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PREPARATION OF ALLYLIC ALCOHOLS BY ALKENE TRANSFER FROM ZIRCONIUM TO ZINC

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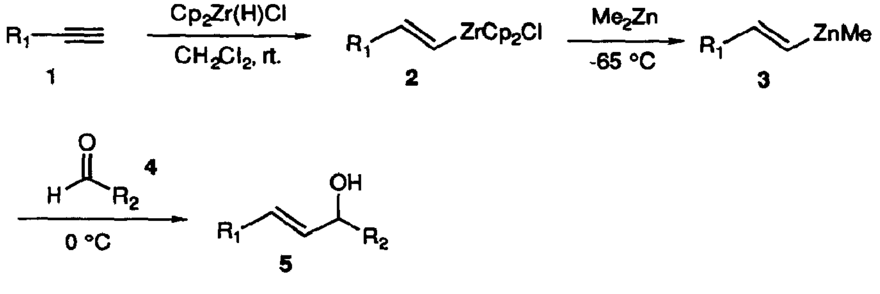
Abstract: Transmetalation of alkenyl zirconocenes **2** to the corresponding organozinc compounds **3** occurs rapidly and at low temperature in the presence of stoichiometric amounts of commercially available dimethyl- or diethylzinc. Subsequent addition of aldehydes provides an *in situ* protocol for the conversion of alkynes **1** into allylic alcohols **5** in good to excellent yields.

The hydrozirconation of alkynes and alkenes with Cp_2ZrHCl (Schwartz's reagent) allows the convenient preparation of a wide range of functionalized organozirconocenes.[2] However, the organozirconium species are relatively unreactive toward organic electrophiles, therefore catalysis or transmetalation procedures are often required in alkylation reactions. These aspects of zirconium chemistry are well illustrated by the transmetalation to other transition metals such as Cu and Ni in conjugate addition and cross-coupling reactions,[3] and the additions of cationic organozirconium reagents to oxiranes[4] and aldehydes.[5]

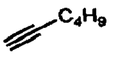
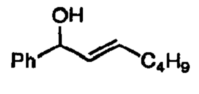
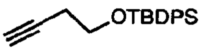
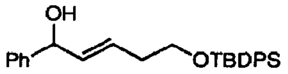
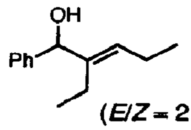
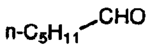
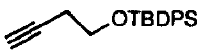
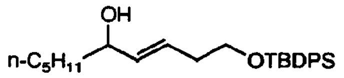
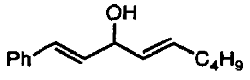
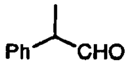
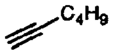
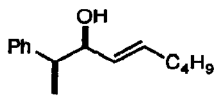
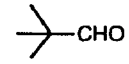
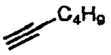
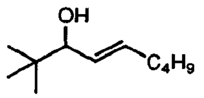
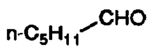
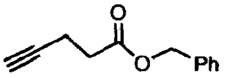
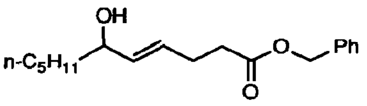
In the course of our investigations of transmetalation reactions,[6] we have studied the additions of alkenylzirconocene complexes to aldehydes via transmetalation reactions to zinc species.[7] In this paper we report that this methodology indeed significantly accelerates the addition of organozirconocenes to aldehydes, thereby offering a new pathway for stereocontrolled C-C bond formation (Scheme 1).

Scheme 1



Hydrozirconation of alkynes **1** with zirconocene hydrochloride gave (*E*)-alkenylzirconocenes **2** that were directly treated with Me_2Zn at -65 °C. The Zr→Zn transmetalation was complete within a few minutes.[8] Addition of aldehydes **4** to the resulting zinc reagents **3** provided allylic alcohols **5** in 54-94% yield. These results are summarized in Table 1.

Table 1. Reaction of *in situ* generated alkenylalkylzinc reagents with aldehydes.[a]

entry	aldehyde	alkyne	time (hr)	product[b]	yield[c] (%)
1	PhCHO		1		86[d], 93[e], 93[f], 87[g,f], 0[f,h]
2	PhCHO		2		89[f]
3	PhCHO		5	 (*E/Z* = 2.5:1)	78[f]
4			2.5		83[f]
5			1.5		94[f]
6			1.5	 (*syn:anti* = 85:15)	92[f]
7			2		54[f]
8			2		72[f]

[a] Me_2Zn was used unless otherwise mentioned. [b] All new compounds were characterized by IR, ^1H and ^{13}C NMR, and MS. [c] Yields are based on aldehydes and refer to isolated, purified products. [d] Solvent was hexane. [e] Solvent was toluene. [f] Solvent was CH_2Cl_2. [g] Et_2Zn was used. [h] No dialkyl zinc was used.

Examination of Table 1 reveals the following trends. CH_2Cl_2 is as good a solvent as either hexane or toluene for the transmetalation to zinc and the subsequent addition to aldehydes (entry 1). The advantage of using CH_2Cl_2 is that hydrozirconation proceeds much faster in CH_2Cl_2 than in toluene or hexane. The use of either Me_2Zn or Et_2Zn has a similar effect. No methyl- or ethyl-transfer products could be found, consistent with an exclusive alkenyl vs. alkyl group transfer from **3** to the aldehydes. The formation of (*E*)-allyl alcohols from terminal alkynes reveals stereochemical retention in transmetalation and addition steps **2**→**3**→**5**. However, the 2.5:1 (*E*/*Z*) ratio of the product in entry 3 is quite surprising. Since neither hydrozirconation[2] nor addition of alkenylzinc reagents to aldehyde[9] seems likely to induce isomerization, the configuration inversion leading to (*Z*)-product occurred probably during the migration of the alkenyl group from zirconium to zinc. The use of α,β-unsaturated aldehyde results in bisallylic alcohols, and no conjugate addition product is observed (entry 5). Silyl ether and ester functional groups can be tolerated in these reactions (entries 2, 4, and 8). Addition to the sterically hindered pivaldehyde occurs in 54% yield (entry 7). In the absence of dialkylzinc reagent, no reaction occurs (entry 1).

The reactivity of the alkenylzinc reagents prepared in this transmetalation protocol is comparable to the standard organozinc halide/Lewis acid combination.[10] The residual organozirconium species probably serve as activating co-reactants. In contrast to the Ag(I)-catalyzed reaction of organozirconocenes,[5] the addition to α-substituted aldehydes can be achieved stereoselectively via the zinc intermediates (entry 6). The *syn*-isomer is formed predominantly, as was found to be the case for organometallics of the type R-Cu(CN)ZnI in the presence of BF_3-etherate.[11]

A typical procedure is as follows: A solution of 1-hexyne (52 mg, 0.64 mmol) in 2 mL of CH_2Cl_2 was kept under an atmosphere of N_2 and treated at room temperature with zirconocene hydrochloride (160 mg, 0.64 mmol). The mixture was stirred at room temperature until a homogenous solution formed and cooled to -65 °C. Dimethyl zinc (0.33 mL, 2.0 M solution in toluene) was added over 5 min. The reaction mixture was immersed in an ice bath and a solution of trans-cinnamaldehyde (70 mg, 0.53 mmol) in 2 mL of CH_2Cl_2 was added over 10 min. The reaction mixture was stirred at 0 °C for 1.5 h. After addition of saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and filtered through florisil. Evaporation of the solvents and chromatography of the residue on SiO_2 (EtOAc/hexanes, 1 : 3) yielded (1*E*, 4*E*)-1-phenyl-1,4-nonadien-3-ol (108 mg, 94%).

In summary, we have described the successful addition of alkenylzirconocene reagents to aldehydes via *in situ* transmetalation to organozinc species. Applications of this methodology to alkylzirconocene reagents[12] as well as the asymmetric synthesis of secondary allylic alcohols[13,14] are the subject of further studies in our laboratories.

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References and Notes

1. Eli Lilly Grantee, 1993-1994; Alfred P. Sloan Research Fellow, 1994-1995; recipient of an American Cyanamid Faculty Award, 1994.

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8. According to our preliminary NMR investigations, the ligand exchange between Zr and Zn appears to be almost complete. Upon addition of dimethyl zinc to hexenylzirconocene at -65 °C, the doublet at 7.00 ppm (1 H, J = 18.0 Hz), characteristic for Zr-C_{sp^2}(H), was significantly reduced in intensity, and a new doublet at 6.24 ppm (1 H, J = 22 Hz) appeared. For reference spectral data, see: (a) Erker, G.; Kropp, K. *Organometallics* **1983**, *2*, 1555. (b) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. (c) Visser, H. D.; Oliver, J. P. *J. Organometal. Chem.* **1972**, *40*, 7.

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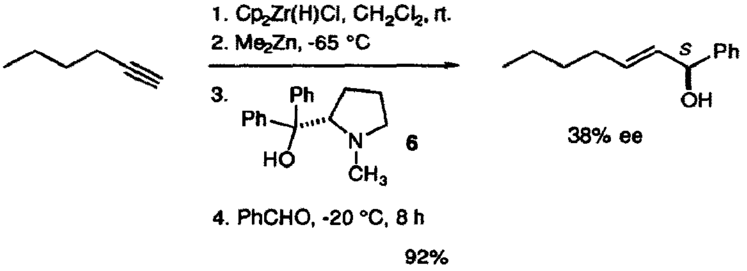
12. Stepwise treatment of 1-hexene with zirconocene hydrochloride, dimethyl zinc and benzaldehyde gave only 28-30% yield of 1-phenyl-1-heptanol after 10 h at room temperature.

13. In the presence of catalytic amounts (8 mol%) of proline-derived ligand **6**, the addition of 1-hexenyl zirconocene chloride to benzaldehyde via *in situ* transmetalation to zinc resulted in optically active product:



14. For the catalytic asymmetric synthesis of allylic alcohols from alkynes or alkenes and aldehydes via hydroboration and B→Zn transmetalation, see: (a) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (b) Langer, F.; Waas, J.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 5261.

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