First Practical Hydrozincation of Dienes Catalyzed by Cp_2TiCl_2. Generation of Allylzinc Reagent and Its Reaction with Carbonyl Compounds

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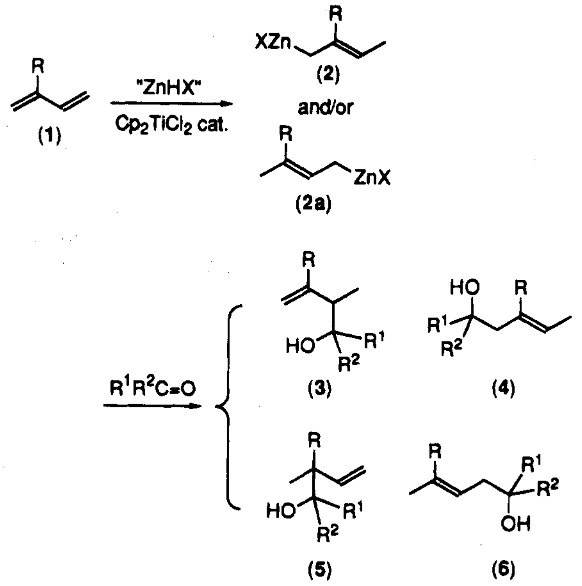
Received June 2, 1994[®]

Summary: The first practical hydrozincation of butadiene and 2-alkylbutadienes has been achieved by a combination reagent including ZnI_2, LiH, and Cp_2TiCl_2 in a ratio of 1:2.2:0.1 to yield the corresponding allylzinc reagents in THF, which, in turn, react with a variety of carbonyl compounds.

Though organozinc compounds of the type RZnX (R = alkyl; X = halogen, R, etc.) are long studied organometallics,[1] their importance in organic synthesis has been growing recently owing to their unique and selective behavior as carbon nucleophiles.[2,3] These zinc compounds are usually prepared by conventional methods including reductive metalation of organic halides with zinc metal or dialkylzinc (RX → RZnX) or by transmetalation of appropriate organolithium, -magnesium, -mercury, or -boron compounds with either zinc metal or zinc salt (R-metal → RZnX).[4] Some newer, synthetically useful modifications based on these methodologies have also appeared.[2] Besides the foregoing methods, we conceived that hydrozincation of olefinic substrates could provide a third, straightforward method to prepare these organozinc compounds. Even though hydrozincation of olefins with ZnH_2 was mentioned almost 10 years ago, it met with limited success, and no further synthetic applications of the resultant zinc species to carbon–carbon bond formation have been reported.[5] Encouraged by our earlier demonstration of Cp_2TiCl_2-catalyzed hydromagnesation and -alumination of olefinic compounds,[6] we revisited the above reaction and are very pleased to disclose our findings on some aspects of the hydrozincation reaction.

Since simple alkylzinc compounds such as alkylzinc halides or dialkylzincs are reluctant to undergo carbonyl additions,[2,3] we experienced some difficulty in utilizing trapping experiments with an aldehyde in order to determine the content of organozinc species generated by the hydrozincation reaction. To circumvent this inconvenience we focused our attention on preparing allylzinc species, i.e., allylzinc halide and/or diallylzinc, both of which are known to react smoothly with aldehydes and ketones without additional promotors.[2,7,8] Thus, the feasibility of hydrozincation was easily demonstrated by the reaction of isoprene (**1**, R = Me) and a variety of zinc hydride reagents ("ZnHX") in the catalytic presence of Cp_2TiCl_2 followed by simple trapping of the resultant allylzinc species **2**[9] with benzaldehyde as $R^1R^2C{=}O$ in eq 1.



(1)

It is expected that the reagent "ZnHX" must play a critical role in this reaction. We tried isolated ZnH_2[10,11] as well as that prepared *in situ* by a combination of a zinc salt such as $ZnCl_2$, $ZnBr_2$, or ZnI_2 and a hydride species including LiH, NaH, or KH.[11] To our surprise, ZnH_2 itself did not give the homoallyl alcohols shown in eq 1 in an acceptable yield (**3**; R = Me, R^1 = Ph, R^2 = H; 20%), but a combination reagent consisting of ZnX_2 and LiH in THF did![12] Of the three zinc salts examined, ZnI_2 is apparently better than $ZnCl_2$ and is comparable to $ZnBr_2$. Both NaH and KH were far less effective than LiH. A mixture of ZnI_2 and LiH in a stoichiometry of 1:2.2 provided the most active hydrozincation agent in the presence of 10 mol % of Cp_2TiCl_2. No reaction took place in the absence of Cp_2TiCl_2 or with $TiCl_4$ in place of Cp_2TiCl_2. The use of the above combination of reagents

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[®] Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) Sheverdina, N. T.; Kocheshkov, K. A. In *The Organic Compounds of Zinc and Cadmium in Methods of Element-Organic Chemistry*; Newsmeyanov, A. N., Kocheshkov, K. A., Eds.; North-Holland Publishing Co.: Amsterdam, 1967.

(2) Review: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. Erdik, E. *Tetrahedron* **1992**, *48*, 9577. Knochel, P. In *Comprehensive Organic* Synthesis; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 211.

(3) Review: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

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

(5) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 1195; Engl. Trans. **1983**, 1080. Review: Dzhemilev, U. M.; Vostrikova, O. S.; Tolstikov, G. A. *J. Organomet. Chem.* **1986**, *304*, 17.

(6) Review: Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53; *Janssen Chim. Acta* **1990**, *8*, 3. See also ref 5. Eisch, J. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, p 733.

(7) Review: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

(8) Thiele, K.-H.; Zdunneck, P. *J. Organomet. Chem.* **1965**, *4*, 10. Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974; **1963**, 1475.

(9) The structure **2** is a simple formulation which may represent all isomers of **2** with respect to the position of zinc such as $CH_2{=}CRC(ZnX)HMe$ and $[CH_2{\cdots}CR{\cdots}CHMe^+]^-\ [ZnX]^+$.

(10) de Koning, A. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1980**, *186*, 159.

(11) Watkins, J. J.; Ashby, E. C. *Inorg. Chem.* **1974**, *13*, 2350.

(12) That the chemical reactivity of ZnH_2 was influenced by the methods of its preparation was briefly mentioned in ref 10.

0022-3263/94/1959-5521$04.50/0

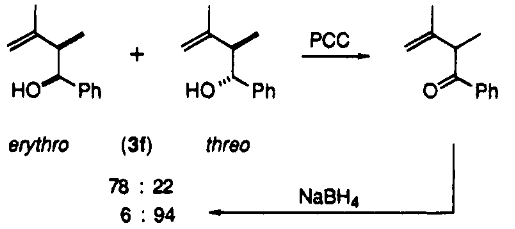
Table 1. Homoallyl Alcohols from Dienes via Hydrozincation Reaction[a]

entry	R in 1	$R^1R^2C{=}O$	3	yield of 3[b] (%)	diastereoselectivity[c]
1	H	PhCHO	**a**	81	60:40 (*erythro*/*threo*[d])
2	Me	$C_5H_{11}CHO$	**b**	78	71:29
3		$(CH_3)_2CHCHO$	**c**	77	70:30
4		$C_4H_9CO(CH_2)_4CHO$	**d**	77[e,f]	65:35
5		(*E*)-PhCH=CHCHO	**e**	85	60:40
6		PhCHO	**f**	74	78:22 (*erythro*/*threo*[d])
7		2-furylaldehyde	**g**	82	75:25
8		*m*-BrC_6H_4CHO	**h**	87	71:29
9		*p*-$(CHO)C_6H_4CO_2Me$	**i**	91[f]	66:34
10		$C_5H_{11}COCH_3$	**j**	67	65:35
11		cyclohexanone	**k**	72	
12		$PhCOCH_3$	**l**	57	57:43
13		CO_2	**m**	70[g]	
14	$(CH_3)_2C{=}CH(CH_2)_2$	PhCHO	**n**	75	80:20

[a] The reactant ratio: $1:ZnI_2:LiH:Cp_2TiCl_2:R^1R^2CO = 2.2:1:2.2:0.1:0.8$ unless otherwise noted. For the reaction conditions, see the typical procedures. [b] Isolated yields based on R^1R^2CO. [c] Determined based on ^1H NMR spectra of crude samples. [d] The structures are shown in eq 2. [e] The $ZnI_2:R^1R^2CO$ ratio of 1:0.95 was applied to prevent the reaction at the ketone moiety. [f] Exclusive reaction at the aldehyde moiety. [g] Excess CO_2 gas was used and the yield of the product, 2,3-dimethyl-3-butenoic acid, was based on ZnI_2.

in the indicated stoichiometry resulted in good yields of the homoallyl alcohols **3** from a variety of dienes **1** and carbonyl compounds as shown in Table 1.[13]

The procedure is operationally simple: after a mixture of LiH and ZnI_2 had been stirred in THF at room temperature for a few hours, diene and a catalytic amount of Cp_2TiCl_2 were added, followed by a carbonyl compound. Butadiene and 2-alkylbutadienes were readily incorporated in this reaction to yield the corresponding allylzinc species **2** rather than isomeric **2a** as evidenced by their regioselective trapping with aldehydes (*vide infra*), but 1-alkylbutadienes or 1,3-cycloalkadienes like cyclopentadiene were not incorporated. The zinc species thus prepared can react with a variety of carbonyl compounds involving aldehydes (Table 1, entries 1–9 and 14), ketones (Table 1, entries 10–12), and carbon dioxide (Table 1, entry 13). Remarkably, in each case, the single homoallyl alcohol (**3**) (or single carboxylic acid in case of carbon dioxide) of the four possible regioisomers (**3**–**6**) shown in eq 1 was found in the crude reaction mixture. This result clearly indicates that both allylzinc formation (**1** → **2**) and carbonyl addition (**2** → **3**) proceeded in a highly regioselective manner, and indeed the latter of these transformations was precedented by the reaction of allylzinc halides with carbonyl compounds.[7,14] On the other hand, the diastereoselectivities with respect to the produced homoallyl alcohols are not outstanding, falling within a range of 1:1.5–1:4 for aldehydes and 1:1–1:2 for ketones. Selectivities in this range are comparable to those reported elsewhere for the additions of allylzinc halides to aldehydes although the sense is known to vary from *threo* to *erythro*.[7,14] The major diastereoisomers in the present reaction were verified to be *erythro* in a couple of cases (Table 1, entries 1 and 6) based on the reported ^1H NMR data[15] or by the following transformation with a known stereochemical outcome (eq 2).[16] Thus, the *erythro* structure was tentatively assigned to the major diastereoisomers formed in the other reactions of isoprene or myrcene and aldehydes by analogy. A few functional groups like aryl bromide, ester, and isolated olefin, which may be reduced with hydride species and/or a low-valent titanium,[17] survived the reaction conditions (Table 1, entries 5, 8, 9, and 14). Chemoselective addition to an aldehyde in the presence of another ketone moiety was also possible (Table 1, entry 4).



(2)

Mechanistic aspects of this reaction would be of particular interest, but have not been extensively explored to date. Lithium hydride and the catalytic amount of Cp_2TiCl_2 unaccompanied by ZnI_2 afforded no trace of the product (**3**). Its use in a large excess (6–10 equiv) to ZnI_2 again inhibited the reaction. These observations clearly exclude the possibility of hydro*lithiation*. The interception of the metallic species **2** with excess H_2O in place of carbonyl compounds yielded a monohydrogenated diene in 110–140% yield based on Zn. Thus, this control experiment ruled out the possibility that catalytic η^3-allyltitanium species **7** (see eq 3 or 4) directly added to carbonyl compounds with a turnover close to 10. Moreover, it reinforces a scenario that the organometallic species **2** is the allylzinc iodide, hydride, and/or diallylzinc. As a result, the mechanism of this reaction should resemble those of other titanium-catalyzed hydrometalation reactions which are suggested to involve the initial addition of "Cp_2TiH" species[18] (generated *in situ* from Cp_2TiCl_2) to the olefinic bond[19] followed by transmetalation with an appropriate, stoichiometric metal hydride species.[6,20] Equation 3 shows an illustrative catalytic cycle of the present hydrozincation based on this hypothesis.

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

(14) Ding, Y.; Zhao, G. *Tetrahedron Lett.* **1992**, *33*, 8177.

(15) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969. Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.

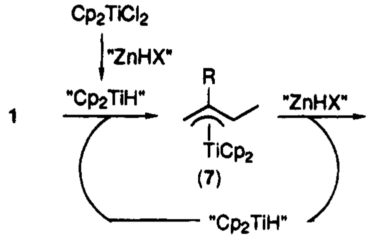
(16) The "Cram" addition of hydrides to ketones gives the *threo* isomers; see: Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Sato, F.; Takeda, Y.; Uchiyama, H.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1132.

(17) Review: Trost, B. M., Ed. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 8. Low-valent titanium has been reported to reduce these functional groups; see: Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367. Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2171; **1980**, *21*, 2175.

(18) Dimeric Cp_2TiH itself is known; see: Bercaw, J. E.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1969**, *91*, 7301.

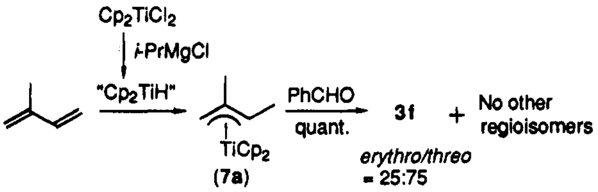
(19) Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1968**, *12*, 149; **1967**, *8*, 115.

(20) Cf. recent discussion on Cp_2TiCl_2-catalyzed hydrometalation: Djadchenko, M. A.; Pivnitsky, K. K.; Spanig, J.; Schick, H. *J. Organomet. Chem.* **1991**, *401*, 1. Burgess, K.; van der Donk, A. *Tetrahedron Lett.* **1993**, *34*, 6817.



(3)

In accord with this formulation, the direction and degree of regioselection in the step of the formation of allylzinc species **2** in eq 3 are identical with those of the generation of $Cp_2(\eta^3\text{-allyl})Ti$ complex (**7**) from butadienes and a stoichiometric amount of Cp_2TiCl_2,[19] as exemplified by the synthesis of **3f** in eq 4.[21,22] (Note that the diastereoselection found in **3f** was reversed this time.) Thus, this fact reasonably justifies the involvement of the common allyltitanium intermediate **7** also in the catalytic cycle of hydrozincation depicted in eq 3.



(4)

The above hydrozincation will be extended to other unsaturated substrates. Applications of the resultant organozinc reagent in organic synthesis and further studies to provide insight into the course of the reaction are currently underway in our laboratory.

Supplementary Material Available: Typical procedures for the preparation of **3d**, **f**, and **m**, structural determination of **3f**, and physical properties of **3a**–**n** (9 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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[21] Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett* **1981**, *22*, 243. Klei, E.; Teuben, J. H.; Meijer, H. J. de L. *J. Chem. Soc., Chem. Commun.* **1981**, *342*. Klei, E.; Teuben, J. H.; Meijer, H. J. de L.; Kwak, E. J.; Bruins, A. P. *J. Organomet. Chem.* **1982**, *224*, 327.

[22] Gao, Y.; Iijima, S.; Urabe, H.; Sato F. *Inorg. Chim. Acta* **1994**, *222*, 145.