



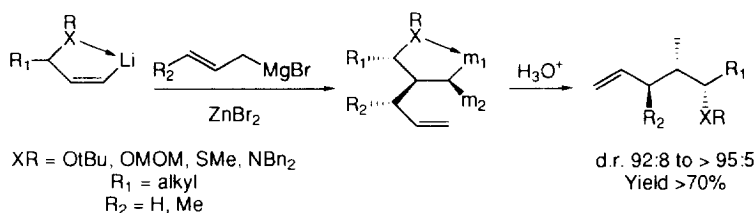
Diastereoselective Carbometalation of δ -Mono and γ - δ -Bisubstituted Z Vinyl Metals

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abstract: the allylzincation reaction of δ -substituted and γ - δ -bisubstituted Z vinyl metals proceeds highly diastereoselectively and represents a synthetic approach to construct four stereogenic centers from two preexisting ones in a single-pot operation.
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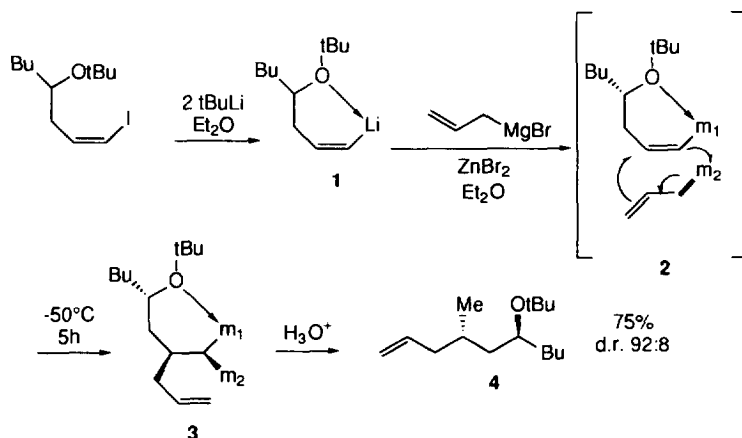
The establishment of defined, vicinal stereorelationships in the construction of organic molecules is a central requirement for efficient synthesis of many structurally complex substances¹. The intermolecular carbometalation reaction of unactivated alkenes is an approach involving formation of the carbon-carbon bond and can often provide a useful solution, although still limited, to this problem, particularly in acyclic systems². With this end in view, we have been developing for a few years, the diastereoselective allylmatalation of vinyl metals leading to the interesting field of the organogembimetallic chemistry. Particularly, we have already reported on the high diastereoselections which operate when an allylzinc reagent adds to a γ -heterosubstituted vinyl metal at low temperature in ether³. This facial selectivity was interpreted as a result of chelation between an heteroatom and metal, in a chair-like metallo-ene-transition state where the allyl moiety is delivered on the unshielded face of the five membered ring.



Scheme 1

In this letter, we report our results in the case of a substrate with a remote stereocenter β to the site of attack (i.e. a homoallylic metalated vinyl ether) in order to determine if the intramolecular chelation, and then the diastereoselective carbometalation, is still valid. In this case, a 1,3-induction will be created.

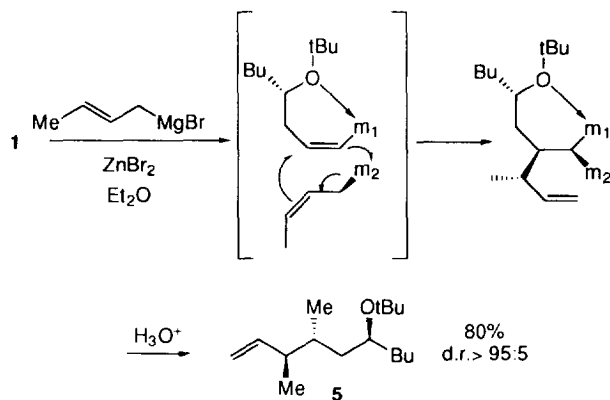
The starting material for this work, is (Z)-4-tertbutoxy-1-iodo-1-octene⁴, which was lithiated via metal-halogen exchange and then respectively 2 equiv of allylmagnesium bromide and zinc salt were added at -50°C⁵. After 5 h, the stable 1,1-dimetallic species **3** was hydrolyzed to the compound **4** in 75% yield, which displays two asymmetric centers in a 1,3 *anti* relationship^{6b} with a diastereoselectivity of 92 : 8.



Scheme 2

The allylmetalation of a δ -heterosubstituted vinyl metal shows a similar face discrimination (allyl metal *anti* to the butyl group in the chair-like metallo-ene transition state) leading to **3** as was the case for a secondary allylic ether^{3a,5} (scheme 1).

The combination of this facial selectivity with the selectivity arising from the use of a substituted allylzinc bromide^{6a} (i.e. crotyl zinc bromide) leads to **5** and to the creation of three stereogenic centers^{6b} in a single-pot operation with a > 95 : 5 diastereoselectivity.

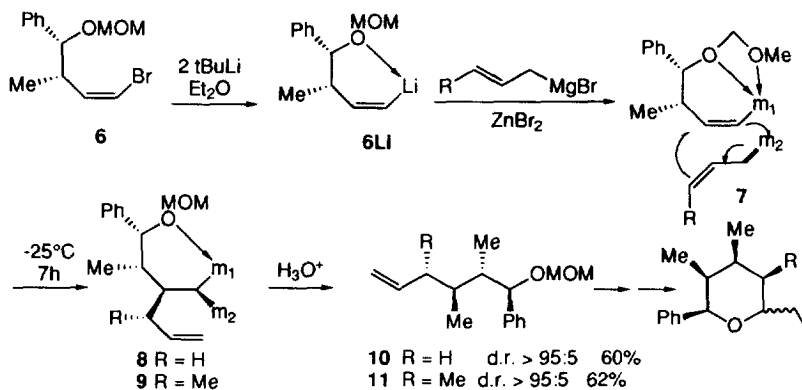


Scheme 3

Considering that in five-membered chelates (scheme 1) as well as in six-membered ones (schemes 2 and 3), the face selection of the approaching allylzinc reagent is governed by the substituent located on the ring, it was interesting to study the effect of two substituents borne by a six membered chelate : one in allylic and the second in homoallylic position (see **6** scheme 4 or **12** scheme 5). Both may be on the same side of the chelate (match pair) or on opposite side (mismatch pair). In order to promote a better chelation a methoxymethyl ether (MOM) was used in both cases.

Carbometalation reaction on the match pair 6

The *Z* vinyl metal⁷ **6Li** was treated with 2 equiv of allyl or crotyl magnesium bromide in ether and zinc salt at -25°C for 7h and the corresponding organogembismetals **8** and **9** were hydrolyzed to **10** and **11**.

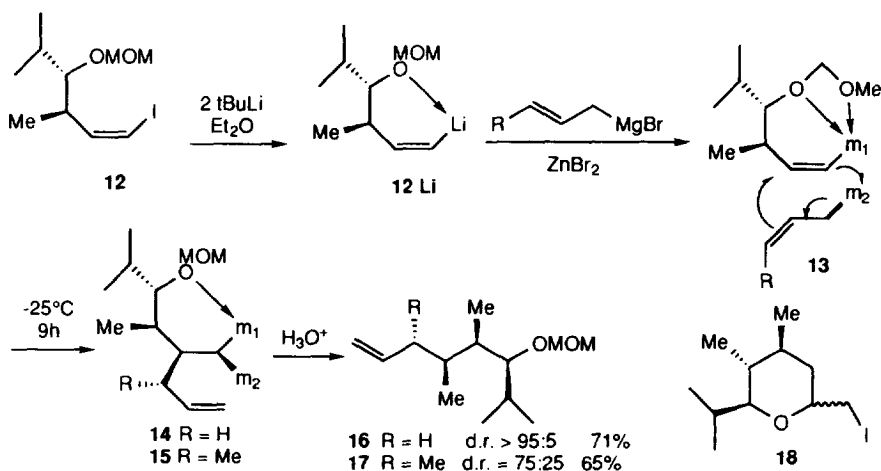


Scheme 4

The examination of the NMR spectra of the crude mixture revealed in both cases the presence of only one diastereomer⁸. These results confirm that the heteroatoms of the methoxymethyl ether chelates the vinyl metal to form a rigid six-membered ring. Thus, the allyl or crotyl moiety approaches the vinyl moiety with a diastereofacial selectivity *anti* to the two substituents and with a *Z* stereochemistry in the case of the crotyl metal to lead respectively to **10** and **11** with a total diastereoselectivity. The relative configuration in each diastereomer were determined by NOE effects and by the measurement of all coupling constants on the corresponding polysubstituted tetrahydropyran⁷ (obtained after deprotection of the methoxymethyl ether to the alcohol⁹ and intramolecular iodo etherification¹⁰).

Carbometalation reaction on the mismatch pair 12

The starting material that we studied first for this purpose (due to its easy access⁷) was *R**,*S**-(*Z*)-2,4-dimethyl-3-methoxymethoxy 6-iodo-5-hexene **12** (scheme 5).



Scheme 5

12 was treated sequentially in the same way as **6** (scheme 4) but stirring was applied at -25°C for 9h. The stable 1,1-bismetallics **14** or **15** derived respectively from allyl- and crotyl zinc bromide, were hydrolyzed respectively to give **16** (71%) and **17** (65%). The former displays ^1H and ^{13}C NMR spectra typical for a single isomer, and it was submitted to O-deprotection⁹ and then to iodo etherification¹⁰ of the free δ alken-ol (iodine, K_2CO_3) to give the corresponding α -iodomethyl tetrahydrofuran⁷ **18**. NOE effects and coupling constants in the ^1H NMR spectrum of **18** point to the stereochemistry depicted for **18** i.e. the allyl moiety (see **13** scheme 5) enters exclusively *anti* to the isopropyl group and *syn* to the methyl group, although the latter is vicinal to the reacting sp_2 center. Thus, in this mismatch pair, a clear choice is observed between the two competing substituents (iPr and Me).

We are presently studying other mismatch pairs to delineate the competition of various substituents.

In the case of crotylmetalation, **17** was obtained as a mixture of two diastereoisomers (d.r. = 75:25). NOE experiments on the α -iodomethyl tetrahydropyran⁷ derived from O-deprotected **17** showed, however that these two isomers were derived from the *same* facial selectivity as for **16** (namely crotylmetalation *cis* to the methyl group, *anti* to the *iso*Propyl group), but differed only by the configuration of the allylic secondary carbon atom. This is the first case where the crotylzincation of a vinyl metal in ether does not correspond to the reaction of a Z crotyl zinc reagent as shown in scheme 4, but to a possible addition of the *E* reagent derived from the former by metallatropy. The origin of this isomerization lies probably in the presence of the methyl group located in allylic position on the vinyl metal partner.

In conclusion, the allylzincation reaction of δ -substituted and γ - δ -bisubstituted Z vinyl metals proceeds highly diastereoselectively and represents a synthetic approach to construct four stereogenic centers from two preexisting ones in a single-pot operation. We are currently exploring the scope of this methodology, particularly in the case of the mismatch-pair with the aim to understand the steric effect of both substituents.

References and notes

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7. The preparation of each pure diastereomer and the determination of the structure of all iodo methyl tetrahydropyrans will be reported in due course.
8. During the halogen-exchange step, the formation of $\sim 30\%$ of alkyne was identified. This side product arose from an elimination process either via β or α -metalation of **6**. This reaction was already pointed out in the literature. Suffert, J. ; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550-3551.
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18 is present as a mixture of 2 diastereomers for the $\text{CH}_2\text{-I}$ position