

Carbolithiation of Cinnamyldialkylamines. Stereochemistry of the Li to Zn Transmetalation and Configurational Stability of Benzylic Organozinc Halides

Sophie Klein, Ilane Marek,* and Jean-F. Normant*

Laboratoire de Chimie des Organoéléments, Université P. et M. Curie, associé au CNRS URA 473, 4 Place Jussieu, 75252 Paris Cedex 05, France

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Summary: α -Substituted benzylic zinc halides have observable configurational stability in hexane/ether solvent.

The establishment of defined, vicinal stereorelationships in the construction of organic molecules is a central requirement for efficient synthesis of many structurally complex substances.¹ The carbometalation² reaction is an approach involving formation of the carbon-carbon bond and can often provide a useful solution to this problem, particularly in acyclic systems.³ Although the carbolithiation of isolated and unstrained double bonds is rather limited,⁴ the presence of a donor group in the proximity of the double bond of this alkene promotes the carbolithiation reaction.⁵ Thus, it has been reported that the C=C bonds of allylic alcohols undergo addition of some alkyllithiums to generate the corresponding lithium species,⁶ and the stereochemical outcome of the reactions of this newly created carbon-metal bond with electrophiles was recently investigated⁷ in the case of cinnamyl alcohol.

In this paper, we report our preliminary results in the area of acyclic stereocontrol in the carbolithiation of cinnamylamines and the stereochemical outcome of the lithium-zinc transmetalation.

Thus, (*E*)-cinnamylamine 1 was treated with 1.5 equiv of butyllithium at 0 °C in hexane in the presence of 1.5 equiv of TMEDA, and the resulting red solution was quenched with electrophiles.⁸ Evidence for the stereo-

chemical assignment of the product 3 was obtained by comparison with an authentic sample, prepared by an independent way.⁹ The high diastereoselectivity observed in this reaction may be accounted for by thermodynamic control of the organolithium intermediate 2,¹⁰ as shown by the obtention of the same product starting from the (*Z*)-cinnamylamine 1Z.¹¹ Thus, after thermodynamic equilibration, a tertiary amino group (NEt₂ or NMe₂) on the γ position blocks the configuration of the benzyllithium through coordination. This allows a diastereoselective introduction of electrophiles with retention.¹⁰ This diastereoselectivity is dependent on the reaction temperature in hexane. When the reaction is performed in 5 h at -30 °C or 3 h at 0 °C, the diastereoselectivity is, respectively, 80/20 and 85/15, but if the reaction mixture is allowed to warm to room temperature, the diastereomeric ratio grows up to 95/5.¹² This observation is consistent with thermodynamic control of the benzylic organolithium (see Scheme 1).

With the chiral benzylic organolithium in hand, we then studied its transmetalation reaction into organozinc derivatives, the main goal of this research being to investigate the configurational stability of organozinc halides. Thus, the transmetalation of 2Li with a solution of zinc bromide in Et₂O at -60 °C, slowly warming to -30 °C and quenching with DCl, occurred with complete inversion of stereochemistry!¹³ Deuteration with DCl (or MeOD)^{13j} leads to 4 *syn*⁹ (Scheme 2). One hypothesis to explain this result is that the transmetalation (Li to Zn) occurred with inversion of configuration and quenching with DCl with retention and lead to 4 *syn*, but we may also consider the opposite process. In order to discriminate between these two hypotheses, we investigated the configurational stability of organozinc¹⁴ derivatives after varying lengths of time (Table 1).

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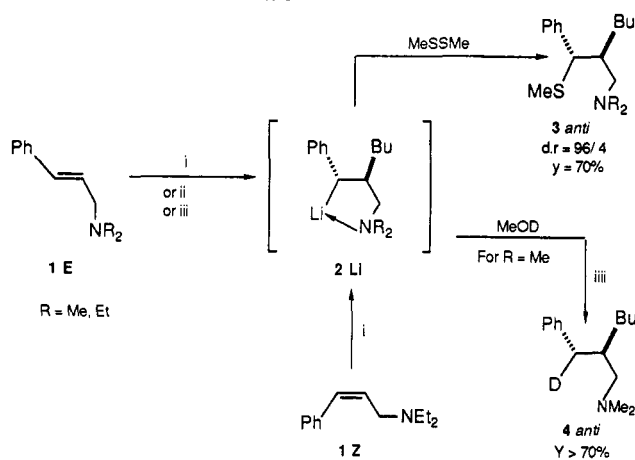
(9) The correlation was made from the alcohol prepared according to ref 7a by tosylation and displacement with dimethylamine. When 2Li or 2Zn are hydrolyzed, the two benzylic protons are well distinguished by ¹H NMR (ABX system). Then, the diastereomeric ratio of 4 is easily established.

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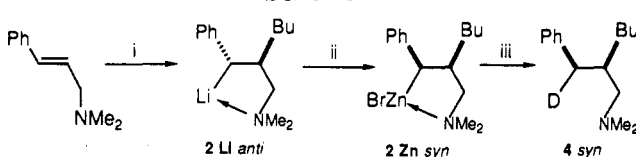
(12) The isolated pure products gave satisfactory ¹H and ¹³C NMR data. The diastereoisomer ratio was determined by 400-MHz ¹H NMR.

Scheme 1



^a Key: (i) BuLi/hexane, TMEDA; (ii) BuLi/THF TMEDA; (iii) BuLi/THF; (iiii) 4 *anti*/4 *syn* = 93/07 when path ii or iii is used, but for i 4 *anti*/4 *syn* = 80/20 at -30 °C/5 h, 4 *anti*/4 *syn* = 85/15 at 0 °C/3 h, and 4 *anti*/4 *syn* = 95/5 at 0 °C/3 h then 20 °C/1 h.

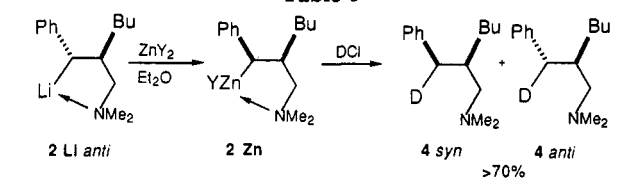
Scheme 2



^a Key: (i) BuLi/hexane TMEDA; (ii) ZnBr₂/Et₂O; (iii) DCl.

The stereochemical results reported in Table 1 fulfill our expectations: The transmetalation from Li to Zn (for a benzylic organometallic) occurred with inversion of configuration and led to the less stable 4 *syn* isomer (compare entry 1 with entries 2 and 3), and the configurational stability of this organozinc bromide derivative is dependent on the temperature (compare entries 2 and 3 with entries 4 and 5): the benzylic organozinc bromide slowly epimerizes to produce the more stable diastereoisomer 4 *anti*. This epimerization is remarkably slow enough to observe varying ratios of products as a function of time.¹⁵ By heating the reaction mixture at 50 °C for 2 h (entry 6), the thermodynamic product is obtained quantitatively. Although the electronegativity of the chlorine atom in ZnCl₂ should allow a more tight cyclic

Table 1



entry	zinc addns ^a	T (°C)/time before quench with DCl ^b	4 <i>syn</i> /4 <i>anti</i> ^c
1	none	20/30 min	8/92
2	ZnBr ₂	-30/30 min	95/5
3	ZnBr ₂	-30/4 h	95/5
4	ZnBr ₂	-30 to 0/15 min	70/30
5	ZnBr ₂	0/1 h	50/50
6	ZnBr ₂	50/2 h	≈5/95
7	ZnCl ₂	-30 to 0/15 min	70/30
8	BuZnBr	-30 to 0/30 min	30/70
9	Et ₂ Zn	0/1 h	≈20/80
10	Et ₂ Zn	-50/30 min	≈20/80

^a The zinc derivative is slowly added at -60 °C in Et₂O solution. ^b DCl is introduced at -60 °C. ^c A value of 95/5 indicates that only one stereoisomer was detected by ¹H NMR (400 MHz) with approximately 70–90% deuteration.

transition state in favor of 4 *syn*, the diastereomeric ratio is unchanged (entry 4 versus entry 7). Meanwhile, if the lithium is replaced by an alkylzinc moiety (entry 8) or a zincate (entries 9 and 10) the diastereomeric ratio is in favor of the thermodynamic product; this points to the big difference between an organozinc halide and a bisorganozinc or zincate reagent as for their configurational stability. The diastereoselectivity is also dependent on the reaction solvent. In the more polar solvent THF, the oxygen atom of the solvent competes efficiently with the nitrogen atom of the intermediate 2Zn and the diastereoselectivity of the reaction is poor (4 *syn*/4 *anti* = 40/60), whereas THF has no detrimental effect, as expected, when 2Li prepared in this solvent is quenched with DCl (4 *anti*/4 *syn* = 93/7, see Scheme 1).

From a synthetic point of view, the equilibration of the organolithium obtained from the carbolithiation of cinnylamine to a single isomer is useful, since the resultant single species reacts stereoselectively with electrophiles, producing diastereomerically pure derivatives. Another significant finding from this preliminary work is the observation that the Li to Zn transmetalation in a benzylic species occurs with inversion of configuration, and these studies show for the first time that acyclic benzylic zinc halides have observable configurational stability at -30 °C, due to their highly covalent character. We are currently investigating the transmetalation reaction, the configurational stability of organozinc halides in several other systems, and particularly the reaction of electrophiles other than DCl or MeSSMe.

Note Added in Proof. After submission of this paper, a study of the configurational stability of norbornyl zinc reagents appeared: Dudder, R.; Eckhardt, M.; Furlong, M.; Knoess, P.; Berger, S.; Knochel, P. *Tetrahedron* 1994, 50, 2415–2432.

Supplementary Material Available: Typical experimental procedures and spectral data of products (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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