Stereochemistry of the Organocuprate Reactions of Two *cis–trans* Isomeric Allylic Ethers

By ALF CLAESSON* and LARS-INGE OLSSON

(*Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, Box* 574, S-751 23 *Uppsala, Sweden*)

Summary (*S*)-*cis*-4-(1-Ethoxyethoxy)pent-2-en-1-ol reacts with methylmagnesium iodide in the presence of CuI to give (*S*)-2-methylpent-3-en-1-ol in an overall *trans* substitution, whereas (*S*)-*trans*-4-(1-ethoxyethoxy)pent-2-en-1-ol gives rise to the (*R*)-enantiomer, also in a *trans* substitution.

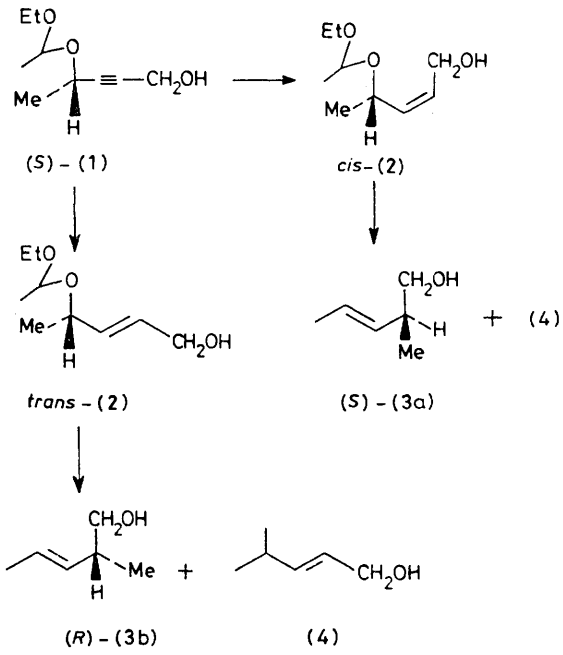
A GRIGNARD reagent in combination with catalytic amounts (5—20%) of a Cu^{I} halide is a readily available, inexpensive reagent which, among other things, effects substitutions in prop-2-ynylic[1,2] and allylic[1,3] methyl and tetrahydropyranyl ethers and acetals. Most of these reactions cannot be effected with the better known lithium dialkylcuprates.†

The stereochemistry of the substitution reactions, with or without allylic rearrangement, of allylic esters with lithium dialkylcuprates is of current interest. The mode of substitution was shown to be exclusively *trans* (*anti*) in two different cyclohexenyl systems when allylic rearrangement occurred. For the direct substitution inversion was observed.[4,5]

We report here the stereochemistry of the reactions[1] of MeMgI–CuI with the allylic substrates *cis*- and *trans*-(**2**).

† However, the combination of butyl-lithium with 10% CuI gives a powerful reagent which even cleaves THF to give octanol, J. Millon and G. Linstrumelle, *Tetrahedron Letters*, 1976, 1095.

Hydrogenation over a Lindlar catalyst of the (*S*)-(−)-alkynol (**1**), prepared‡ from resolved (*S*)-but-3-yn-2-ol,[6,7] gave, in an occasionally sluggish reaction,[8] the alkenol *cis*-(**2**) in almost quantitative yield (*cis*:*trans*, 97:3). The alcohol *trans*-(**2**) was obtained in 85% yield (>98% *trans*) by treatment[7] of (**1**) with lithium aluminium hydride in



tetrahydrofuran (THF) at −10 °C for 3 h. The compounds (**2**) were allowed to react with 5 equiv. of MeMgI–CuI (9:1) at room temperature.[1] Compound *cis*-(**2**) reacted quantitatively in diethyl ether within 2 h to give the alcohols (**3a**) and (**4**) in a 4:1 ratio. Compound *trans*-(**2**) did not react in ether; however, in a mixture of THF and ether (3:1) 85% conversion was obtained after 20 h yielding the alcohols (**3b**) and (**4**) in a 1:2 ratio. The alcohols (**3**) were isolated by preparative g.l.c. (Carbowax 20 M, 6 m column); (**3a**), $[\alpha]_D^{20}$ −23·8° (*c* 7·9, MeOH) and (**3b**), $[\alpha]_D^{20}$ +20·0° (*c* 2·3, MeOH).§ The alcohol (**3a**) was hydrogenated (Pd–C) to give (*S*)-(−)-2-methylpentan-1-ol, $[\alpha]_D^{20}$ −12·0° (*c* 2·5, MeOH) [lit.[9] for the (*R*)-enantiomer $[\alpha]_D^{20}$ +12·9° (neat)], thus establishing the absolute configuration of (**3a**) as (*S*) and of (**3b**) as (*R*). The enantiomeric compositions of (**3a**) and (**3b**) were determined by ^{1}H n.m.r. spectroscopy using the chiral shift reagent Eu(hfbc)$_3$.[10] With $CDCl_3$ as the solvent the difference in the enantiomeric shifts of the α-methyl protons is 0·1 p.p.m. making it possible to detect the presence of *ca.* 5% of the other enantiomer in the alcohols (**3a**) and (**3b**), *i.e.* both are *ca.* 90% enantiomerically pure.

The alcohols (**4**) from both reactions have predominantly *trans* configurations as judged by the strong absorption at 965 cm^{-1} (essentially identical i.r. spectra).

Since the alcohols *cis*- and *trans*-(**2**) both have (*S*)-configuration and give rise to the enantiomeric alcohols (*S*)-(**3a**) and (*R*)-(**3b**), respectively, it can be concluded that in both cases the mode of substitution is *trans* (*ca.* 95% or greater).§

Goering and Singleton,[4] and Kreft[5] found the lithium dimethylcuprate reactions of six different cyclohex-2-enyl-acetates to be highly stereoselective in that *trans* substitution (>97·5%)[4] always accompanied the allylic rearrangement. It was remarked[4] that the high stereoselectivity might be due to 'an inconspicuous steric bias, unique to the cyclohexenyl system, that favours inversion of configuration.' Our two allylic systems allow in principle full conformational mobility in the transition state, but the substitutions nevertheless are highly stereoselective. The present findings suggest that when the organocuprate substitutions of allylic substrates proceed with allylic rearrangement, a highly ordered reaction pathway is followed which ignores conformational mobility. By this and the following reasoning we assume that the reactions with lithium dialkylcuprates have essentially the same mechanisms as the present reactions.

It has been repeatedly stated that organocuprate reactions proceed *via* Cu^{III} intermediates[11] and proof of the existence of such complexes at low temperature has also been claimed.[12] In the case of at least some allylic substrates one might imagine the formation of a Cu^{III}–π-allyl complex[4] which maintains stereochemical integrity for a period of time sufficient for the reductive elimination to occur stereoselectivily on one side of the allylic system. Alternatively, sufficiently stable σ-complexes are formed as transient intermediates. In this connection it is of considerable interest to note that the oxidative addition of Pd^0 to allylic acetates gives a π-allyl complex which retains *cis–trans* configuration from *trans* expulsion of the acetate. The *in situ* alkylation of this complex with diketonates occurs with *trans* substitution resulting in complete net retention of configuration at the carbon undergoing displacement.[13] An analogous kinetically controlled reaction *via* π-allyl intermediates is an attractive possibility for organocuprate reactions of many allylic substrates; the most important difference from the Pd reactions is, of course, that the Cu^{III} intermediate undergoes reductive elimination giving alkylation on the same side of the allyl face from which Cu^I leaves.

Although this mechanism offers a quite reasonable explanation for the stereochemistry of the alcohols (**3**),§ it does not account for the predominant *trans* configuration of the alcohol (**4**) from the reaction of *cis*-(**2**). If this compound is formed from the same conformationally rigid π-allyl complex as is (**3a**), one would expect predominantly *cis* configuration. It seems therefore that the formation of the alcohol (**4**) from *cis*-(**2**) is preceeded by a rotation of 180° within the complex before the reductive elimination.

‡ The corresponding tetrahydropyranyl derivative was prepared recently (ref. 7).

§ According to ^{1}H n.m.r. spectroscopy the purified (+)-enantiomer (**3b**) contains 10—15% of another, unidentified compound whose n.m.r. spectrum is similar to that of (**3b**) but which was detected because of slightly different shifts of the methyl signals [it may be *cis*-(**3b**)]. The presence of this compound most likely explains the lower optical rotation of (**3b**) as compared with (**3a**). However, the determination of the enantiomeric purity of the *trans*-alkenol (**3b**) by n.m.r. spectroscopy is unambiguous and the further discussion refers to this compound only.

Although identification of all the products is not complete yet,§ we feel that the present results will be of value in understanding the mechanism of reactions of the synthetically important organocuprate reagents of different origin.

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