

Diastereoselective allylzincation of γ -oxygenated vinylolithiums bearing functionalized side-chains

Sandrine Cheramy, Franck Ferreira* and Jean F. Normant

Laboratoire de Chimie Organique, Université Pierre et Marie Curie, UMR 7611, 4 place Jussieu, Boîte 183, 75252 Paris Cedex 05, France

Received 15 March 2004; revised 5 April 2004; accepted 6 April 2004

Abstract—Allylzincation of γ -oxygenated vinylolithiums bearing functionalized side-chains proved to be more difficult than that reported in the case of γ -oxygenated vinylolithiums with unfunctionalized side-chains. However, when allylzincation occurs it gives the corresponding linear compounds with high diastereoselection as a consequence of the zinc being coordinated by the two oxygen atoms of the methoxymethyl ether moiety.

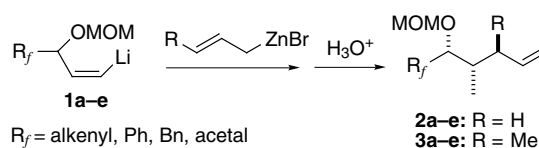
© 2004 Elsevier Ltd. All rights reserved.

Allylzincation of vinylolithiums has been well investigated in our laboratory over the past years.¹ More particularly, the carbometallation of primary and secondary γ -heterosubstituted vinylolithiums by zincated allylic ethers allowed the preparation with high stereoselectivities of 1,3-dialkoxy-2-methyl-4-pentenes^{2,3} and cyclopropyl carbinols,⁴ respectively. More recently,⁵ we have developed a new formal synthesis of (\pm)-serricornin, which includes the highly diastereoselective carbometallation of a secondary γ -oxygenated vinylolithium by zincated allylsilane giving an *E* vinylsilane intermediate. Although high selectivities are generally obtained, the main drawback of these carbometallation reactions is that only secondary γ -oxygenated vinylolithiums with alkyl side-chains have been used precluding so far a wider use of these reactions in organic synthesis. Thus, in order to expand the field of synthetic applications, we have investigated the reaction of secondary γ -oxygenated vinylolithiums bearing unsaturated or oxygenated side-chains with allyl- or crotylzinc bromides since the resulting products would enable easy further transformations.

We report herein our preliminary results on the allyl- and crotylzincation of vinylolithiums **1a–e**, which afford

an access to linear compounds **2a–e** and **3a–e** with two and three vicinal stereocentres, respectively, (Scheme 1). In all the cases we have examined, vinylolithiums **1a–e** were prepared from the corresponding diastereomerically pure *Z* vinyl iodides. The latter were obtained either from *Z* β -iodo acrylate (in the case of **1a–c**) in a two-step procedure^{6,7} or from aldehydes (in the case of **1d** and **1e**) in a multi-step synthesis, the key step of which is the selective monohydrogenation of ethynyl iodide intermediates by dipotassium diazadicarboxylate, which behaves as a synthetic equivalent of hydrazine in acidic conditions.^{8,9}

In a typical procedure, vinylolithiums **1a–e** were generated in situ by the reaction of the corresponding vinyl iodides with *t*-BuLi (1.7 M in pentane, 2 equiv) in Et₂O at -80°C for a few minutes until no starting material was detected by GC. Allyl- or crotylmagnesium bromide (2.0 M in Et₂O, 3 equiv) and ZnBr₂ (1.0 M in Et₂O, 3 equiv) were then successively added dropwise to the solution and the resulting mixture was allowed to warm to -50°C and stirred at this temperature until no evolution was observed by GC. After the usual work-up,



Scheme 1. Allyl- and crotylzincation of secondary vinylolithiums **1a–e**.

Keywords: Carbometallation; Vinylolithiums; Zinc reagents; Diastereoselection.

* Corresponding author. Tel.: +33-0-144275571; fax: +33-0-144277567; e-mail: ferreira@ccr.jussieu.fr

Table 1. Zincation of vinylolithiums **1a–e** via Scheme 1

Entry	R _f	Vinylolithium	R	d.r. ^a	Yield (%) ^b
1		1a	H	>98/2	50
2		1a	Me	94/6	30
3		1b	H	—	— ^c
4		1c	H	>98/2	53
5		1c	Me	>98/2	37
6		1d	H	—	— ^c
7		1e	H	>98/2	66

^aSelectivities were measured by ¹H NMR at 400 MHz on the crude reaction mixtures.

^bYields in the purified products.

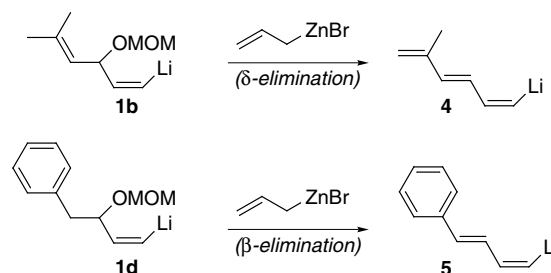
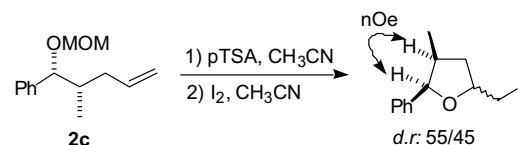
^cOnly unidentified products were obtained.

the corresponding linear compounds **2** and **3** were then isolated. Our results are compiled in Table 1.

With allylzinc bromide (i.e., with R = H), linear compounds **2a**, **2c** and **2e** containing two stereogenic vicinal centers were obtained with high diastereoselectivity as determined by ¹H NMR (Table 1, entries 1, 4 and 7). After flash chromatography on silica gel, they were isolated as diastereomerically pure products albeit in moderate yield. Similarly, the reaction of crotylzinc bromide (i.e., with R = Me) with vinylolithiums **1a** and **1c** afforded the corresponding linear products containing three vicinal stereogenic centers. However, although an excellent stereoselectivity was also observed for products **3a** and **3c**, they were isolated in lower yields than those obtained with allylzinc bromide (Table 1, entry 1 vs 2 and entry 4 vs 5).

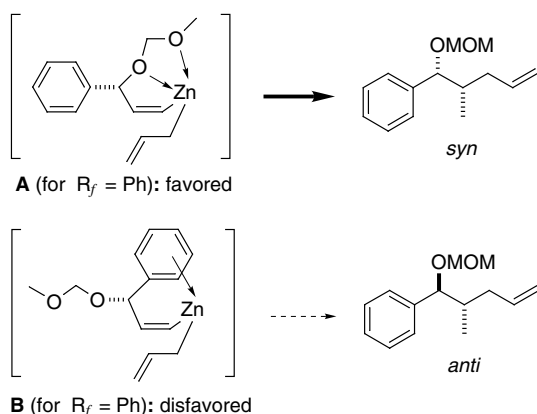
By contrast, in the case of vinylic vinylolithium **1b** and benzylic vinylolithium **1d** only unidentified products were obtained (Table 1, entries 3 and 6). These results could be explained by the organometallic species promoting a δ- and a β-elimination of the methoxymethyl ether moiety in **1b** and **1d**, respectively. Thus, under the reaction conditions described above, **1b** and **1d** would lead to vinylmetals **4** and **5**, respectively, the hydrolysis of which would then afford volatile products (Scheme 2).

The relative stereochemistry of compounds **2a** and **2c** has been unambiguously shown to be *syn* by NOE experiments performed on the two isomeric furans derived from **2c** by deprotection of the ether moiety under acidic conditions followed by iodoetherification^{4,10,11} and for which a *cis* stereochemistry was found (Scheme 3).

**Scheme 2.** Elimination reactions in **1b** and **1d**.**Scheme 3.** NOE experiments on isomeric furans derived from **2c**.

From these NOE experiments, it could be reasonably assumed that compounds **2a** and **2c** are formed via a chelate chair-like intermediate **A** analogous to that previously postulated in the case of vinylolithiums with saturated side-chains. In intermediate **A** the allyl moiety approaches the vinylolithium from the less hindered face (i.e., opposite to the substituent) as a consequence of the zinc being coordinated by the two oxygen atoms of the methoxymethyl ether group (Scheme 4).

Furthermore, the high *syn* stereochemistry totally excludes a possible π-zinc interaction with the double bond

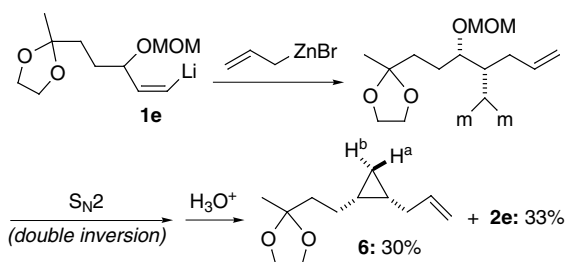


Scheme 4. Intermediate A versus intermediate B.

or the arene, which proved to be strong enough to give high stereoselectivities in some zinc enolate carbocyclizations,^{12,13} allylzincation of vinylmetals¹⁴ and cyclopropanation reactions.^{15,16} This latter interaction would lead to the *anti* isomer via another chelate chair-like intermediate **B** (Scheme 4). Thus, this result strongly suggests that the zinc atom is better coordinated by a methoxymethyl ether than by any unsaturation.

As regards compound **2e**, the same *syn* stereochemistry was determined by performing the carbometallation reaction at -50°C and then warming the reaction mixture to -20°C . Under these conditions and after the usual work-up, compound **2e** (33%) was formed along with disubstituted cyclopropane **6** (30%). Since compounds **2e** and **6** are obtained from the same organo *gem* bismetallated intermediate by hydrolysis and through an $\text{S}_{\text{N}}2$ process with double inversion,^{4,17} respectively, the stereochemistry of **6** reflects that of **2e**. Thus, the *cis* stereochemistry of the disubstituted cyclopropyl ring, characterized by *trans* coupling constants for proton H^b ($^3J_{1,3a} = ^3J_{2,3a} = 4.8 \text{ Hz}$) and *cis* ones for proton H^a ($^3J_{1,3b} = ^3J_{2,3b} = 8.4 \text{ Hz}$) as measured by ^1H NMR, implies a *syn* stereochemistry for linear compound **2e** (Scheme 5). The high selectivity in favor of the *syn* isomer observed for **1e** can then be explained by intermediate **A** (postulated above for **1a** and **1c**) and suggests that the coordination of the zinc by the methoxymethyl ether group is much stronger than that by the acetal group through which an *anti* stereochemistry would have been obtained via intermediate **B**.

Concerning compounds **3a** and **3c**, an intermediate analogous to **A** could be invoked to explain their for-



Scheme 5. Determination of the stereochemistry of **2e**.

mation in a highly stereoselective manner so that a *syn,anti* stereochemistry can be reasonably assumed for these compounds. Indeed, as shown in the case of unfunctionalized vinylolithiums,^{18–21} crotylzinc reacts with a good facial selectivity under the preferred *cisoid* form, the methyl substituent of the crotylzinc adopting a pseudo-axial position in an intermediate similar to **A**.

In summary, we have shown that allylzincation of γ -oxygenated vinylolithiums with unsaturated or oxygenated side-chains is possible provided that no elimination of the ether moiety occurs. Moreover, this reaction allows the formation of linear compounds with two or three vicinal stereogenic centers with excellent *syn* and *syn,anti* stereoselectivity, respectively. These preliminary results are promising especially regarding the possibility of further functionalization of the side-chains, for example through oxidative processes. This work is currently under investigation in our group and will be reported in due course.

Acknowledgements

The authors thank the Ministère de l'Enseignement Supérieur et de la Recherche for a grant to Sandrine Cheramy (1999–2002).

References and notes

- For a general review see: Marek, I.; Normant, J. F. In *Metal-catalysed cross-coupling reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: Weinheim, 1998; pp 271–337.
- Marek, I.; Lefrançois, J.-M.; Normant, J. F. *J. Org. Chem.* **1994**, *59*, 4154.
- Knochel, P.; Xia, C.; Yeh, M. C. P. *Tetrahedron Lett.* **1988**, *29*, 6697.
- Ferreira, F.; Herse, C.; Riguet, E.; Normant, J. F. *Tetrahedron Lett.* **2000**, *41*, 1733.
- Ferreira, F.; Normant, J. F. *Eur. J. Org. Chem.* **2000**, 3581.
- Marek, I.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1991**, *32*, 5329.
- Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243.
- Bernard, N.; Chemla, F.; Ferreira, F.; Mostéfai, N.; Normant, J. F. *Chem. Eur. J.* **2002**, *8*, 8139.
- Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 9256.
- Marek, I.; Lefrançois, J.-M.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1994**, *131*, 910.
- Marek, I.; Lefrançois, J.-M.; Normant, J. F. *Tetrahedron Lett.* **1992**, *33*, 1747.
- Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 566.
- Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 2442.
- Brasseur, D.; Rezaei, H.; Fuxa, A.; Alexakis, A.; Mangeney, P.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1998**, *39*, 4821.

15. Marek, I.; Beruben, D.; Normant, J. F. *Tetrahedron Lett.* **1995**, 36, 3695.
16. Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, 60, 2488.
17. For a discussion of such a mechanism see: Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, 60, 2488.
18. Brasseur, D.; Marek, I.; Normant, J. F. *Tetrahedron* **1996**, 52, 7235.
19. Marek, I.; Lefrançois, J.-M.; Normant, J. F. *J. Org. Chem.* **1994**, 59, 4154.
20. Marek, I.; Lefrançois, J.-M.; Normant, J. F. *Synlett* **1992**, 633.
21. Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1991**, 32, 5973.