Remarkable Equatorial Selectivity in the Aldol Coupling between Enol Silyl Ethers and Cyclohexanone Acetals

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Lewis acid-catalysed aldol coupling of enol silyl ethers and substituted cyclohexanone acetals shows a markedly higher ratio of equatorial attack than the reaction of the parent ketones.

Addition of a carbon nucleophile to 3- and 4-substituted cyclohexanones has not been a useful synthetic sequence owing to its moderate stereoselectivity, while the reaction with 2-substituted cyclohexanones has proved to be a reliable method.[1] We have found that the title reaction exhibits a prominent equatorial stereoselectivity irrespective of the position of the substituent, and therefore provides a useful synthetic strategy.

Table 1. Equatorial selectivity in the reaction of nucleophiles with cyclohexanones and their dimethyl acetals.

			% Equatorial adduct[e]			
Nucleophile	Catalyst	Substrate	2-Me	3-Me	4-Me	4-Bu^t
(1)[a]	$TiCl_4$	Acetal (**2a**)	95	95	92[f]	93
(1)[a]	TMSOTf	Acetal (**2a**)	97	95	—	95
(1)[b]	$TiCl_4$	Ketone	98	80	76	83
$PhCH_2CH_2MgBr$[c]	—	Ketone	97	87	—	73
EtMgBr[d]	—	Ketone	95	68—80	—	71

[a] Performed with 1 equiv. of the catalyst at −78 °C for 20 min in methylene dichloride. The yield was 70—80%. The n.m.r. spectra of the adduct show two singlets due to the methylene group α to the carbonyl group and the methoxy-group at δ 2.90—3.07 and 3.06—3.11, respectively. [b] Performed at room temperature for 2 h in methylene dichloride with 1 equiv. of the catalyst. [c] Performed in ether at 0 °C to room temperature. [d] Taken from ref. 1. [e] The isomeric ratio was determined by ^1H n.m.r. and capillary column g.l.c., using OV-101 and PEG-20M, 20 m, and is the minimum value (*cf.* note f). [f] The minor isomer (8%) was detected by ^1H n.m.r. spectroscopy.

We have chosen the reaction between the silyl ether (**1**) and the substituted dimethyl acetals (**2a**) as a model system, since such a combination is free of undesired regiochemical and diastereoisomeric problems as well as extraneous steric factors. The results obtained with both $TiCl_4$[2] and trimethylsilyl trifluoromethanesulphonate (TMSOTf)[3] as catalyst are summarized in Table 1 (entries 1 and 2). The selectivity with 2-methylcyclohexanone is not unexpected, since the chiral centre responsible for the stereoselection is close to the reaction centre. The selectivity with 4-t-butylcyclohexanone dimethyl acetal is at least 93%.† Given the constraints imposed by the bulky 4-t-butyl group, this value may be considered to be the minimum for the intrinsic equatorial preference of the nucleophile in such a system. The value of 92% with the 4-methyl compound seems to reflect the population of the minor conformer. The high equatorial percentage observed for the 3-methyl acetal is remarkable, and probably related to the low population of axial 3-methyl conformer due to the presence of the axial 1-methoxy group; this effect is the particular merit of the strategic use of acetals for stereocontrol.

The reaction of dibenzyl acetals also showed a high degree of equatorial selection. The adducts (**3b**) are readily converted (H_2, Pd–C, AcOH, EtOH) into the tertiary alcohols (**4**), which are identical with the major isomers of the Grignard reaction

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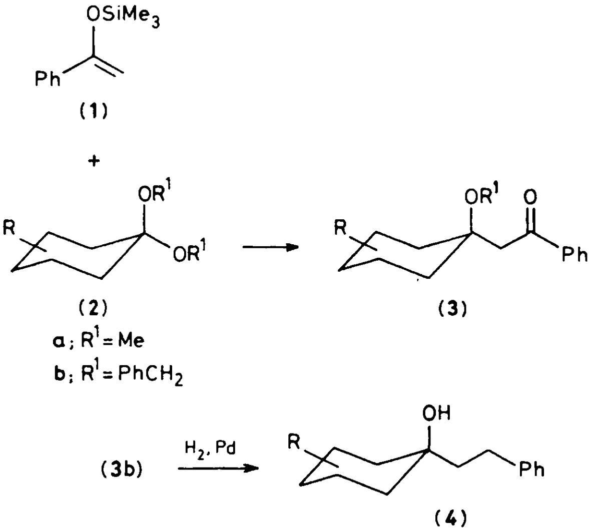
† This value is based on the minor unidentified product and the actual selectivity is likely to be much higher.



(1)

(2)
a; $R^1 = Me$
b; $R^1 = PhCH_2$

(3)

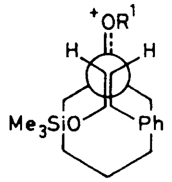
(3b)

(4)

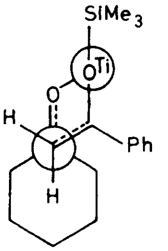
of the corresponding ketones. The equatorial selectivity is not restricted to the acetophenone enolate; the reaction of the enol silyl ether of pentan-3-one with the dimethyl acetals of 4-t-butylcyclohexanone and 2-methylcyclohexanone gave only the equatorial adducts. The BF_3-catalysed reaction of 1,2-bis-(trimethylsilyloxy)cyclobut-1-ene[4] with 4-t-butyl- and 3-methyl-cyclohexanone dimethyl acetal was also 100% equatorial selective.

Interestingly, such a high degree of equatorial attack does not emerge in the related reaction[5] of enol silyl ethers with ketones; the observed profile of selectivity (Table 1, entry 3) is very similar to that for the Grignard reaction (entries 4 and 5).

Our speculation as to the possible reasons for the enhanced equatorial attack with the acetal substrates[6] assumes the 'extended' transition state proposed for the reaction of acetals.[3] Such a transition state (**5**), in which the enol oxygen is placed on the far side of the acetal oxygen, increases the effective bulk of the approaching nucleophile and therefore greatly disfavours axial attack of the enol silyl ether. The chair transition state (**6**), which is assumed to operate in the Lewis acid-catalysed reaction between enol silyl ethers and carbonyl compounds,[5] resembles the transition state of the Grignard reaction in that it places the bulky moiety away from the ring.



(5)



(6)

Finally, in view of the availability of the stereoselective conversion of C–O chirality into a new C–C chirality,[4] the present findings should provide a solid basis for solving problems of stereochemistry at quaternary carbon centres.[7]

Added in proof: The reactions of the enol trimethylsilyl ether of pinacolone with the dimethyl acetals of 2-phenylpropanol and 2-benzyloxyheptanal showed only moderate diastereoselectivity (2:1 and 7:3 respectively). This stands in contrast to the recent report concerning the respective aldehydes (C. H. Heathcock and L. A. Filippin, *J. Am. Chem. Soc.*, 1983, **105**, 1667).

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References

1 E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 1975, **75**, 521.
2 T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 1974, 15.
3 S. Murata, M. Suzuki, and R. Noyori, *J. Am. Chem. Soc.*, 1980, **102**, 3248.
4 E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1977, **99**, 961.
5 T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503.
6 *Cf.* R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, 1981, **37**, 3899; T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 71.
7 J. Shimada, E. Nakamura, and I. Kuwajima, *J. Am. Chem. Soc.*, submitted for publication.