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SYNTHESIS AND FUNCTIONALISATION OF INTERMEDIATES DERIVED FROM ALLYLMAGNESIATION OF (*E*)-1-(TRIMETHYLSILYL)-BUT-1-EN-3-OL

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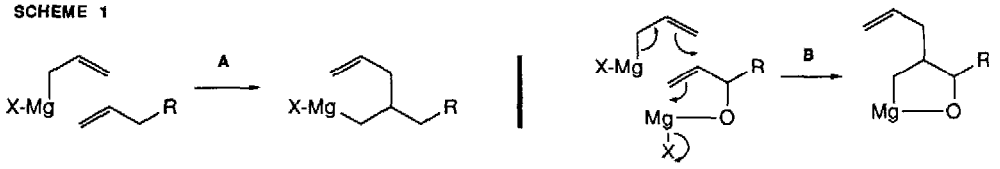
Abstract. Allylmagnesium bromide adds to (*E*)-1-(trimethylsilyl)-but-1-en-3-ol diastereoselectively. The carbon-magnesium bond of the intermediate adducts reacts with a range of electrophiles to give synthetically useful products.

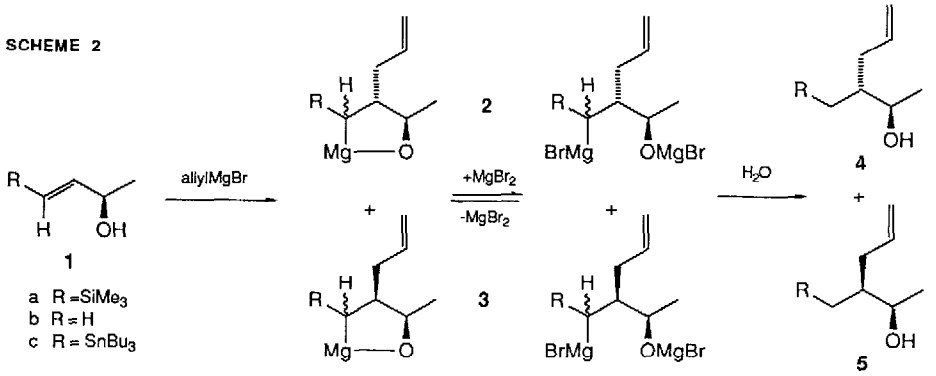
At elevated temperatures allylic Grignard reagents add regioselectively to unactivated terminal alkenes[1] and intramolecular variants of this reaction are particularly useful in annulation reactions of considerable value in natural product synthesis[2,3]. Unfortunately the synthetic utilty of alkene carbometallations is limited by incompatibility of the reaction conditions with most functional groups. However, Eisch[4] and Felkin[5] and their associates showed that allylic hydroxy groups facilitate the allylmagnesiation reaction[6,7] thereby pointing the way to a more synthetically versatile procedure. Two distinct mechanisms have been proposed to differentiate the course of the reaction in simple alkenes on the one hand and allylic alcohols on the other. Lehmkuhl and coworkers have suggested that simple alkenes react *via* a cyclic transition state corresponding to a magnesium-ene reaction (path A, Scheme 1)[1]. In the case of allylic alcohols, allylmagnesiation is promoted by co-ordination of the alkene π-bond to a covalently bound magnesium atom (path B)[8]. We now report the results of a study of the allylmagnesiation of (*E*)-1-(trimethylsilyl)-but-1-en-3-ol (**1a**)[9] and the functionalisation of the resultant adducts which indicates that (a) the silicon substituent reinforces the substantial activation already provided by the proximate heteroatom and (b) an intramolecular magnesium-ene mechanism may account for the stereochemical course of the reaction.

SCHEME 1



The value of the silicon substituent in promoting the allylmagnesiation reaction[10] is apparent by comparing the reactions of but-1-en-3-ol (**1b**) and (*E*)-1-(trimethylsilyl)-but-1-en-3-ol (**1a**) as outlined in Scheme 2. In the latter case, reaction of **1a** with allylmagnesium bromide (2.1 eq) in refluxing Et_2O was complete in 18 h and hydrolysis of the intermediates **2a** and **3a** afforded a mixture of alcohols **4a** and **5a** (81% yield) in a ratio of 20:1 respectively. By contrast but-1-en-3-ol required a large excess of allylmagnesium bromide in refluxing Et_2O for 170 h to achieve a 16% yield of alcohols **4b** and **5b** (8:1)[5]. The silicon substituent is not unique in its activating effect since the corresponding stannane derivative **1c** also reacted under similar conditions (refluxing Et_2O, 24 h) to give the alcohols **4c** and **5c** (10:1) in 61% yield. The following observations made on **1a** and its derivatives give some indication of the scope and limitations of the reaction:

SCHEME 2

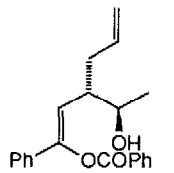


Solvent. The rate and stereochemistry of allylmagnesiation was solvent and temperature dependent. Higher boiling solvents gave comparable yields to those observed in Et_2O and reaction times were substantially reduced but the diastereoselectivity was also reduced. Thus **4a** and **5a** were obtained in 89% yield (**4a**:**5a** = 8:1) after 2 h in refluxing *n*-Pr_2O whereas the reaction was complete in refluxing toluene-Et_2O (*ca.* 9:1) after only 10 min to give **4a** and **5a** (9:1) in 89% yield. Additional $MgBr_2$ did not accelerate the rate of allylmagnesiation[8].

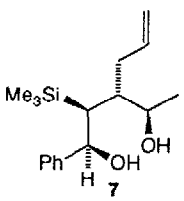
Grignard reagent. Carbometallation was only successful with allylmagnesium bromide. The reaction failed with *t*-BuMgCl, *i*-BuMgCl, *i*-PrMgCl, EtMgBr, and Et_2Mg in the presence of Cp_2ZrCl_2[11].

Oxygen substituent. Protection of the hydroxyl function as the benzyloxymethyl ether or the methyl ether totally suppressed the allylmagnesiation reaction.

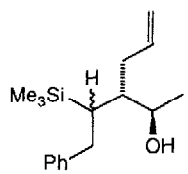
A prime objective of this work was the diastereoselective synthesis of α-alkyl-β-substituted alcohols. To that end, the mixture of adducts **2a** and **3a** was treated with a variety of electrophiles to give the products **6-13**[12]. Of the carbon electrophiles examined, best results were obtained with CO_2, HCHO, BnBr, PHCHO, and PhCOCl. MeI and DMF failed to react and phosgene, dimethyl carbonate, and methyl chloroformate gave complex mixtures. Heterofunctionalisation reactions such as bromination and phenylthiolation were also achieved in modest yield.



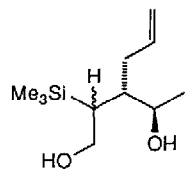
6
2.5 equiv. PhCOCl
PhMe-THF-HMPA
reflux, 3h 64%



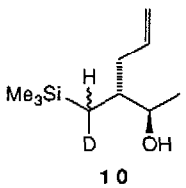
7
1 equiv. PhCHO
PhMe-Et_2O
-78°C, 29%



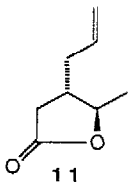
8
$PhCH_2Br$
Et_2O
reflux, 4h, 66%



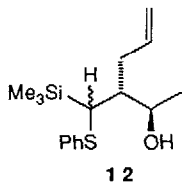
9
excess HCHO gas
PhMe-Et_2O
-78°C, 89%



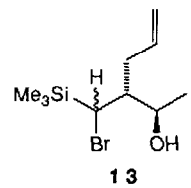
10
excess D_2O
n-Pr_2O
-20°C, 89%



11
CO_2; then TBAF
PhMe-Et_2O
0°C, 61%



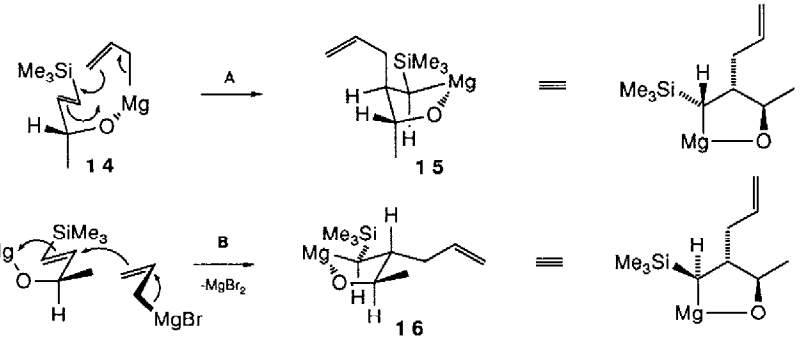
12
1 equiv. PhS-SPh
PhMe-THF-HMPA
66%



13
NBS
PhMe-Et_2O-THF
-78 to 0°C, 45%

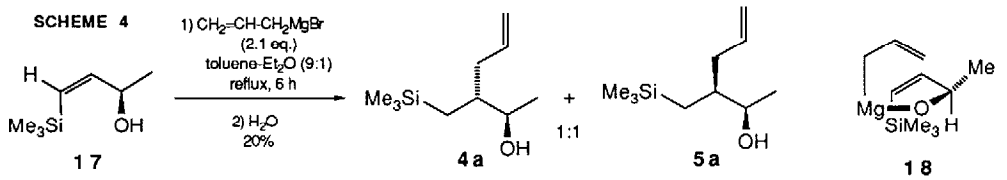
Significant stereochemical information was gleaned from the reaction of the adducts **2a** and **3a** (*ca.* 9:1) with D_2O and PhCHO at low temperature. The deuterolysis reaction gave **10** as a mixture of diastereoisomers (8:1) which suggests that formation of the C-Mg bond in the adducts **2a** and **3a** was diastereoselective[13]. The stereochemistry of the allylmagnesiation was ascertained by reaction of the adducts with benzaldehyde. A pure crystalline diastereoisomer (m. p. 121°C/Et_2O-hexane) was obtained in 29% yield from a chromatographically inseparable mixture of diastereomeric diols. A single crystal x-ray analysis revealed structure **7** and thereby defined the *anti* relation between the hydroxyl and allyl groups. These stereochemical results invite speculation on the mechanism of the allylmagnesiation of **1a**. As can be seen in Scheme 3 the two mechanisms previously proposed[5,7,8] are stereochemically distinct: path A corresponds to a *cis*-addition to the π-bond whereas path B corresponds to a *trans*-addition. Assuming that electrophilic cleavage of the adduct proceeds with retention of configuration, the formation of **7** from the reaction of **1a** with PhCHO would suggest that the Felkin mechanism is correct and that the adduct has the stereochemistry depicted in **16**. However, **7** was obtained in low yield as one component of a mixture of diastereoisomers. Since the deuterolysis experiment indicated that the intermediate adduct was formed with a high degree of diastereoselectivity, the reaction with PhCHO must have occured with substantial racemisation of the C-Mg bond[14]. Hence, the formation of **7** is not conclusive proof of the path B mechanism.

SCHEME 3



The unique reactivity of allylmagnesium bromide, the comparative ease of the reaction, the observed stereochemistry, and the requirement of a free hydroxy group in **1a** are also consistent with a mechanism involving a magnesium-ene reaction in which intramolecular delivery of the allyl group is ensured by covalent linkage *via* a magnesium alkoxide bond as in intermediate **14**. Molecular models suggest that **14** can adopt a conformation favourable to a magnesium-ene reaction leading to the observed stereochemistry as indicated in Figure 1. A further pertinent observation is the slow rate and stereochemistry observed in the allylmagnesiation of (*Z*)-1-(trimethylsilyl)-but-1-en-3-ol (**17**) (Scheme 4) under conditions similar to those used for the (*E*)-isomer **1a**. In this case allylmagnesiation gave a 20% yield of **4a** and **5a** after 7 h at reflux[15] with no diastereoselectivity; *i.e.* **4a**:**5a** = 1:1. Figure 2 depicts a conformation of the putative intermediate **18** favourable to a magnesium-ene reaction leading to diastereoisomer **5a**. Further experiments aimed at unravelling the scope, stereochemistry and mechanism of these reactions are currently underway.

SCHEME 4



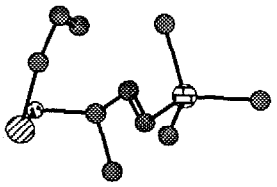


Figure 1. Conformation of intermediate **14** leading to a magnesium-ene reaction.

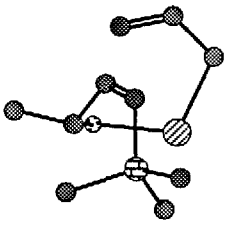


Figure 2. Conformation of intermediate **18** leading to a magnesium-ene reaction.

In conclusion we have shown that allylmagnesiation of silyl-substituted allylic alcohols is an efficient and diastereoselective process which provides intermediates of interest in the elaboration of functionally dense aliphatic chains.

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References and Notes

1. Lehmkuhl, H. *Bull. Soc. Chim. France*, **1981**, 87. Alkene carbometallation reviews: Hill, E. A. *J. Organometallic Chem.*, **1975**, *91*, 123; Vara Prasad, J. V. N.; Pillai, C. N. *Ibid.*, **1983**, *259*, 1.
2. Oppolzer, W. *Angew. Chem. Int'l Ed. Engl.*, **1989**, *28*, 38 and references therein.
3. For recent intramolecular carbometallations involving organolithium reagents see Bailey, W. F.; Rossi, K., *J. Am. Chem. Soc.*, **1989**, *111*, 765; Chamberlain, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *Ibid.*, **1988**, *110*, 4788; Broka, C.; Shen, T. *Ibid.*, **1989**, *111*, 2981; Krief, A.; Barbeaux, P *J. Chem. Soc., Chem. Commun.*, **1987**, 1214.
4. Eisch, J. J.; Husk, G. R. *J. Am. Chem. Soc.*, **1965**, *87*, 4194.
5. Cherest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G *Tetrahedron Lett.*, **1966**, 875.
6. For leading references on the heteroatom-promotion of carbometalation reactions see the reviews by Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas*, **1986**, *105*, 1 and Beak, P.; Meyers; A. I. *Accts. Chem. Res.*, **1986**, *19*, 356.
7. Homoallylic alcohols also promote allylmagnesiation: Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.*, **1979**, *44*, 587; Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.*, **1979**, *101*, 1148.
8. Felkin, H.; Umpleby, J. D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.*, **1972**, 2285; Felkin, H.; Kaeseberg, C *Ibid.*, **1970**, 4587.
9. Prepared by the method of Kitano, Y.; Matsumoto, T.; Sato, F *Tetrahedron*, **1987**, *44*, 4073. All the reactions reported herein were performed with racemic **1a**.
10. Utimoto, K., Imi, K.; Shiragami, H.; Fujikara, S.; Nozaki, H. *Tetrahedron Lett.*, **1985**, *26*, 2101; Lehmkuhl, H.; Hauschild, K.; Bellenbaum, M *Chem. Ber.*, **1984**, *117*, 383 and references therein.
11. Dzhmilev, V. M.; Vostrikova, O. S.; Tolstikov, G. A. *J. Organometallic Chem.*, **1986**, *304*, 17.
12. Allylmagnmesiation of **1a**: Neat (*E*)-1-(trimethylsilyl)-but-1-en-3-ol (**1a**)(4.32 g, 30 mmol) was added dropwise *via* syringe to allylmagnesium bromide (1.98 M in Et_2O, 32 ml, 63 mmol) and toluene (20 ml) at 0°C with vigorous stirring. After 10 min, the solution was warmed to 20°C and the mixture concentrated *in vacuo* (20 mm Hg) until a white precipitate began to form at which point the composition of the solvent was *ca.* 9:1 toluene: Et_2O. After refluxing for 10 min followed by cooling to room temperature, the resultant mixture of intermediates **2a** and **3a** was then quenched by adding the electrophiles indicated.
13. Attempts to obtain definitive spectroscopic evidence for the magnesiocycle intermediates have so far proved fruitless.
14. Geminal silicon substituents are known to increase the stereochemical lability of alkenyl-lithiums which are otherwise configurationally stable: Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.*, **1986**, *108*, 3402.
15. Volatile non-polar products accounted for the bulk of the remaining mass.

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