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Use of metallated allylic ethers for the elaboration of vicinally trisubstituted linear substrates or cyclopropyl carbinols

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Abstract

Allyl zinc reagents derived from allylic ethers carbometallate vinyllithiums derived from secondary allylic ethers, leading to linear 3,5-dialkoxy-4-methyl-1-alkenes, or to 1-vinyl-2-alkoxyalkyl cyclopropanes diastereoselectively. © 2000 Elsevier Science Ltd. All rights reserved.

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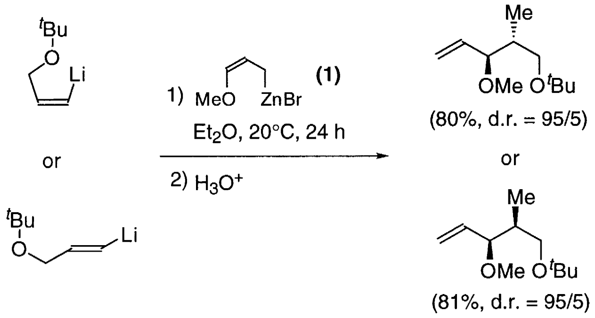
Allyl zincation of vinyl metals by heterosubstituted allyl zinc reagents is an efficient stereoselective process for the elaboration of *syn*- or *anti*-1,3-dialkoxy-2-methyl-4-pentenes[1] (Scheme 1).



Scheme 1.

Such high diastereoselection is obtained when Et_2O (and not THF) is used as solvent, but this less basic solvent raises some difficulties for the preparation of the lithiated precursor of **1**.[2] *sec*-Butyllithium deprotonates allyl methyl ether in Et_2O when a molar equivalent of TMEDA is used[2] but the subsequent carbometallation then requires 24 h at 20°C.

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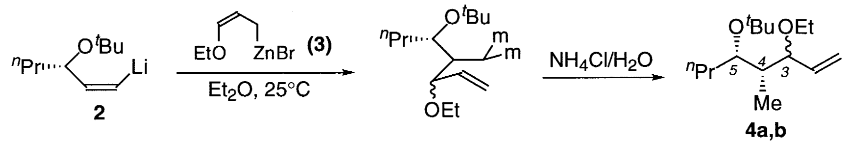
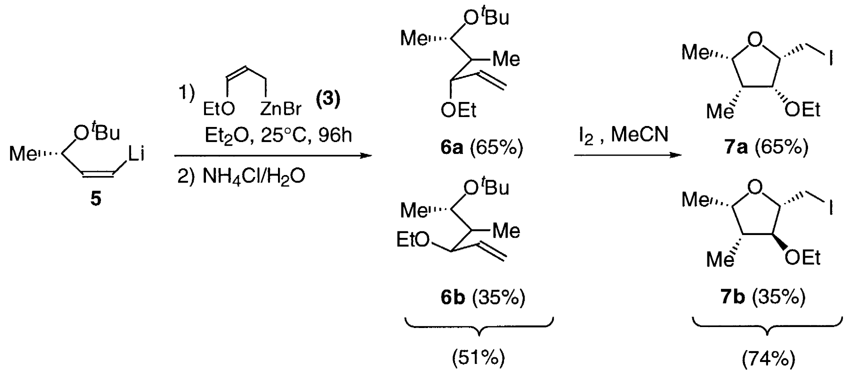
We report here the carbometallation by reagent **3** of a lithiated *secondary* allylic ether **2**,[3] in order to create three vicinal stereogenic centres (Scheme 2).



Scheme 2.

When the reaction is performed as in the previous case, **4** is obtained in only 28% yield after 72 h at 25°C, and as a mixture of two diastereomers in a 65:35 ratio. Assuming that the presence of TMEDA slows down the addition reaction, we first checked that the metallation of allyl ethyl ether in Et_2O was possible in the presence of only 10% TMEDA. In these conditions **4** was then obtained in 52% yield, although with the same (65:35) diastereomeric ratio. As compared with the 95:5 ratio in Scheme 1, this result could be either due to a competitive face choice on substrate **2** (affecting the C4/C5 relationship in **4**) or to the *cisoid* or *transoid* nature of **3** in the transition state (affecting the C3/C4 relationship in **4**).

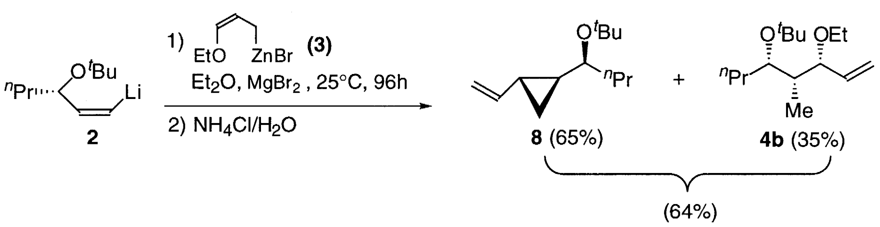
The structures of **4a**,**b** could not be established by iodoetherification[4] followed by NOE measurements. Nevertheless, the methylated homologue **5** of **2** led to the same ratio of stereomers **6a**:**6b**=65:35 which gave the cyclised products **7a**:**7b**=65:35, where NOE was perfectly discernible (see Scheme 3) and showed that they differed only by the position of the ethoxy group.



Scheme 3.

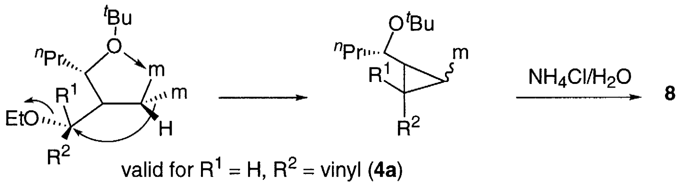
Thus, organozinc **3** has reacted under both *cisoid* (major) and *transoid* (minor) forms, with a good facial selectivity, on **5**.

We then checked a possible acceleration of the reaction by $MgBr_2$. This was indeed the case, but this Lewis acid also promoted a γ-elimination of the ethoxy moiety, so that the initial 65:35 ratio of isomers became a 65:35 ratio of a pure cyclopropyl derivative **8** and a pure linear compound **4b** (Scheme 4).



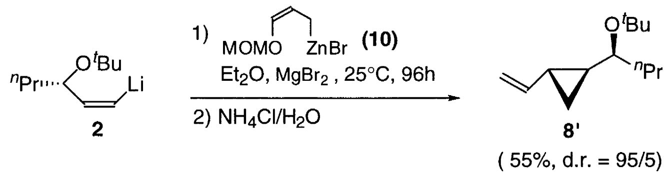
Scheme 4.

In other words, during this cyclisation, only the stereochemistry at C3 is involved, one diastereomeric bismetallic species (the major) is prone to γ-elimination, and the other is not. Considering that this elimination arises from a conformer where the *m*-C-C-LG arrangement adopts a W shape,[5] it seemed plausible that among the two diastereomers only the one with R^1=H and R^2=vinyl will obviate a steric interaction between the vinyl and the –CH(^{n}Pr)O^{t}Bu neighbours, and will adopt the required conformation (Scheme 5).



Scheme 5.

Although **8**[6] and **4b** could be separated by column chromatography, we looked for a more selective substrate and turned to the lithiated MOM ether **10**, corresponding to **3**. The metallated allyl ether **10** was also prepared in Et_2O with *sec*-butyllithium and a catalytic amount of TMEDA, at −70°C, followed by treatment with $ZnBr_2$ and $MgBr_2$ (Scheme 6).



Scheme 6.

The carbometallation proceeded in the same way, and although yield remained modest, we were pleased to see that the diastereomeric ratio of the intermediate *gem*-bismetallics was enhanced to 95:5, leading to **8**′ identical to **8**. The minor diastereomer was present in such a small amount that its stereochemistry could not be established.

Thus, we now have at hand an expeditious access to 2-substituted *trans* cyclopropyl *syn* secondary carbinols with three defined stereocentres. This pattern is present in several metabolites found in marine invertebrates and algae, which have been the target of several synthetic approaches,[7] particularly the diastereoselective cyclopropanations.[8] In our case, the vinyl synthon allows for chain extention and functionalisation.

Acknowledgements

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6. Cyclopropane **8**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.62 (1H, dt, J=4.8, 8.6 Hz), 0.73 (1H, ddd, J=4.8, 5.8, 8.5 Hz), 0.93 (3H, t, J=7.4 Hz), 1.18 (9H, s), 1.37 (4H, m), 1.52 (2H, m), 3.04 (1H, q, J=6.3 Hz), 4.85 (1H, dd, J=1.7, 10.2 Hz), 5.03 (1H, dd, J=1.7, 17.2 Hz), 5.43 (1H, ddd, J=8.7, 10.2, 17.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.0, 14.9, 19.1, 21.5, 26.9, 29.3, 40.5, 73.1, 73.6, 111.9, 141.8.
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