Copper (I) Mediated Conjugate Addition of Grignard Reagents to 2-Oxoethylcyclohexenols. A Versatile, Efficient and Diastereoselective Route to *anti, Z* 6-Alkyl-2-trialkylsilyloxy-1-(2-trimethylsilyloxypropylid-1-ene)-cyclohexanes

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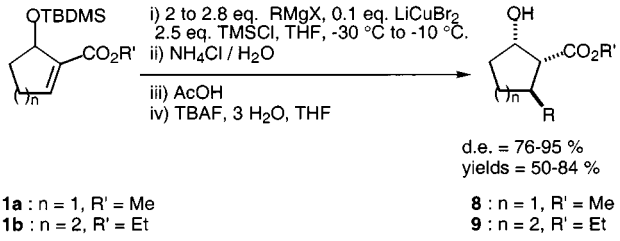
Abstract: The copper (I) mediated conjugate addition reactions of Grignard reagents to 2-silyloxycyclohexenyl methylketones lead exclusively to the corresponding *anti, Z* 1-(2-trimethylsilyloxypropylid-1-ene)-cyclohexan-2-ols in almost quantitative yields and with high diastereoselectivities (d.e. ≥ 95%).

Key words: conjugate addition, polyfunctional Michael acceptor, enolate trapping, silyl enols ethers, diastereoselectivity

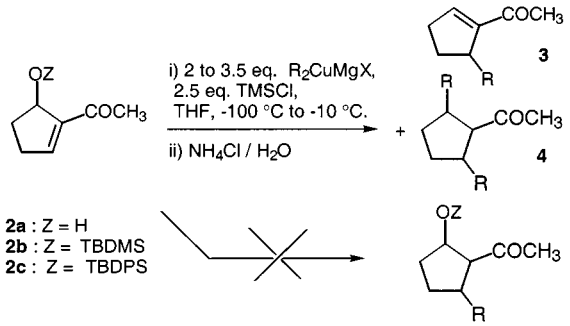
In our continuing interest towards the synthesis of 5- and 6-membered ring cycloalkanol carboxylates substituted at three contiguous atoms, we would like to report our recent results concerning the behaviour of acetyl-substituted analogues. While, in the case of 2-silyloxycycloalkenes carboxylates[1], copper (I) mediated conjugate addition reactions of Grignard reagents afforded related alkylated cycloalkanols in high yields and diastereoselectivities (Scheme 1), ketocycloalkenols have led to quite unexpected results.



Scheme 1

Under the same conditions the keto analogs **2a-b** led always to quantitative formation of **3**, probably through an addition-elimination process, while no desired cycloalkanols could be observed (Scheme 2).

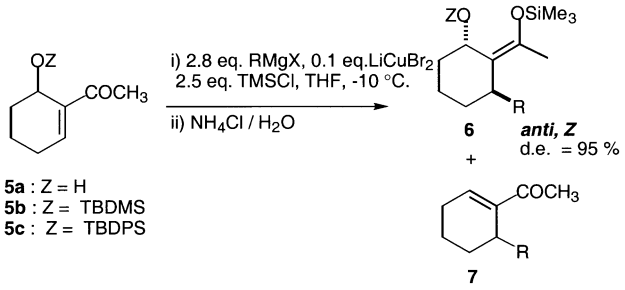
The use of stronger electrophiles in order to trap the intermediate enolate (TMSBr, TMSI, TMSOTf or TBDMSCl) yielding to a potentially more stable enoxysilane, however did not provide any change in the course of the reactions. Besides, in the presence of HMPA (0.5 eq.) or at reaction temperatures up to - 30 °C, concomitant formation of **4**



Scheme 2

(inseparable mixture of diastereoisomers) was observed as resulting from conjugate addition to **3**.

Conjugate addition to the 6-membered ring analogues **5b-c** was less disappointing. In this case, the reaction proceeded smoothly at -10 °C affording the corresponding enoxysilanes **6a-i**, *without formation of* ***7*****,** in almost quantitative yields (no cyclohexene was recovered) and high diastereoselectivities (one single isomer detected, according to ^{1}H- and^{13}C NMR) (Scheme 3 and Table 1).



Scheme 3

As previously reported for the ester analogues, the formation of **6** and **7** must be considered as the result of concurrent *O*-silylation and β-elimination on the intermediate keto-enolate resulting of the addition reaction. It seems to be a reflection of the nucleophilic behaviour of these enolates for *O*-silylation. This phenomenon seems to be

Table 1 Preparation of the enoxysilanes **6a-i**

Z (cyclohexene **5**)	**6** / **7**[a]	R (adduct **6**[b])	d.e. (%)[d]
H (**5a**)	0 / 100	*n*-Bu (**6a**)	-
$SiPh_2$*t*-Bu (**5c**)	100 / 0	*n*-Bu[c] (**6a**)	≥ 95
$SiMe_2$*t*-Bu (**5b**)	100 / 0	*n*-Bu (**6b**)	"
"	"	Me (**6c**)	"
"	"	Et (**6d**)	"
"	"	*i*-Pr (**6e**)	"
"	"	*t*-Bu(**6f**)	"
"	"	H_2C=CH (**6g**)	"
"	"	Ph (**6h**)	"
"	"	Bn (**6i**)	"

[a]Estimated according to ^{1}H NMR. [b]Quantitative crude yields without purification over silica gel in order to prevent from β-elimination. [c]Silica gel chromatography could be achieved successfully on this compound (96%). [d]Estimated since no other diastereoisomers could be observed in ^{1}H and ^{13}C NMR.

strongly ring-size dependent since *cyclopentylidene enolates seems to be much less stable than cyclohexylidenes enolates*. As a consequence, subsequent rate-limiting *O*-silylation with TMSX is much more favoured in the 6-membered ring series.

Structure determination of **6** could be accomplished by comparison with our previous results[1] on 6-membered ring silyl ketene acetals. Indeed spectral data analogy with a related 3-*n*-butyl-2-(ethoxytrimethylsilyloxymethylene)-cyclohexan-1-ol dimethyl-*tert*-butylsilyl ether led us to assign the exclusive relative *anti*, *Z* configuration for **6b**. All attempts to purify over silica gel (with or without Et_3N) or basic alumina, however *consisted in the sole formation of the β-elimination by-products **7***. The same results were obtained by trying to regenerate the carbonyl moiety with various acids (including aqueous HF, CF_3CO_2H, Amberlyst (15)), with TBAF[2] or with MeLi, whereas acetic acid did leave the enoxysilanes **6** unchanged. Despite this, the method seems particularly attractive by enabling a short and diastereoselective synthesis of numerous disubstituted exocyclic 6-membered ring enoxysilanes under very simple operating conditions.[3] Furthermore, it can be considered as an alternative and efficient route to the previously described methods (zinc enolate silylation,[4] ketene alkylation-silylation,[5] C. Ainsworth[6]).

There is no doubt that those preliminary results will offer new opportunities in the field of multi-step synthesis involving asymetric aldolisation and related Mukaiyama reactions.[7]

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References and Notes

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(3) ***Typical procedure*** : *anti, (Z)-6-n-Butyl-2-dimethyl-tert-butylsilyloxy-(2-trimethylsiloxypropylid-1-ene)-cyclohexane **6b**.*
To a solution of 2.5 mmol (1 eq.) of **5b** in 40 mL THF at -10 °C was added 0.25 mL (0.1 eq.) of a 1N solution of $LiCuBr_2$ in THF and trimethylsilyl chloride (0.8 mL, 6.25 mmol, 2.5 eq.). After 5 min, a solution of the Grignard reagent (7 mmol, 2.8 eq.) was slowly added during ca. 1 h and the mixture was stirred for another hour until completion. Then the mixture was quenched with saturated aqueous NH_4Cl. After extraction with diethyl ether, the combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvents under vacuum yielded the crude silyl enol **6b** as a colourless viscous oil, which was not purified over silica gel in order to prevent β-elimination (1.05 g, quant.), d.e. > 95%. ^{1}H NMR (200 MHz, $CDCl_3$ / TMS) : δ 4.40 (1H, *m*, *H*C-OSi), 2.84 (1H, *m*, *H*C-nBu), 1.97 (3H, *s*, CH_3), 1.79-1.27 (12H, *m*), 0.90 (9H, *s*, *t*-Bu), 0.9 (3H, *broad t*, CH_3 (n-Bu)), 0.18 (6H, *s*, *Me*-Si), 0.08 (9H, *m*, $SiMe_3$).
^{13}C NMR (50 MHz, $CDCl_3$) : δ 139.7 (C=COSiMe_3), 123.0 (*C*=COSiMe_3), 69.5 (*C*H-OSi), 36.1 (H*C*-*n*-Bu)), 35.9 (C=C-*C*H_3), 30.7 (*C*H_2), 30.6 (2*C*H_2), 26.3 (*C*H_2), 25.9 (C(*C*H_3)$_3$), 25.7 (*C*H_2), 22.8 (*C*H_2), 19.8 (*C*(CH_3);), 14.2 (*C*H_3), 0.66 ($SiMe_2$ and $SiMe_3$).
MS m/z (CI) 385 ($M\text{-}H^+$)
IR ν max (thin film) 1673 (C=C), 1096 (broad, O-Si).

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