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LETTERS

Copper (I) mediated Highly Diastereoselective Conjugate Addition of Grignard Reagents to functionalised 6-membered ring cycloalkenols. Synthesis of cyclohexanes derivatives substituted on three contiguous atoms.

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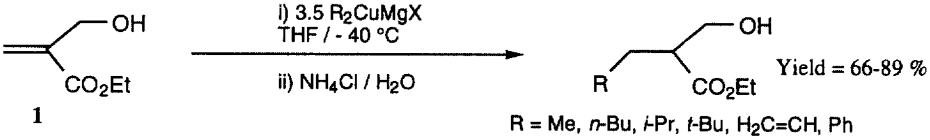
***Abstract** : Copper catalysed conjugate addition of Grignard reagents to 2-silyloxycyclohexene carboxylates in the presence of an excess chlorotrimethylsilane, leads diastereoselectively to related (anti) (Z) silylketene acetals. Subsequent hydrolysis and desilylation afford 2-hydroxycyclohexane carboxylates in high yields and diastereoselectivities.*

Conjugate addition of organocopper reagents and related Copper (I) mediated addition of Grignard reagents has proven to be highly effective in promoting C-C bonds formation for many years[1]. The ability of such species to realise the β-alkylation of α,β-unsaturated carbonyl derivatives in a stereoselective way has also been extensively used as a key-step in numerous natural products syntheses and has been widely reviewed[2].

We have previously described[3] the conjugate addition of magnesium organocuprates (3.5 eq.) to *acyclic* alkenols **1**, affording 1,4-adducts in high yields *without any protection of the alcohol moiety* (Scheme 1).



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Scheme 1.

Nevertheless, such a method could not be applied to 5-membered and 6-membered ring analogues without exclusive formation[4] of the SN_2' reaction type by-products **3** (Scheme 2) probably formed *via* an addition / β-elimination process.

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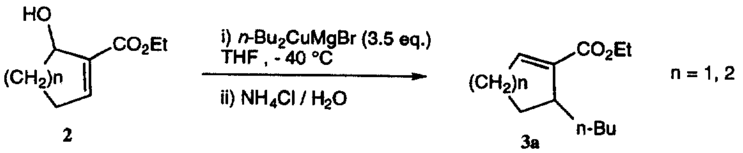
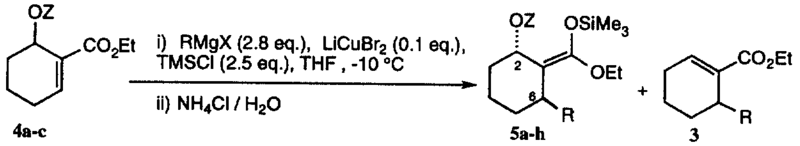


Scheme 2

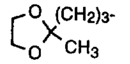
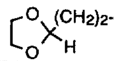
In a recent paper[5] we have reported a new strategy, starting from sterically hindered *O*-silyl derivatives of cyclopentenols and using an excess (2.5 eq.) of trimethylsilyl chloride (TMSCl) to trap the intermediate enolate[6]. Under these conditions, the reaction proceeded quantitatively at – 35 °C and less than 10 % of the β-elimination product was formed. Subsequent deprotection with tetra-*n*-butylammonium fluoride (TBAF) afforded the desired *syn-anti* cyclopentanols in moderate-to-good yields with a high diastereoselectivity (d.e. ≥ 95 %).

In our continuing interest in the synthesis of such buildings blocks, we turned our attention towards the preparation of functionalised 6-membered cycloalkanols as described in this letter. In our set of experiments we explored the behaviour of *O*-silylcyclohexenes carboxylates **4a-c** in conjugate addition reactions of *n*-butylmagnesium bromide (2 eq.) in the presence of 0.1 eq. of $LiCuBr_2$ (1N solution in THF) and 2.5 eq. of TMSCl in THF at - 35 °C[7]. Surprisingly, under these conditions the substrates remained totally unreactive, while performing the reaction at - 10 °C and using a larger excess (2.8 eq.) of Grignard reagent finally achieved conjugate addition (Scheme 3) quantitatively (no cyclohexene carboxylate was recovered). The results obtained were summarised in table 1.



Scheme 3

Table 1. $LiCuBr_2$ mediated conjugate addition of Grignard reagents to cyclohexenes **4a-c**.

Cyclohexene **4**	Z	R	**5 / 3** [a]	d.e. (%) (**5**)[b]
a	$SiMe_3$	*n*-Bu	80 / 20	≥ 95 (**5a**)
b	$SiMe_2$*t*-Bu	"	100 / 0	≥ 95 (**5b**)
c	$SiPh_2$*t*-Bu	"	100 / 0	≥ 95 (**5c**)
b	$SiMe_2$*t*-Bu	Et	100 / 0	≥ 95 (**5d**)
"	"	*i*-Pr	100 / 0	≥ 95 (**5e**)
"	"	$EtO(H_3C)CH\text{-}O\text{-}(CH_2)_5\text{-}$	100 / 0	≥ 95 (**5f**)
"	"		100 / 0	≥ 95 (**5g**)
"	"		100 / 0	≥ 95 (**5h**)

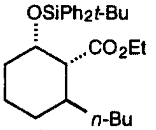
[a] The 5 / 3 ratio was calculated according to ^1H-NMR by relative integration of the H-C_2 of 5 and the olefinic proton of 3. [b] The others diastereoisomers were not detected by ^1H- (400 MHz) and ^{13}C- (100 MHz) NMR.

As shown in table 1, the protection of the alcohol moiety as a silyl ether and the *in situ* trapping of the magnesium enolate allow the minimisation of the β-elimination. Surprisingly, the related silyl ketene acetals have proven to be stable enough under hydrolysis conditions, *e.g.* NH_4Cl / H_2O, and could be fully characterised by ^1H- (400 MHz), ^{13}C-NMR (100 MHz), GC-MS (chemical ionisation with NH_3) and IR. Furthermore, experiments have been carried out and have shown a positive (+ 6 %) and mutual nOe effect between $SiMe_3$ and H-C_2 on **5b** (Z = $SiMe_2$*t*-Bu) that we have linked to a *Z* configuration. Concerning the *anti* relative configuration of H-C_2 and H-C_6, it has been established retrospectively with respect to X-Ray analysis performed on a related ester (*vide infra*).

Following the pioneering work of C. Ainsworth *et al.*[8], our own results could be regarded out as the first example of diasteroselective synthesis of (*Z*) (*anti*) disubstituted cyclohexylidene silyl ketene acetal. The characterisation of those intermediates is particularly interesting to understand the process involved in the competitive formation of **3** and could be related to our previous results[5]. *Indeed, increasing the size of the ring dramatically enhance the stability of the exocyclic silylketene acetal and this phenomenon could be considered as responsible for the univocal formation of 5b-e.*

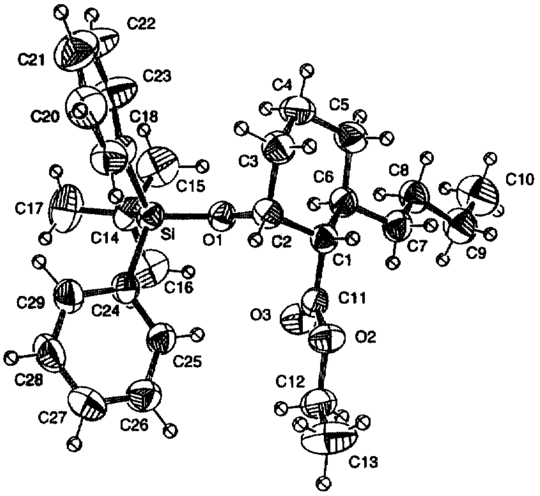
It is also noticeable that the protection of the alcohol moiety as a trimethylsilyl ether does not totally avoid β-elimination, as noted for 5-membered ring analogues[5].

A chromatographic purification of **5c** over silica gel in hexane / CH_2Cl_2 (95 / 5) afforded the β-silyloxy ester **6a** with a 78 % overall yield as a single diastereoisomer, according to ^1H- and ^{13}C-NMR. A crystal structure of **6a** has permitted to establish the relative configuration as being H-C_1-C_2-H (*syn*) and H-C_1-C_6-H (*anti*) (scheme 4).

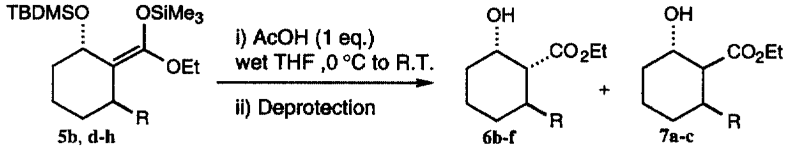


6a

Scheme 4



Attempts in order to purify **5b** or **5d-g** by a same way have irremediably led to the β-elimination products even when performed with triethylamine or over basic alumina. Finally, we have found that glacial acetic acid (1 eq.) in "wet" THF is best suitable for the hydrolysis of such silyl ketene acetals. The reaction proceeds smoothly between 0 °C and room temperature, giving the related β-silyloxy esters as single *syn-anti* diastereoisomers, which were desilylated with TBAF (starting from **5b** and **5d-e**) or in acidic medium[10] (starting from **5f-h**), leading to the desired alcohols in good overall yields and diastereoselectivities (scheme 5 and table 2).



Scheme 5

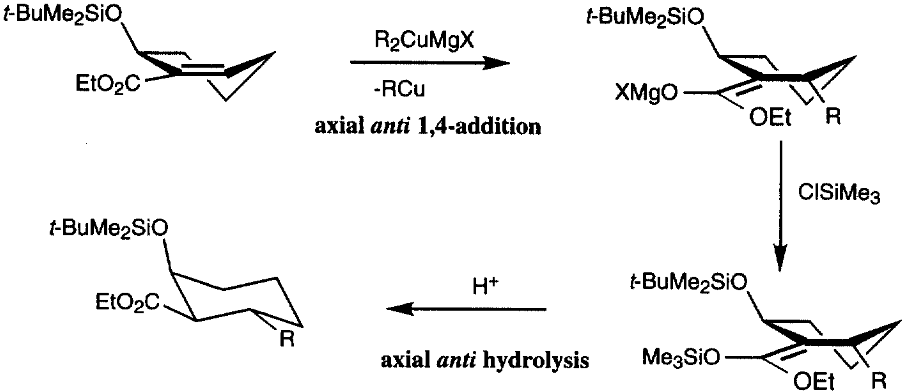
Table 2.

R	Major epimer	Minor epimer	Yield (%)[a]	d.e. (%)
n-Bu	**6b**	**7a**	70	90
Et	**6c**	**7b**	84	76
i-Pr	**6d**	**7c**	64	84
HO-$(CH_2)_5$-	**6e**	-[c]	67	≥ 95
$H_3C(O)$-$(CH_2)_3$-	**6f**	-[c]	65	≥ 95
HC(O)-$(CH_2)_2$-	**8**[d]	-[c]	60[d]	≥ 95

[a]Overall isolated yield calculated from **4b**. [b]Estimated according to ^1H NMR. [c]No epimerisation occurs since deprotection was performed in acidic medium. [d]Crude yield of β-silyloxyester.

Despite a few epimerization of the C_1, occurring in the desilylation step *performed with TBAF*, our own method seems to be very efficient in the synthesis of cyclohexanols **6**. ***Moreover such a drawback is easily solved by a careful chromatography leading to pure single diastereoisomers.***

As obviously described, conjugate addition as well as silyl ketene acetal hydrolysis are very stereoselective steps and could be related to the presence of the bulky *t*-butylsilyloxy moiety involving strong steric interactions responsible for *anti* addition and hydrolysis (with regard to TBDMS) (scheme 6).



Scheme 6

As a conclusion, this catalytic chemo- and diastereoselective conjugate addition to cyclohexene carboxylates bearing an hydroxyl group can be considered as a new promising alternative route for the synthesis of 6-alkyl 2-hydroxycyclohexane carboxylates to the one previously described by D. Seebach *et al.*[11].

Studies are now in progress to extend this new methodology and will be soon reported.

Acknowledgements.

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References and notes.

1 For papers of related interest see : (a) J. F. Normant, *Synthesis*, **1972**, 63-80. (b) G. H. Posner, *Org. Reac.*, **1972**, *19*, 1-113. (c) B. H. Lipshutz, *Synthesis*, **1987**, 325-41. (d) J. A. Kozlowski *in* "Comprehensive Organic Synthesis", B. M. Trost, I. Fleming, Eds., Pergamon Press (Oxford), **1991**, Vol. 4, Chapter 1.4.

2 See *inter alia* : (a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.*, **1992**, *92*, 771-806. (b) A. Alexakis, *in* "Organocopper reagents - A practical Approach", Oxford University Press (New-York), **1994**, Chapter 8. (c) N. Krause, A. Gerold, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 186-204.

3 H. Amri, M. Rambaud, J. Villiéras, J. *Organomet. Chem.*, **1986**, *308*, C27-C32.

4 (a) H. Amri, J. Villiéras, *Tetrahedron Lett.*, **1987**, *28*, 5521-5524. (b) H. Amri, M. Rambaud, J. Villiéras, *Tetrahedron*, **1990**, *46*, 3535-3546.

5 V. Dambrin, M. Villiéras, C. Moreau, H. Amri, L. Toupet, J. Villiéras, *Tetrahedron Lett*, **1996**, *37*, 6323-6326.

6 Concerning the use of TMS Halide in conjugate addition reactions see for instance (a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.*, **1985**, *26*, 6019-6022. (b) R. J. K. Taylor, *Synthesis*, **1985**, 364-392. (c) A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.*, **1986**, *27*, 1047-1050.

7 **Typical procedure :** 0.5 mmol of $LiCuBr_2$ (1N solution in THF) and TMSCl (12.5 mmol) were added under nitrogen to a solution of **4b** (5 mmol) in dry THF (40 mL) at - 10 °C. Then, a solution of Grignard reagent (14 mmol) was slowly added (40 min.). After completion (*ca.* 1 hour), the mixture was quenched with aqueous NH_4Cl, extracted with diethyl ether and the combined organic layers were washed with brine. Drying over $MgSO_4$ and concentration *in vacuo* afforded crude silyl ketene acetal which was stirred with glacial acetic acid (5 mmol) in "wet" THF between 0 °C and R. T. for 2 hours. Subsequent neutralization with aqueous $NaHCO_3$ and extraction with diethyl ether finally furnished β-silyloxy ester. The last deprotection step was accomplished according to known procedures (see 9 and 10).

8 The synthesis of ethyl cyclohexylidene trimethylsilylketene acetal was first reported by C. Ainsworth, F. Chen, K. Yu-Neng, J. *Organomet. Chem.*, **1972**, *46*, 59-71.

9 E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.*, **1972**, *94*, 2549-2550.

10 The diol **6e** was obtained after treatment with 2N aqueous HCl in aceton for 2 hours at R. T. Removal of the dioxolane moiety was performed with potassium periodate at reflux of a mixture of dioxane and 0.1 N aqueous HCl. The same subsequent treatment as for **6e** finally afforded **6f**.

11 D. Seebach, B. Herradon, *Tetrahedron Lett.*, **1987**, *28*, 3791-3794.