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Zinca-ene-allene and Zinc-enolate Cyclization. Towards the Synthesis of Polysubstituted Pyrrolidines

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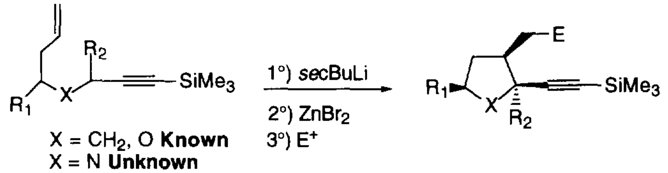
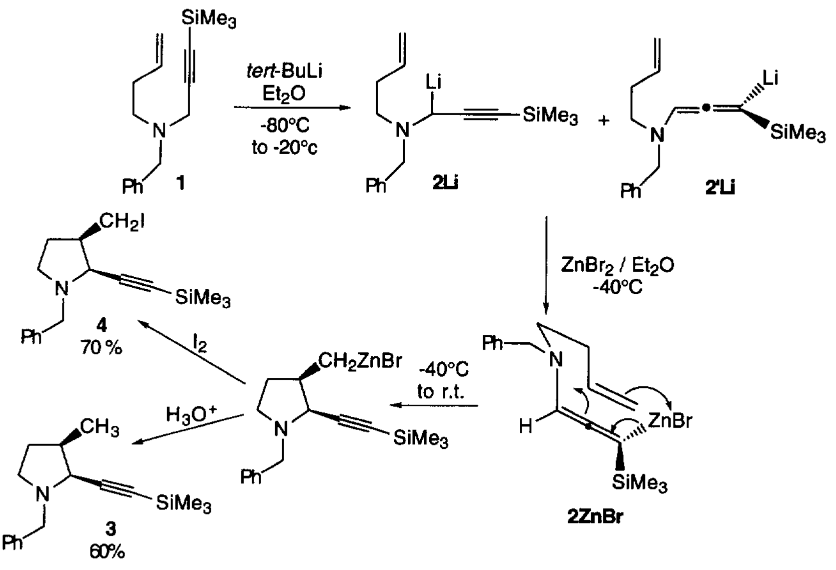
Abstract. The synthesis of polysubstituted pyrrolidines can be easily achieved in a diastereoselective and enantioselective way via the zinca-ene-allene and zinc-enolate cyclization.Copyright © 1996 Elsevier Science Ltd

We have recently described a new intramolecular carbometalation reaction, in which an allenyl-zinc bromide undergoes a diastereoselective 5-exo-trig[1] or 5-exo-dig[2] cyclization on a terminal unsaturation. This method was successfully applied to the stereocontrolled synthesis of linear and angular triquinanes skeletons in a few chemical steps[3], as well as to the synthesis of polysubstituted tetrahydrofurans[4] (Scheme 1).



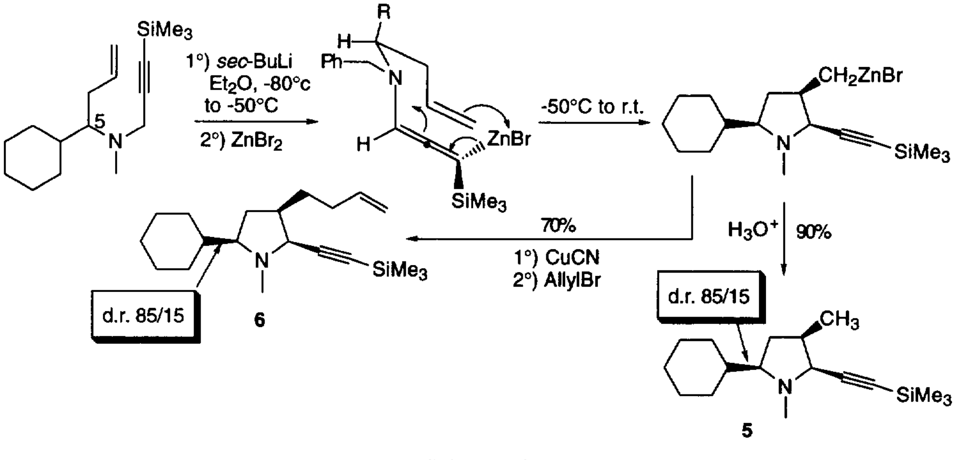
Scheme 1

The ease of this intramolecular carbometalation combined with the diastereoselectivity generated in this process led us to consider the stereocontrolled synthesis of substituted pyrrolidines, which remains an intensive research area[5]. The starting material, easily prepared by known reactions[6], was subjected to our carbocyclization conditions as described in Scheme 2. Compound **1** was cleanly metalated with *tert*-BuLi (1.5 equiv) in ether at low temperature to give the corresponding propargyl lithium derivative **2Li**, which is in metallotropic equilibrium with its allenic counterpart **2'Li**. Both organolithium species react with zinc bromide (1.5 equiv) to give only the allenyl zinc bromide **2ZnBr** intermediate[7]. By warming the reaction mixture to room temperature, the cyclic product was formed *via* the diastereoselective zinca-ene-allene reaction and was further protonated or iodinolyzed. In both cases, the pyrrolidines were isolated as single isomers, due to the chair-like transition state in which the N-substituted double bond of the allenyl zinc bromide and the remote olefin are coplanar.



Scheme 2

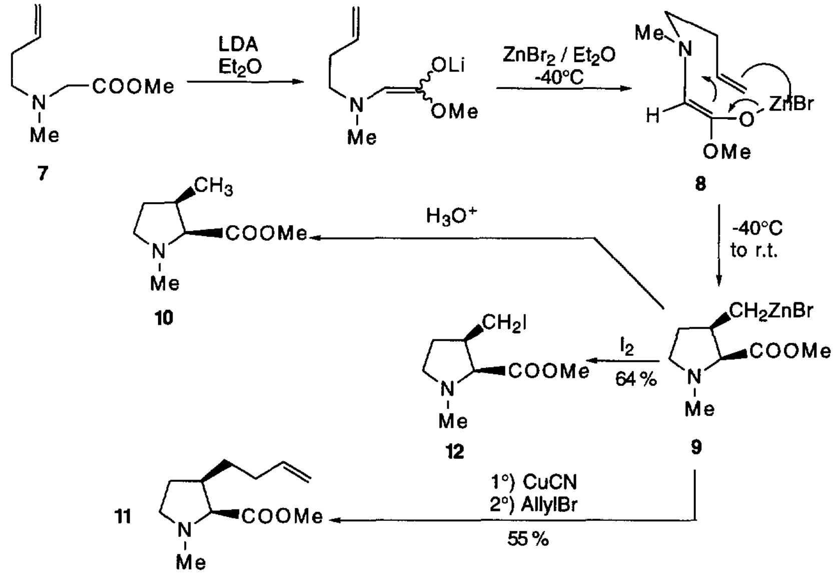
An extra substituent R was then added on C-5, a position which is known to be the most difficult one to control during the carbocyclization reaction. According to our previous described experimental conditions, the cyclization was performed by warming up the reaction mixture which led, after hydrolysis or allylation (after a transmetalation step) to the corresponding products **5** (90%) and **6** (70%) with a 85/15 diastereomeric ratio in favor of the *cis* diastereomer. The relative configuration of the 3 stereogenic centers was determined on the basis of differencial nuclear Overhauser effect.



Scheme 3

In this case, although the cyclohexyl substituent preferentially occupies a pseudo-equatorial position in the metallo-ene-allene transition state, this extra stereogenic center is far from the two reacting centers and then a lower diastereoselection is obtained.

Parallel to this work, we studied the carbocyclization of zinc enolates which were not reported[8]. Our first investigation concerned the achiral substrate **7** as a model, bearing both an acidic hydrogen, and a beneficial nitrogen atom. The formation of the lithium enolate in ether, which is unable to cyclize[9], was easily achieved by treatment of **7** with LDA, followed by the addition of an excess of zinc salt to give the corresponding zinc-enolate. This latter undergoes a clean and fast 5-exo-trig cyclization accross the double bond to give after hydrolysis the *cis* β-methyl proline derivative. The ^1H and ^{13}C NMR chemical shifts of **10** were established by using standard COSY techniques and unambiguous configurational assignments were found on the basis of differencial nuclear Overhauser effect spectra.

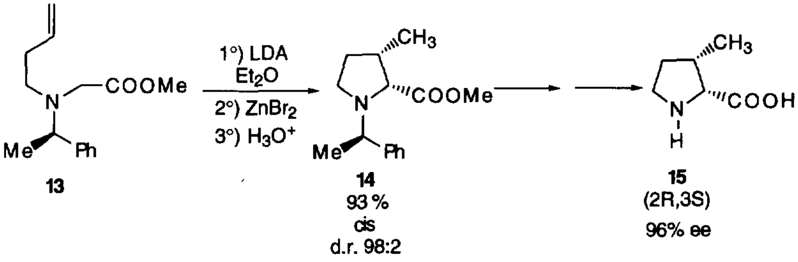


Scheme 4

The *cis* relative configuration was attributed to a chair-like transition state in which the zinc-enolate and the olefinic residue are coplanar as described in **8**. The resulting organozinc bromide can be functionalized by iodinolysis or by reaction with allyl bromide after transmetalation of **9** into an organocopper reagent.

We then turned to the chiral substrate[10] **13** prepared from the commercially available (R)-methyl benzyl amine. According to our experimental procedure (metalation-transmetalation-cyclization-hydrolysis) the chiral β-methyl proline[11] was obtained as a single *cis* diastereomer[12] with a 98:2 diastereomeric ratio in 93% yield.

At the same time, P. Karoyan and G. Chassaing (see accompanying paper[13]) reached the same goal and the absolute configuration of **14** is quoted according to their determination (hydrogenolysis to the secondary amine, saponification of **14** and comparison of the optical rotation of **15** with the known value[14] for (2R,3S)-β-methyl proline).



Scheme 5

In conclusion, the synthesis of polysubstituted pyrrolidines can be easily achieved in a diastereoselective and enantioselective way *via* the anionic carbometalation reaction. During this study, a new zinc-enolate cyclization was described, and we are currently exploring the scope of this reaction.

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9. This fact points to the big discrepancy between d-organolithium and zinc reagents, as previously described; see references 1 and Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.F; *Tetrahedron* **1994**, *50* 11665-11692
10. The metalation of the chiral propargylic (R)-methyl benzylamine couldn't be obtained.
11. $[\alpha]^{25}_{D}$ = +79.45° (c = 50.7, $HCCl_3$)
12. The chiral inductor was cleaved and a single *cis* diastereomer was formed $[\alpha]^{25}_{D}$ = +8.22° (c = 13.5, $HCCl_3$)
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