

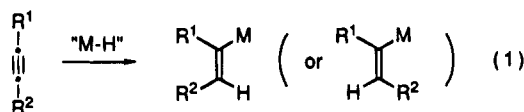
Stereo- and Regioselective Generation of Alkenylzinc Reagents via Titanium-Catalyzed Hydrozincation of Internal Acetylenes

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Hydrometalation of acetylenes illustrated in eq 1 is a superior method for preparing stereodefined alkenyl-metal species, which are particularly useful for the construction of olefinic linkages with predictable stereochemistry. Hydrometalation reactions¹ including hydro-

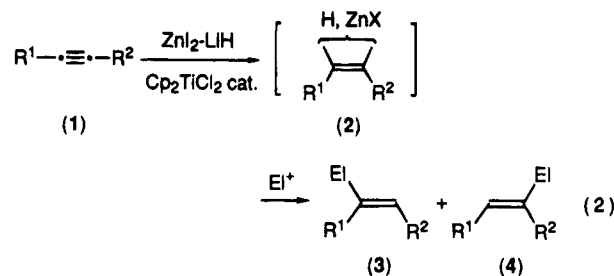


boration,^{1a} -aluminum,^{1b} -magnesium,^{1c} -silylation,^{1d} -stannation,^{1e} and -zirconation,^{1f} etc., have been routinely utilized in the synthesis of complex natural products. Herein we report a new entry to this series of reactions, namely the first hydrozincation of acetylenes, and demonstrate its application to further synthetic transformations.

Recently, organozinc compounds of the type RZnX (R = alkyl; X = halogen, R, etc.) have been widely recognized as versatile carbon nucleophiles in organic synthesis owing to their selective reactivities.² Alkenylzinc compounds are usually prepared via transmetalation of appropriate organometallic reagents, typically organolithium, -magnesium, or -boron compounds, with zinc salts or diethylzinc.^{2a-c,3} Direct reductive metalation of alkenyl halides with zinc metal can also be effected, but the stereochemical integrity of the starting alkenyl halide is not always retained in the zinc reagent.⁴ If hydrozincation of acetylenes (eq 1, "M-H" = "ZnHX") could be executed in a stereoselective manner, this reaction could become a straightforward method to prepare stereochemically defined alkenylzinc reagents. While hy-

drozincation of (mono)olefins with ZnH₂ under zirconium catalysis had been reported almost 10 years ago⁵ and, more recently, hydrozincation of 1,3-dienes with a 1:2 mixture of ZnI₂ and LiH in the presence of 10 mol % of Cp₂TiCl₂ has been described,⁶ there is no precedent for hydrozincation of acetylenes.

We have examined the Cp₂TiCl₂-catalyzed hydrozincation of 6-dodecyne with zinc hydride reagents generated *in situ* from ZnX₂ (X = Cl, Br, I) and MH (M = Li, Na, K) (eq 2).^{6,7} Like the forementioned hydrozincation



of 1,3-dienes, ZnI₂-LiH (1:2) in THF again proved to be the most effective combination. Under these reaction conditions, 6-dodecyne (**1a**) afforded more than a 90% yield of the *cis*-alkenylzinc reagent **2a** as evidenced by its hydrolysis with D₂O, which yielded (*Z*)-6-deuterio-6-dodecene (**3a**, E1 = D, 92% d₁) in 99% yield (eq 2). The *Z/E* ratio of 98:2 for this deuterated compound determined by GC-MS analysis confirmed that the hydrozincation took place in a *cis* fashion across the triple bond with high stereoselectivity. The role of the titanium catalyst, which is essential for the progress of the reaction, is suggested to be basically the same as in the hydrozincation of 1,3-dienes.⁶ Cp₂TiCl₂ is reduced *in situ* with ZnHX to yield a titanium hydride Cp₂TiH. This hydride species undergoes hydrotitanation of the acetylene to yield a Cp₂(*cis*-alkenyl)Ti species, which, in turn, undergoes transmetalation with ZnHX to generate (*cis*-alkenyl)ZnX and Cp₂TiH. The regenerated Cp₂TiH again participates in the hydrotitanation to continue the catalytic cycle.

Table 1⁸ summarizes the results of the hydrozincation of a few types of acetylenes. The hydrozincation of alkyl- and phenylacetylenes **1a-d** involves initial preparation of the zinc hydride reagent from ZnI₂ and LiH in THF at rt for 3 h, followed by successive addition of an acetylene and Cp₂TiCl₂ at 0 °C. After the mixture was stirred at rt for 3 h and introduction of an electrophile, the usual workup afforded the product. The reaction always shows excellent stereoselectivity arising from the exclusive *cis*-hydrometalation. As far as the regioselectivity is concerned, difference of steric hindrance between methyl and a higher alkyl substituent such as hexyl at each of acetylenic termini did not effect any control of the regioselectivity (entry 4). Phenylacetylenes showed the regioselectivity of 84:16–88:12, and the zinc occupies the

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(2) Review: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* 1993, 93, 2117. (b) Erdik, E. *Tetrahedron* 1992, 48, 9577. (c) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 211. (d) Soai, K.; Niwa, S. *Chem. Rev.* 1992, 92, 833. (e) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 49.

(3) Review: Boersma, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 2, p 823. Erdick, E. *Tetrahedron* 1987, 43, 2203.

(4) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* 1990, 31, 4413. However, (*E*)-styrylzinc bromide could be prepared from (*E*)-styryl bromide with highly activated zinc: Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* 1991, 56, 1445.

(5) Review: Dzhemilev, U. M.; Vostrikova, O. S.; Tolstikov, G. A. *J. Organomet. Chem.* 1986, 304, 17. Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1982, 1195; *Engl. Trans.* 1983, 1080. However, the hydrozincation met with limited success, and no synthetic applications of the resultant zinc species to carbon-carbon bond formation have been reported.

(6) Gao, Y.; Urabe, H.; Sato, F. *J. Org. Chem.* 1994, 59, 5521.

(7) The use of isolated ZnH₂ (de Koning, A. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* 1980, 186, 159. Watkins, J. J.; Ashby, E. C. *Inorg. Chem.* 1974, 13, 2350) in place of the one generated *in situ* resulted in a low conversion of the starting material as pointed out in ref 6.

(8) Typical procedures are described in the supplementary material.

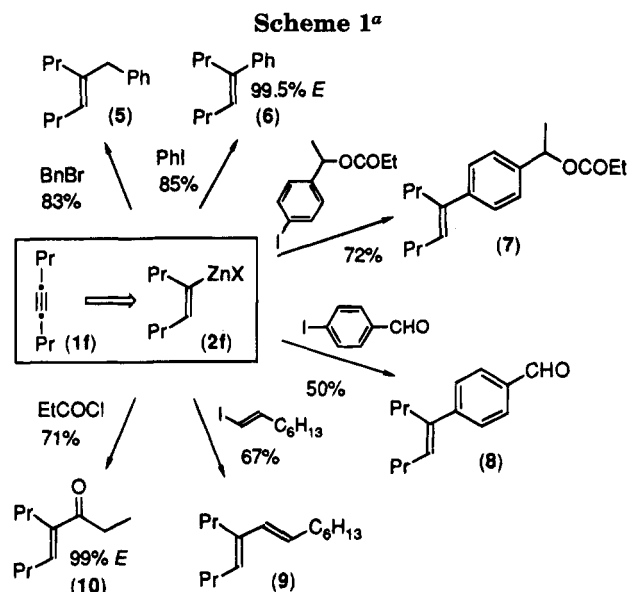
Table 1. Alkenylzinc Reagents Prepared by the Hydrozincation of Acetylenes and Their Reactions^a

entry	R ¹	R ²	1-4	El ⁺	El	yield of 3 and 4, ^b %	Z/E of 3 ^c	3/4 ^c
1	C ₆ H ₁₁	C ₆ H ₁₁	a	D ₂ O	D	99 (92% d ₁ ^d)	98:2 ^d	
2				I ₂	I	83	E ^e	
3				NBS	I	75 ^f	E ^e	
4	C ₆ H ₁₃	Me	b	I ₂	I	71	E ^e	52:48
5	Ph	Me	c	D ₂ O	D	90 (98% d ₁ ^d)	(97:3 ^g)	84:16
6				I ₂	I	78	E ^e	88:12
7				PhI/Pd(PPh ₃) ₄	Ph	86		88:12
8	Ph	C ₃ H ₇	d	I ₂	I	73	97:3	87:13
9	Me ₃ Si	C ₆ H ₁₃	e	D ₂ O	D	87 (91% d ₁ ^d)	(98:2 ^g)	90:10
10				I ₂	I	70	E ^e	91:9
11				PhI/Pd(PPh ₃) ₄	Ph	70	Z ^e	90:10

^a Reactant ratio: 1:ZnI₂:LiH:Cp₂TiCl₂ = 0.7-0.8:1:2.2:0.1 (El = D and I) or 1:ZnI₂:LiH:Cp₂TiCl₂:PhI:Pd(PPh₃)₄ = 1:1:2.2:0.1:0.8:0.04 (El = Ph). ^b Isolated yields based on 1 (El = D and I) or based on PhI (El = Ph). ^c Determined by ¹H NMR and/or GC. ^d Determined by ¹H NMR and/or GC-MS. ^e See text for structural determination. ^f ¹H NMR analysis verified that this isomer was exclusively formed. ^g No contamination by the bromide was observed. ^h Determined by protonation (El⁺ = H₂O) of a mixture of 3 and 4.

proximate position to the phenyl (entries 5-8). Although 1-(trimethylsilyl)-1-alkyne (**1e**) also participated in this reaction, its reactivity in the hydrozincation step was sluggish as compared to the alkyl- or phenylacetylenes. Thus, the following modification of the procedure should be applied. After a mixture of Cp₂TiCl₂ (10 mol %) and ZnI₂ was treated with LiH at rt for 30 min, a silylacetylene was added. The mixture was stirred at rt for 24 h to give a solution of the alkenylzinc reagent. Under the latter conditions, the silylacetylene showed an excellent stereoselectivity as high as 98:2 and a good regioselectivity exceeding 90:10 with respect to the hydrozincation step, where the zinc was located at the silylated carbon atom (entries 9-11). Terminal acetylenes failed to undergo the hydrozincation.

Gratifyingly, the resultant alkenylzinc reagents could be utilized in standard synthetic transformations.⁸ For example, treatment of zinc reagents **2a-e** with I₂ yielded the corresponding (*E*)-alkenyl iodides **3a-e** (El = I) in good yields (entries 2, 4, 6, 8, and 10). Their structures as well as high stereochemical purities were confirmed by lithiation with *t*-BuLi followed by hydrolysis to give **3a-e** (El = H) with an *E/Z* ratio of around 97:3. When NBS (*N*-bromosuccinimide) had been allowed to react with zinc reagent **2a** to prepare alkenyl bromide **3a** (El = Br), the only product detected was the corresponding alkenyl iodide, which should arise from a rapid oxidation of I⁻ (coming from ZnI₂) to I⁺ by NBS *in situ* (entry 3). Palladium-catalyzed coupling reactions with organic halides^{2b} are illustrated in Table 1, entries 7 and 11, and in Scheme 1. Benzyl bromide was alkenylated with **2f** (Scheme 1) to give 4-benzyl-4-octene (**5**) as a single stereoisomer, the structure of which is tentatively assigned to be *E*. Aromatic bromides did not react with **2f** efficiently. Instead, aromatic iodides underwent the coupling with **2c, e**, and **f** in good yields.⁹ The high stereoselectivity observed in the product **6** from **2f** and PhI was verified to be *E/Z* = 99.5:0.5 by ¹H NMR analysis in comparison with authentic samples. Other coupling



^a All reactions were performed in THF in the presence of a catalytic amount of Pd(PPh₃)₄.

products were also obtained virtually as single isomers. The chemoselectivity of organozinc reagents is compatible with functional groups such as esters (**2f** → **7**) and even aldehydes (**2f** → **8**). (*E*)-1-Iodo-1-octene afforded diene **9**, the CH=CH bond of which was confirmed to be *E* by ¹H NMR analysis, and another olefinic bond was assigned to be also *E* by analogy as above. An acyl chloride smoothly reacted with **2f** to give α,β -unsaturated ketone **10** without the formation of the tertiary alcohol.¹⁰

Supplementary Material Available: Typical procedures for the hydrozincation of **1a** and **e**, preparation of **3a** (El = I) and **6**, and structural determination and physical properties of **3-10** (8 pages).

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