H_2O, DCM, −35°C; (iv): PDC, DCM, molecular sieves, rt.

Table 1.



Entry	Substrate	Double bond configuration	*R′*	R, R	Cyclopropanol yield[a] (%)
1	**1a**	*E*	H	Me, Me	87 (**11**[b])
2[c]	**1a**	*E*	H	Me, Me	90 (**11**)
3	**2**	*Z*	H	Me, Me	60 (**11**)
4	**1b**	*E*	H	$(CH_2)_5$	60 (**12**[b])
5	**3**	*E*	Me	Me, Me	81 (**13**[b])

[a] Isolated yields.
[b] NMR data: see notes 8 and 9.
[c] The reaction was run in the presence of HMPA (8 equiv.).

cyclisation of δ-halo-α,β-unsaturated esters, is represented in Fig. 2. Monoelectronic reduction of the aldehydic or ketonic carbonyl group leads, probably in a reversible manner,[10] to ketyl intermediate **14** which adds intramolecularly to the double-bond in a 3-*exo-trig* process. Due to strain energy associated with the cyclopropyl group, such a process is quite unfavorable, but a further easy reduction by a second molecule of SmI_2 of the α-carbalkoxy-substituted cyclopropylcarbinyl radical **15** to enolate **16** would drive the overall reaction towards cyclisation. Radical 3-*exo-trig* cyclisation are known to be reversible.[11] At the present time, however, it is hardly possible to decide whether under our reaction conditions, equilibration between the open and cyclised form does take place (which implies that reopening of cyclised radical is faster than its reduction to **16**) or not. In the latter case, the stereochemistry of the reaction is determined at the cyclisation step and may be explained by a strong preference for a *trans* relationship (as represented in A, Fig. 3) of the ketyl oxygen and the double bond over the *cis* one in the transition state. Such preference, due to stereoelectronic factors,[12] has ample precedents in the literature and has been observed in particular in the samarium iodide-mediated cyclisation of δ-ethylenic ketones to cyclopentanols,[13] of η-oxo-α,β-unsaturated esters to cyclohexanols[14] and ε-oxo-α,β-unsaturated esters to cyclobutanols.[15,16]

If on the contrary a rapid equilibration between uncyclised and cyclised radical occurs before reduction to enolate,[17] application of the Curtin–Hammet principle would suggest to link the observed stereoselectivity to the comparative easiness with which the *cis* and *trans* radical species **C** and **D** are reduced to enolates. The development of strong repulsive electrostatic interactions in the transition state in the case of the *cis* isomer could explain why the reduction of this species is much disfavored.

Finally, it should also be recalled that other mechanistic pathways, involving ionic cyclisation, albeit less likely, may nevertheless be considered such as addition of ketone dianion (or its monoprotonated form)[18] or to the double bond or, contrarily, addition of the dianion from the α,β-unsaturated ester to the carbonyl group.[1a,19]

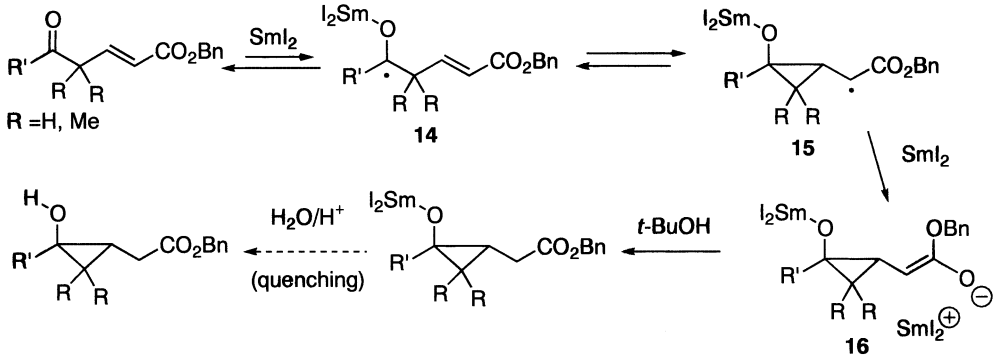


Figure 2.

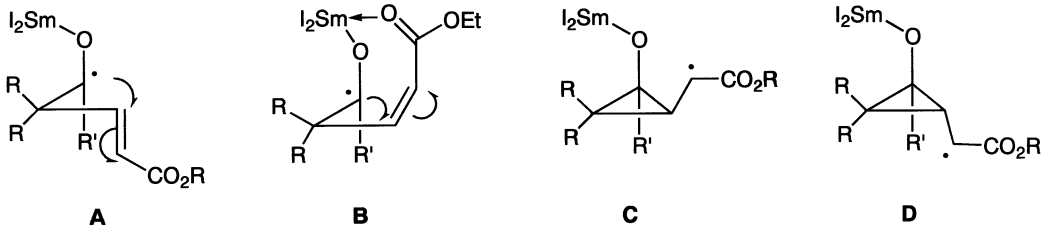


Figure 3.

Examples can be found in the literature in which the geometry of the double bond dramatically influences the stereochemical outcome of samarium induced ketyl olefin cyclisation.[20] Cyclisation of compound **2** with a *Z*-geometry of the double bond was studied in the expectation that it could bring about a reversal of diastereoselectivity. Indeed, a possible chelation of samarium by the ketyl oxygen atom and the ester function could now favor a *syn* transition state as represented in **B** (Fig. 3). In the event, in this case too, only the *anti* product was obtained. Thus, either chelated transition state **B** remains disfavored compared to the *trans* one or the stereochemistry is not determined at the cyclisation step.

In summary, we have shown that cyclopropanols can be obtained by samarium diiodide-mediated cyclisation of δ-oxo-α,β-unsaturated esters. This reaction, contrary to the corresponding cyclisation of δ-halo-unsaturated esters, displays high stereocontrol, leading exclusively to *anti* cyclopropanols. The extension of this reaction to more complex substrates and towards the obtention of highly functionalised cyclopropanols is currently under investigation.

Experimental procedure

The reactions were carried out in Schlenk tubes in dried and degassed THF and under an argon atmosphere.

A solution of 1.3 mmol of *t*-BuOH and 0.43 mmol of carbonyl compound in 1 mL of THF was added dropwise at 0°C to 8.6 mL of a 0.1 M solution of SmI_2 in THF. After complete addition, the reaction mixture was stirred overnight at room temperature and then quenched by addition of water. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with saturated sodium thiosulfate, dried over $MgSO_4$, concentrated in vacuo and purified by chromatography (silica gel, cyclohexane/AcOEt (80/20)). Colourless oils were obtained in all cases.

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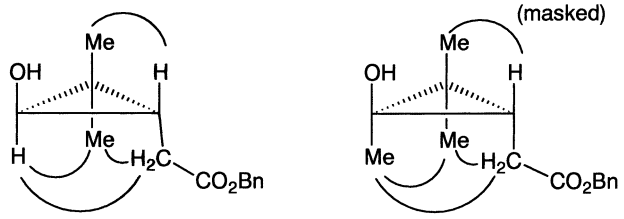
8. ^{1}H NMR (250 MHz, $CDCl_3$); **11**: δ 7.45–7.25 (m, 5H); 5.12 (s, 2H); 2.95 (d, $J=3$ Hz); 2.45–2.25 (two dd, ABX system, $J_{AB}=17$ Hz, $J_{AX}=J_{BX}=7$ Hz, 2H); 1.8 (very broad s, 1H); 1.15 (s, 3H); 0.93 (s, 1H); 0.92–0.82 (m, 1H); **12**: δ 7.45–7.25 (m, 5H); 5.12 (s, 2H); 2.99 (d, $J=3.5$

Hz); 2.44–2.23 (two dd, ABX system, $J_{AB}=16$ Hz, $J_{AX}=7.5$, Hz, $J_{BX}=8$ Hz, 2H); 1.8 (very broad s); 1.6–1.15 (m, 10H); 0.93–0.83 (dt, $J=3.5$ and 7.5 Hz); **13**: 7.45–7.25 (m, 5H); 5.11 (s, 2H); 2.27 ($J=7.5$ Hz, 2H); 1.26 (s, 3H); 1.18 (s, 3H); 0.88 (s, 3H).

9. Important NOE interactions for *gem*-dimethylsubstituted cyclopropanols:



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11. We are not aware of any kinetic or thermodynamic data in the literature pertaining to the interconversion of radicals species **14** and **15** or, more generally, to the interconversion of β,γ-ethylenic ketyl radicals and their corresponding cyclised forms. On the other hand, kinetics data are available for ring closing-ring opening of but-3-enyl radicals and the corresponding cyclopropylcarbinyl radicals, including those bearing a carbalkoxysubstituents on the ethylenic bond. Even in this latter case, the equilibrium constant is still in favor of the uncyclised species ($k_c/k_{-c}=$ca. 50, see Ref. 1a, note 10 and references cited therein).
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13. See inter alia: (a) Molander, G. A.; McKie, J. A. *J. Org. Chem*. **1995**, *60*, 872–882; (b) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem*. **1989**, *54*, 5841–5843.
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17. This appears to be the case for simple α-carbalkoxy cyclopropylmethyl radical (i.e. without oxygen atom attached to the ring). Indeed we have found[1b] that the cyclisation of enantiopure γ-monosubstituted δ-iodo-α,β-unsaturated esters is accompanied by extensive racemisation at the γ centre.
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19. For instance, in the samarium-mediated 4-*exo*-*trig* cyclisation of γ-δ-unsaturated carbonyl compounds to cyclobutanols, a reversal of stereochemistry from *anti* to *syn*, was observed on going from aldehydes to methyl ketones[16d] and has been interpreted as a result of a change in mechanism from addition of the ketyl radical anion to the enoate moiety to addition of the dianion from the enoate moiety to carbonyl function. However, radical 3-*exo*-*trig* cyclisations are much faster than 4-*exo*-*trig* cyclisations and in our case, the *anti* selectivity is maintained with the ketonic substrate.
20. See: Molander, G. A.; Harris, C. R. *Chem. Rev*. **1996**, *96*, 307–338, especially pp. 314–315 and references cited therein.