

## Organobismetallic zinc reagents: Their preparation and use in diastereoselective reactions

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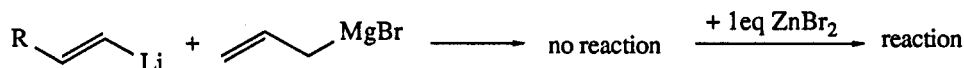
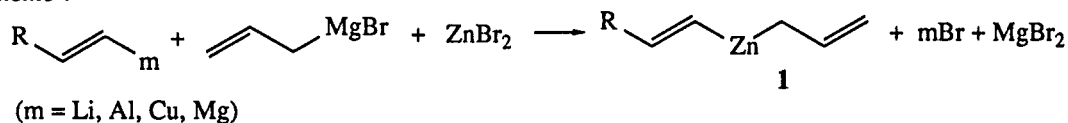
**Abstract.** The allylzincation of various vinyl metals can be performed at low temperatures. If the vinylic partner bears a chiral center, the addition occurs diastereoselectively, and allows the creation of two or three adjacent centers in a *syn* or *anti* relationship, according to the geometry (E or Z) of the vinyl metallic reagent.

### INTRODUCTION

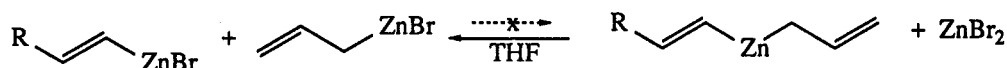
The addition of an allyl metal to a vinyl metal, in order to form a gembismetallic reagent, is a very intriguing reaction. For the first time, M. Gaudemar<sup>1</sup> added allyl zinc bromide to a variety of vinyl Grignards, and a heavy water quench delivered 1,1-dideuteroalk-4-enes in moderate to fair yields.

More recently, we undertook a systematic study of this reaction and showed that excellent yields could be obtained<sup>2</sup>. Also, a vinyl-lithium, -alane<sup>2</sup>, or -copper reagent<sup>3</sup> can be used instead of the magnesium reagent, and/or an allylic Grignard instead of the zinc derivative, provided one Zn (II) equivalent is present in the reaction mixture. Therefore, we postulated that the first step of this reaction is the formation of a mixed zinc species as shown in scheme 1.

Scheme 1

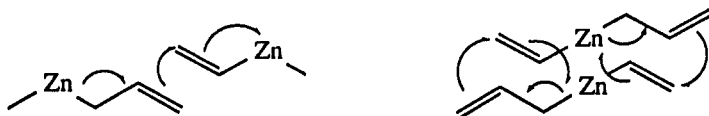


The fact that allyl zinc bromide does not react with a vinyl zinc bromide in THF is considered to result from a totally shifted Schlenck equilibrium in this solvent :

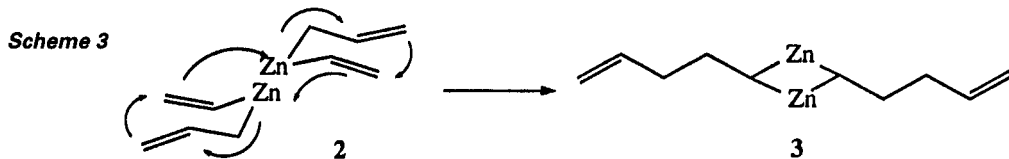


The exact mechanism whereby 1 adds to itself is still under study, and the presence of main group metal salts is not necessary for the reaction to proceed. Whatsoever, 1 leads to a gem bismetallic species if two moles are implied, either in a polymolecular process, or in a bimolecular way (scheme 2).

Scheme 2

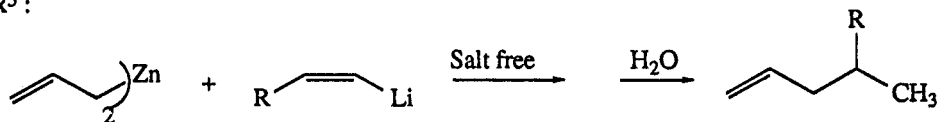


We also considered a bishomomolecular process involving an internal rearrangement akin to the Claisen rearrangement where zinc would play the role of oxygen (scheme 3),



leading to a dizincacyclobutane, although we have not been able, so far, to get an X Ray pattern of this bimetallic species. Dilution experiments showed no change in speed, as if a cluster (dimer ?) would be involved from the start.

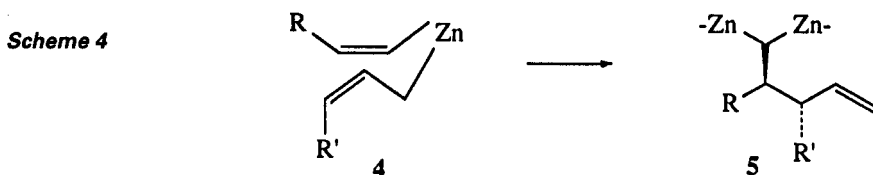
Pure bisallylzinc<sup>4</sup>, in the presence of a salt-free vinyl lithium also gives the reaction, probably via a zincate complex<sup>3</sup>:



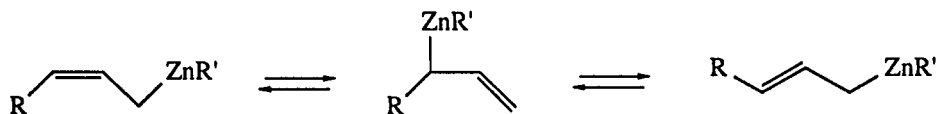
More recently, we found that a weakly basic ethereal solvent (diethyl ether) is much more efficient than THF, and speeds up the reaction which can be carried out at -50°C (instead of 0-60°C in THF)<sup>5</sup>.

#### DIASTEREOSELECTION IN ALLYLZINCATION

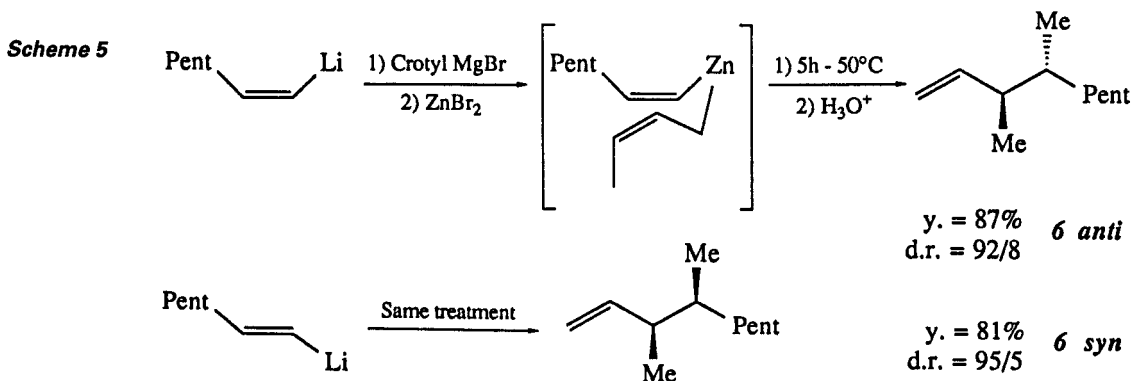
If we consider a chair like transition state in the hypothesis of scheme 3, then an E or Z vinyl metal should react with a substituted allylic reagent to give a predictable diastereoisomer:



Indeed, this selection was observed, even in THF<sup>2e</sup>, but it is improved significantly when the reaction is performed at a low temperature in ether<sup>5</sup>. However, a good diastereoselection implies that the allylic moiety reacts also exclusively in a E or Z configuration, although the metallatropic rearrangement occurs:

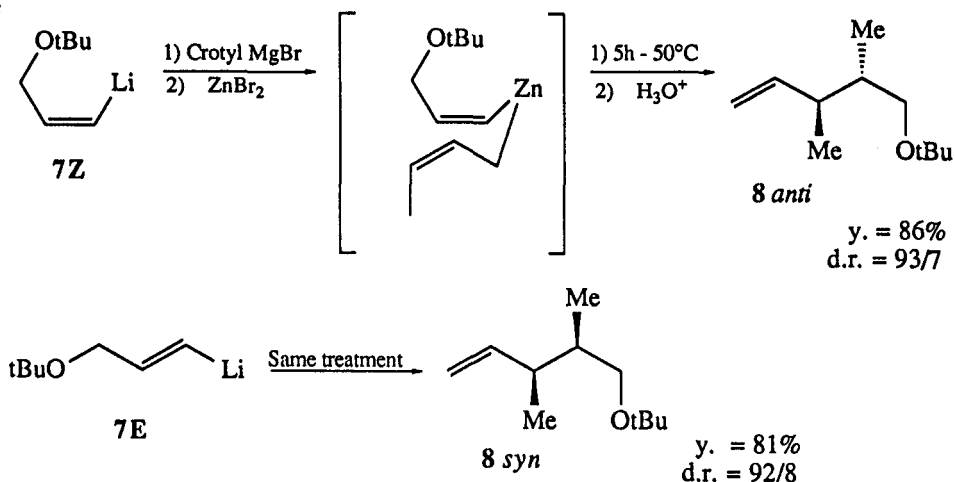


With alkali metals, the more ionic the bond, the more Z isomer<sup>6</sup>. For crotyl magnesium bromide, the Z/E ratio has been established as 60/40 in ether<sup>7</sup>, and for substituted allylic zinc derivatives<sup>8</sup>, the primary Z isomer is also predominant. This leads to the conclusion that a high diastereoselection in our reaction would be obtained in 87% yield diastereoselectively from crotyl zinc bromide and (Z) 1-hepten-1-yl lithium, whereas 6 *syn* is obtained in 81% yield from the Z vinyl lithium analog (scheme 5)<sup>5</sup>.



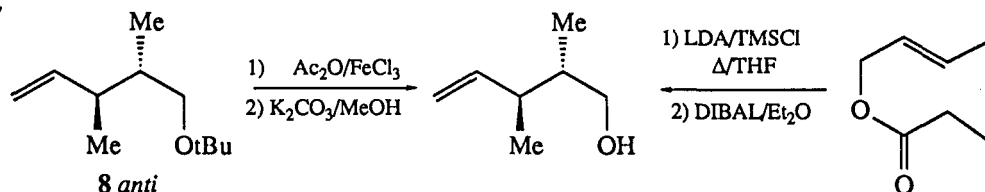
In the same way, a *cis* lithiated allyl ether **7Z** undergoes stereoselectively the addition to give **8 anti**, although chelation by oxygen is not a favourable interaction (as shown above). The corresponding trans lithiated ether **7E** leads to **8 syn** in good yields (scheme 6).

Scheme 6



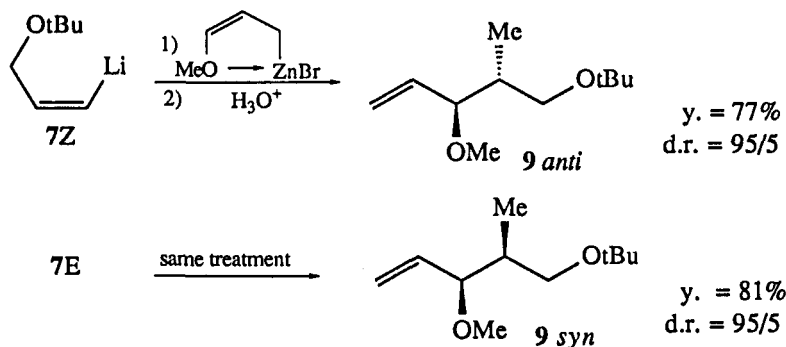
The configuration of **8 anti** is established<sup>5</sup> by comparison with the analogous product derived from a known<sup>9</sup> Ireland-Claisen rearrangement (slightly less selective : d.r. 87/13) according to scheme 7.

Scheme 7



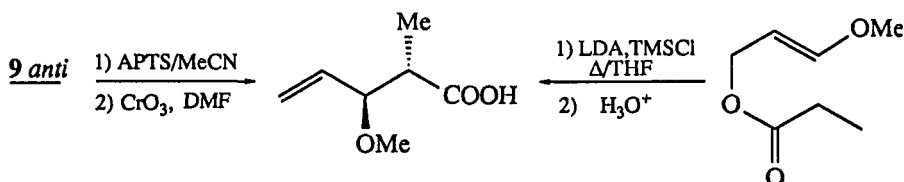
Introduction of an allylic methoxy group, instead of a methyl, is possible if one starts from allylmethylether, metallated according to Evans<sup>10</sup>, and reacted with **7Z** or **7E**<sup>5</sup>:

Scheme 8



In each case the *syn* or *anti* 1,3-glycol diether is obtained diastereoselectively. **9 anti** was converted to the corresponding acid, already prepared by an Ireland-Claisen rearrangement from (*E*) 3-propionyloxy-1-methoxy-propen<sup>9,11</sup> in 61% yield with a d.r. of 87/13 (scheme 9).

Scheme 9

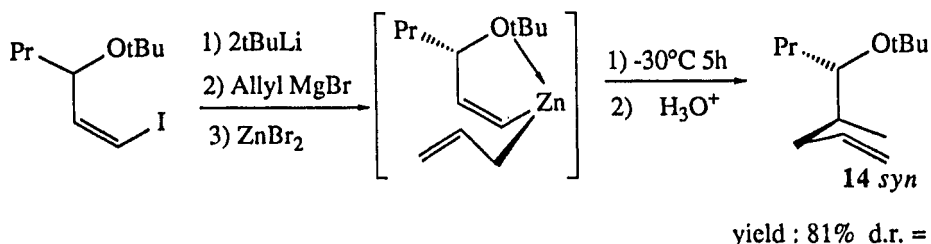


Chelation between zinc and heteroatoms in heterosubstituted bisalkylzinc reagents has been studied. Particularly, van der Kerk *et al*<sup>12</sup> have shown that derivatives of type  $Zn[(CH_2)_3 - Z]_2$  **10** : Z = NMe<sub>2</sub>, **11** : Z = OMe, **12** : Z = SMe are monomeric in benzene and show a down-field shift in <sup>13</sup>C NMR for the CH<sub>2</sub>-Z carbon, as an indication of chelation to zinc, which decreases in the sequence **10** > **11** > **12**. This fact was confirmed by their ability to form complexes with bipyridine which follows the order **10** < **11** < **12**. Thus **11** should be considered as a spiro derivative.



The presence of a C = C linkage, in such a derivative should not impede this chelation, and we were led to study the case of allylic *secondary* ethers **13**, Z-metallated on the terminal C sp<sup>2</sup> carbon. Allylzincation should now occur on the less hindered face of the vinyl moiety (opposite to R : scheme 10). Thus, (*Z*) 1-iodo-3-terbutoxy hex-1-ene was lithiated and treated by allyl magnesium bromide followed by zinc bromide. Hydrolysis of the bimetallic product led to **14** (*syn*) in 81% yield with a *syn/anti* d.r. of 95/5<sup>13</sup> (scheme 10)

Scheme 10

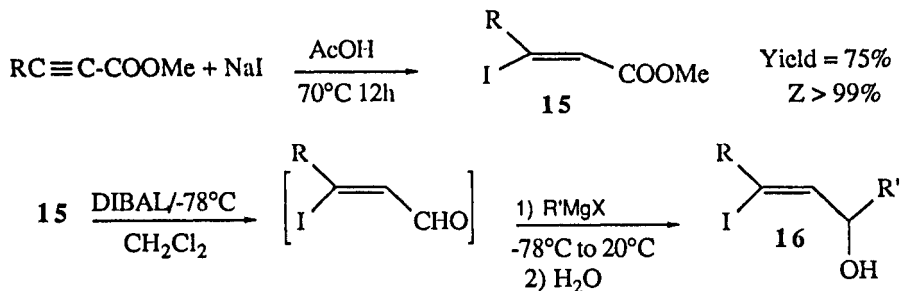


According to this scheme, if the free alcohol (as an alcoholate) is used instead of its tertbutyl ether, the reaction takes place with a similar diastereoselection (92/8) but requires 12 h at -20°C.

The tertbutyl ethers of alcohols **16** (R = H, scheme 11) are rapidly prepared from the corresponding propargylic tertbutylethers by hydroalumination followed by iodolysis<sup>14</sup>.

Alternatively the starting alcohols **16** were prepared from (*Z*) β-iodomethyl acrylate (itself prepared according to Lu<sup>15</sup>) and submitted, in a one-pot reaction, to one equivalent of DIBAL followed by one equivalent of Grignard reagent<sup>16</sup> (scheme 11).

Scheme 11

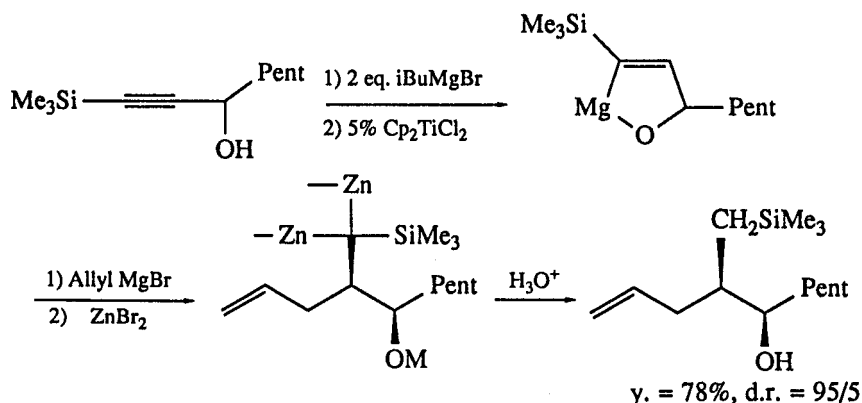


for R = H :  
 R' = Et : 88% ;  
 R' = vinyl : 80% ;  
 R' = allyl : 72% ;  
 R' = 1-hexynyl : 81% ;  
 R' = Me<sub>3</sub>SiC ≡ C- : 65%.

For R = Me :  
 R' = butyl : 81% ;  
 R' = allyl : 65%.

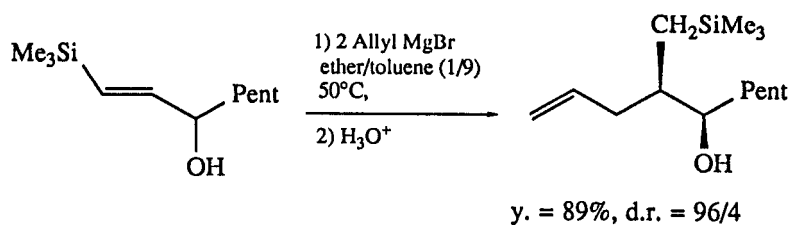
The hydromagnesiation of propargylic alcohols, developed by Sato<sup>17</sup> can be used directly<sup>13</sup> (scheme 12).

Scheme 12



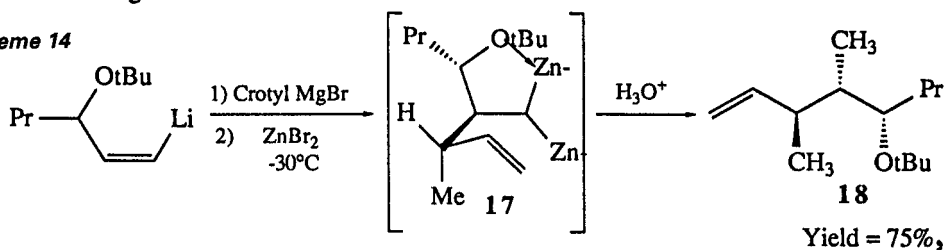
The stereochemistry of the silylated alcohol thus obtained, was ascertained by an allyl magnesianation, according to Kocienski<sup>18</sup>, of (E)-1(trimethylsilyl)-but-1-en-3-ol (scheme 13) leading to the same alcohol. (scheme 13)

Scheme 13



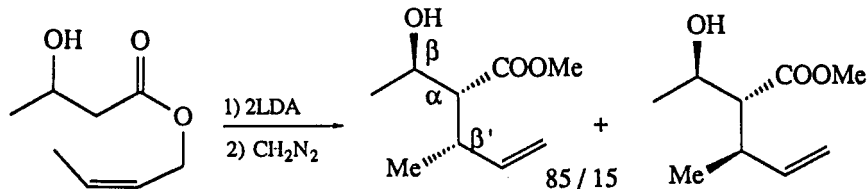
If now one combines this latter facial selectivity with the selectivity arising from the use of crotyl or substituted allylzinc reagents (discussed above), one should be able to create two new adjacent chiral centers, out of the starting one.

Scheme 14



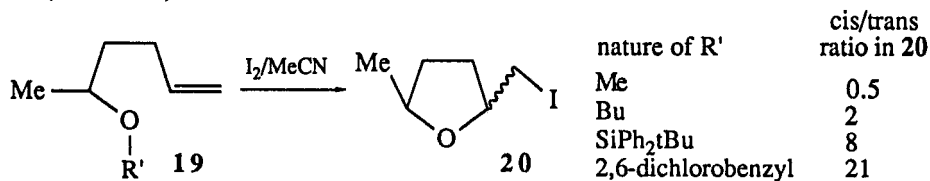
(Z) 1-lithiated 3-terbutoxy-1-hex-1-ene reacts with crotyl zinc bromide to afford a single isomer **18**<sup>19</sup>. It is worth of note that the stereoselectivity observed here is higher than the one observed in Ireland-Claisen rearrangements of chiral  $\beta$ -hydroxyesters of crotyl alcohols (Z or E) studied by Kurth<sup>20</sup> where the relative  $\alpha,\beta$ -stereorelationship is excellent, whereas the  $\alpha,\beta'$  d.r. is only fair (see scheme 15).

Scheme 15

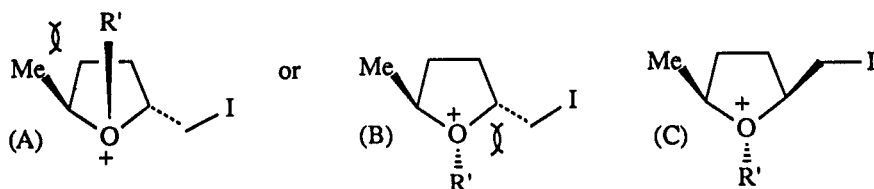


The stereochemistry of **14** and **18** was established after cyclisation into heterocycles (tetrahydrofurans) by iodoalkoxylation according to a known procedure<sup>21</sup>. In fact a new chiral center is thus formed but Bartlett showed that if a secondary  $\gamma$ -ethylenic ether is used, the cyclisation is stereoselective, the more so when a bulky ether is used (scheme 16).

Scheme 16



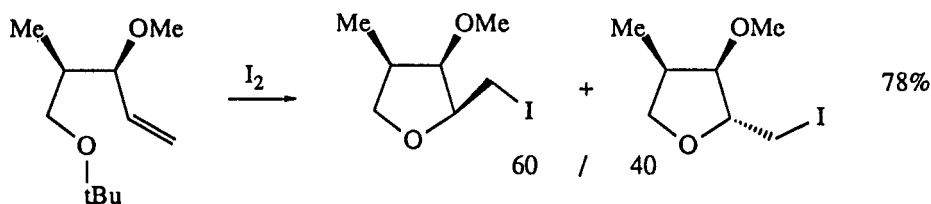
The reason for this<sup>21</sup> is an important steric interaction in the transition state, between R' and Me (A) or R' and the developing CH<sub>2</sub>I moiety (B), if the latter is trans to the Me group. Whereas R' has no such interaction in (C) when it is opposite to both Me and CH<sub>2</sub>I.



We reasoned that a *t*-butoxy group should be even better for such a purpose than an *o,o'*-dichlorobenzoyloxy group and also more easily prepared from the corresponding alcohol (via isobutene + amberlyst<sup>22</sup>).

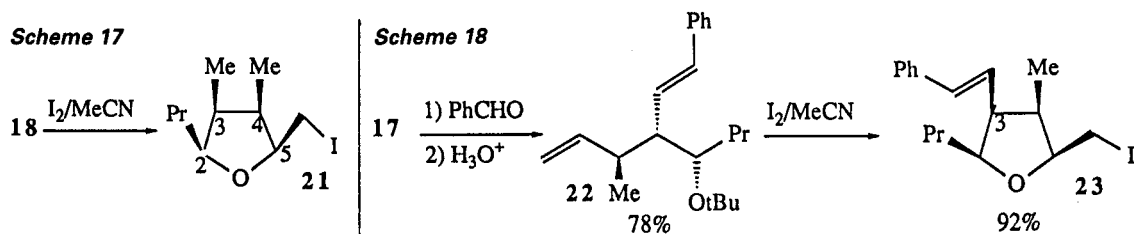
Compound **20** was effectively formed in a 28/1 ratio of *cis*/*trans* isomers starting from **19** (R' = *t*Bu)<sup>23</sup>.

It should be noted that if the ether is *primary*, no selection occurs, even if two substituents are located in position 3,4 on the same face of the tetrahydrofuran :

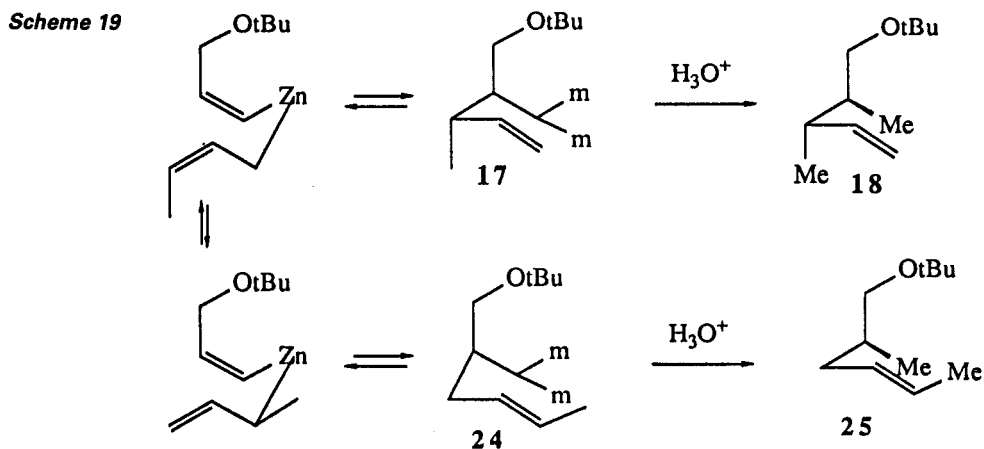


Compounds **14** and **18** were submitted to the Bartlett reaction and gave respectively a substituted tetrahydrofuran in 94% and 92% yield, as single isomers (scheme 17).

NOE experiments on **21** were thwarted by the fact that, although H<sub>2</sub> and H<sub>5</sub> gave separated signals, H<sub>3</sub> and H<sub>4</sub> showed analogous shifts. However, taking advantage of the bimetallic nature of intermediate **17**, we could submit it to a carbonyl olefination of benzaldehyde leading to **22**. In the cyclisation product **23** derived thereof, H<sub>3</sub> is now allylic and NOE experiments clearly show that all substituents of the tetrahydrofuran are located on the same face<sup>19</sup>(scheme 18).

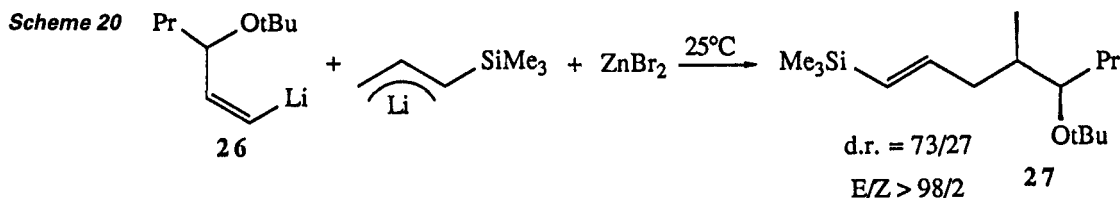


Coming back to the crotyl zincation of scheme 14, we observed that such addition is, in fact, reversible<sup>3</sup> (scheme 19).

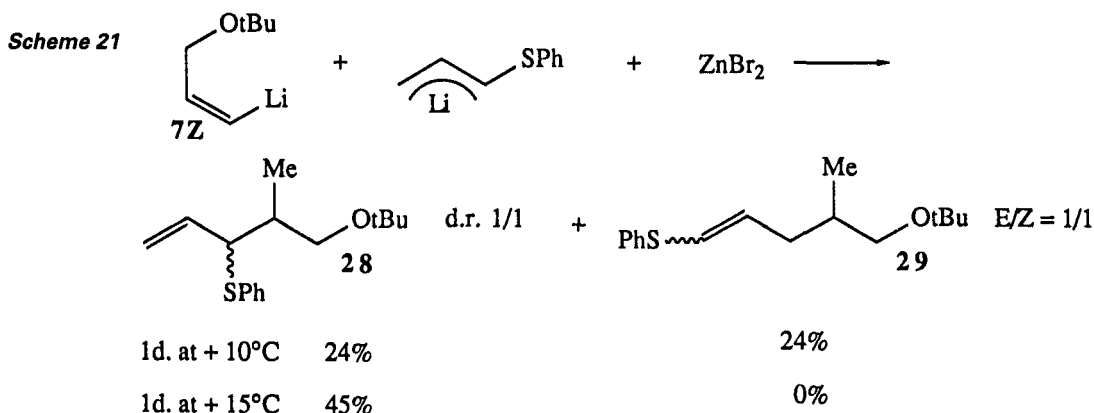


If the mixture is left at room temperature overnight, or heated for a few hours, **17** is converted to **24** and hydrolysis leads to a mixture of **18** (syn/anti = 50/50) and **25**. This is of no concern for the reaction depicted in scheme 14, carried out at low temperature, but when it is conducted at 0°C, the d.r. of **18** drops to 80/20, and this may be a drawback when heterosubstituted allylzinc reagents are used, since they behave more sluggishly.

For example, lithiated allyltrimethylsilane reacted only at 25°C with **26** and afforded **27** *syn* and *anti* in 78% yield with a d.r. of 73/27. **27** *syn* and *anti* are readily separated by chromatography on silica gel.

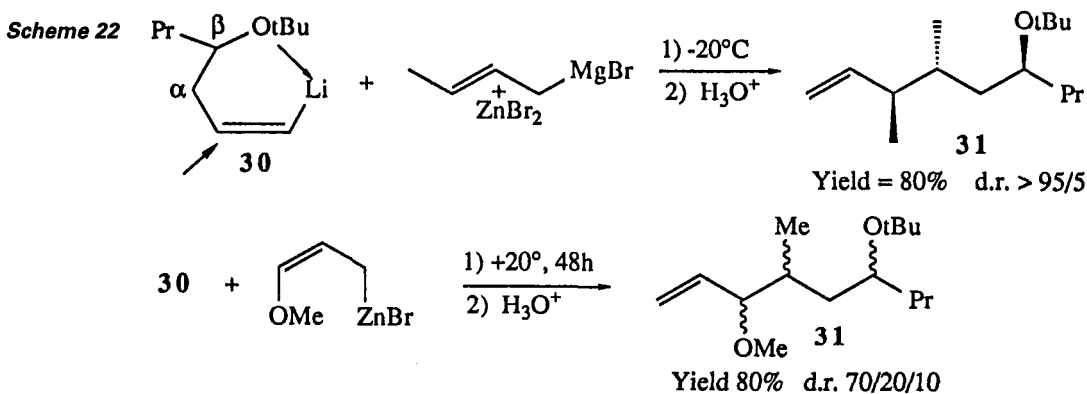


The worst case is provided with metallated allylsulfides which react poorly with the lithiated secondary ether, **26** (yield = 15%, d.r. = 70/30), but better with the primary analog **7Z** (scheme 21, compare to scheme 8).



Both regioisomers are formed at +10°C whereas **28** is the only product formed at +15°C, and at +25°C for 24 h, the bismetallic precursor of **28** cyclises to a cyclopropane<sup>2c,24</sup> in 95% yield. Lithiated allyl methyl ether discussed in scheme 8 behaved much more diastereoselectively towards **7Z** (although lithiated allyl *tert*butyl ether gave no diastereoselection) but it was not reactive with **26** either. In order to delineate the role of steric hindrance in these cases of failure, we considered the secondary *homoallylic* ethers: if chelation is still valid, the stereocenter would be removed  $\beta$  to the site of attack ( $\text{Csp}_2$ ), with less steric hindrance, but could still promote facial selection (scheme 22).

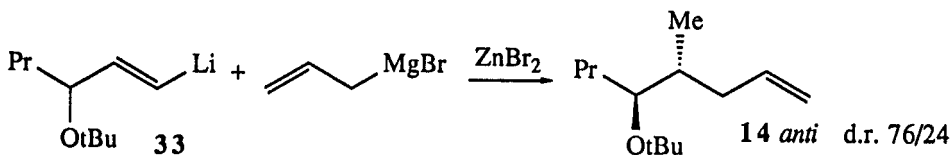
Indeed, not only **30** reacted highly diastereoselectively with crotyl zinc bromide, but also with a lithiated allyl ether (scheme 22) although less stereoselectively<sup>24</sup>.



In the former case, it is remarkable that the face discrimination leading to **31** is as good as it was with a *secondary allylic* ether (scheme 14).

Finally, one may wonder what happens if the chelation does not operate any more in the case of alkoxyated vinyl metals; preliminary studies<sup>3</sup> show that the addition can occur diastereoselectively. Thus the reaction of allylzinc bromide with the E reagent **33** leads to **14 anti**, with a d.r. of 76/24.

Scheme 23



Thus switching from the cis reagent **26** to the trans one **33** delivers the opposite diastereoisomer **14** (scheme 23 and 10).

### CONCLUSION

In conclusion, the allyl zincation of vinyl metals is amenable to proceed highly diastereoselectively from properly hetero substituted partners, at low temperature, and with good yields. It represents a new synthetic approach to construct adjacent chiral centers (up to three so far), and the syn /anti relationship can be modulated from the E or Z nature of the starting vinyl metal.

Studies are in progress to enlarge the scope of this reaction, and to use the bimetallic reagents in reactions with various electrophiles.

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