Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1263-1266, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02483-9

Zinca-en-allene Cyclization Synthesis of Substituted Tetrahydrofurans

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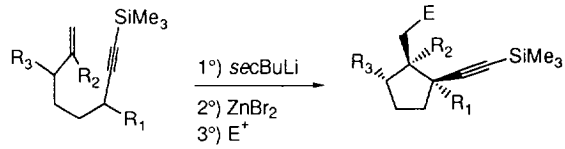
Key Words : Tetrahydrofuran, zinca-en-allene reaction, tetrahydrofurannyl methylzinc

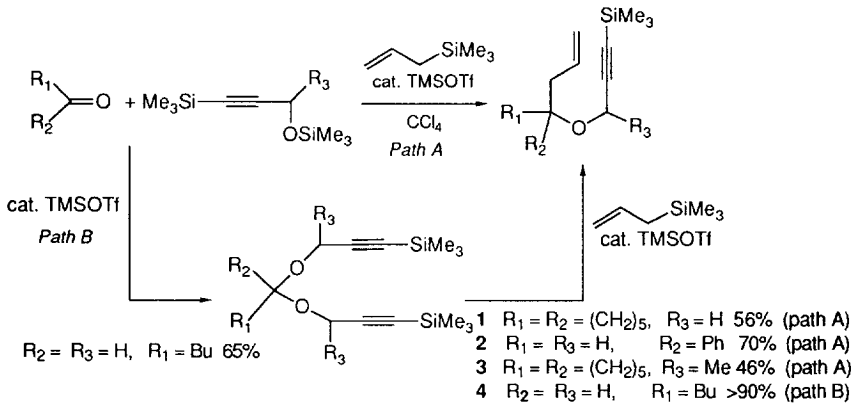
Abstract: The synthesis of polysubstituted tetrahydrofurans, in a two-step procedure from common intermediates, is readily available by the new zinca-en-allene reaction. This strategy allows the creation of vicinal quaternary and tertiary centers or of two quaternary centers as unique isomers.

We have recently described a new intramolecular metallo-en-allene reaction, in which an allenylzinc bromide undergoes a clean and totally regioselective 5-exo-trig[1] (see scheme 1) or 5-exo-dig[2] cyclization on a terminal unsaturation to give stereoselectively the corresponding cyclic products.



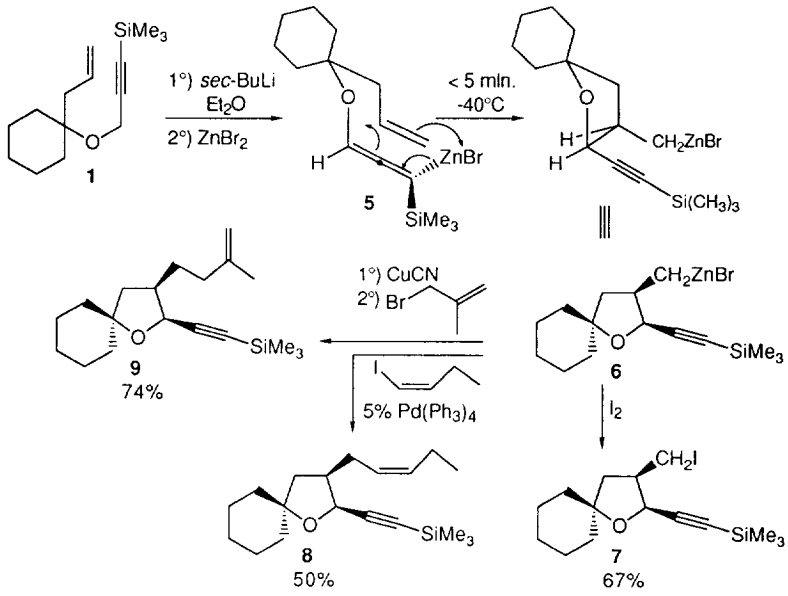
Scheme 1

The ease of this intramolecular carbometallation combined with the very high diastereoselectivity in the creation of three contiguous stereogenic centers, led us to consider the stereocontrolled synthesis of substituted tetrahydrofurans[3], which remains a particularly challenging aspect in the polyether antibiotics synthesis[4]. The propargylic, homoallylic ethers used as precursors were prepared by the three component condensation in a one-step procedure (path A) described recently by Markò[5], and also by the subsequent reactions of preformed bis-propargyl acetals with allylsilane[6] (path B) :



Scheme 2

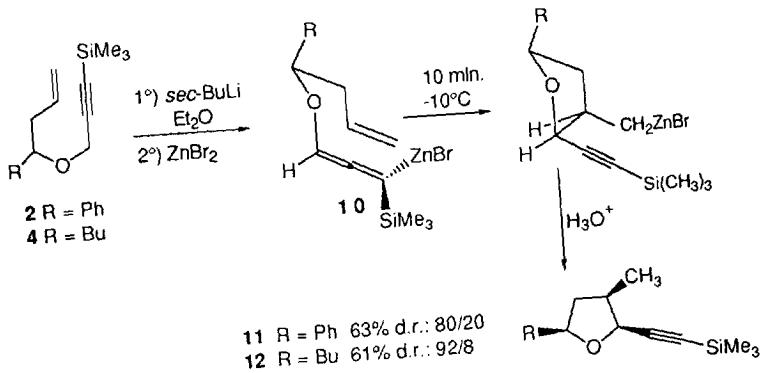
1 was cleanly metallated with *sec*-BuLi in ether at -70°C, then the slow addition of one equiv of $ZnBr_2$ led to the allenylorganozinc bromide which underwent a highly diastereoselective cyclization reaction[7] in less than 5 min at -40°C[8].



Scheme 3

The cyclic organozinc bromide[9] **6** can be functionnalized by iodinolysis, by coupling reactions with vinylic iodides in the presence of a catalytic amounts of $Pd(Ph_3)_4$ or by reaction with methallyl bromide after transmetallation of **6** into an organocopper reagent[10]. In all these cases, the tetrahydrofurans were isolated as *single* isomers, due to the zinca-en-allene transition state **5** in which the allenyl metal moiety plays the role of the ene-counterpart and fixes the *cis* relationship of the two ring substituents[1,11]. This very mild and

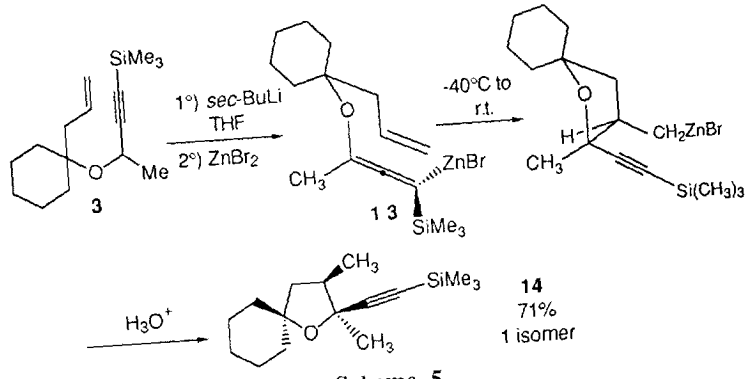
diastereoselective cyclization allows us to study the intramolecular carbometallation of **2** and **4** in which a new stereogenic center was added (scheme 4) :



Scheme 4

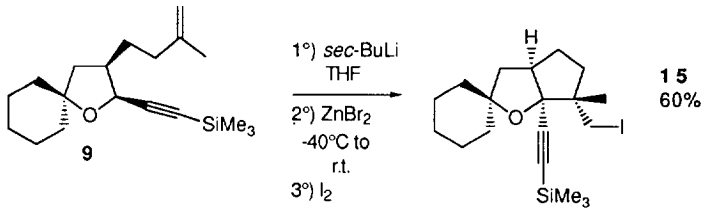
This zinca-en-allene cyclization afforded respectively **11** and **12** as a 80/20 and 92/8 mixture of diastereoisomers. However, the major *cis* isomer can be easily separated by chromatography on silica gel and ^{1}H and ^{13}C NMR chemical shifts were established by using standard COSY techniques and configurational assignments were found for **11** on the basis of differencial nuclear overhauser effect spectra. In this case, the phenyl substituent preferentially occupies a pseudo equatorial position in the metallo-en-allene transition state.

An extra substituent R can be also positioned on the propargylic position. The "metallation-transmetallation-cyclization" was done by treatment of **3** with *sec*-BuLi in THF at -40°C. The cyclization was performed by a slow warming up of the reaction mixture and led, after hydrolysis, to an unique isomer **14** (with vicinal quaternary and tertiary stereogenic centers on the tetrahydrofuran ring) in 71% yield of isolated pure product. The relative configuration is, here again, in full agreement with the metallo-en-allene transition state **13**[12] :



Scheme 5

Finally, we turned our attention on the creation of two consecutive quaternary centers. Thus, **9** was submitted to our cyclization conditions depicted in scheme 5 and after iodinolysis, the corresponding *tricycle* was obtained as a *unique* isomer in 60% yield.



Scheme 6

In conclusion, from simple starting materials, we can elaborated in two steps the diastereoselective synthesis of polysubstituted tetrahydrofurans under very mild conditions by the zinca-en-allene reaction. This strategy ring-closes a THF between positions 2 and 3, and substituents at these positions end up *cis* to each other. It is complementary to the recently developped[7,9] ring closure, where substituents in position 2 and 3 end up *trans* to each other.

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(*Received in France* 28 *November* 1994; *accepted* 18 *December* 1994)