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HIGHLY STEREOSELECTIVE AND GENERAL SYNTHESIS OF (Z)-3-METHYL-2-ALKEN-1-OLS VIA PALLADIUM-CATALYZED CROSS COUPLING OF (Z)-3-IODO-2-BUTEN-1-OL WITH ORGANOZINCS AND OTHER ORGANOMETALS

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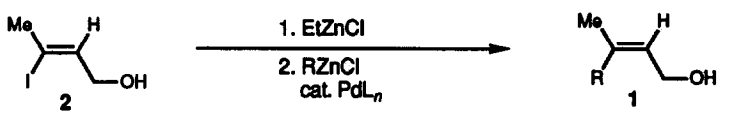
Summary: The reaction of Zn-protected (Z)-3-iodo-2-buten-1-ol with organozincs in the presence of 1-5 mol % of a Pd complex, e.g., $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ and *n*-BuLi (2 equiv), in DMF provides a highly stereoselective (≥96%), general, and high-yielding procedure for preparing (Z)-3-methyl-2-alken-1-ols, while the use of organometals containing B and Sn along with a Pd catalyst or organocoppers alone gives the desired products in moderate to good yields.

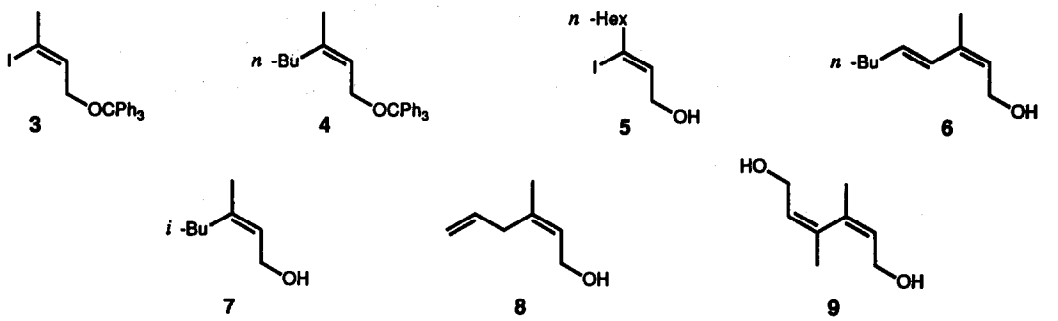
2-Alken-1-ols containing a 2- or 3-methyl group are important as both structural units in and precursors to various natural products. In our recent studies it became desirable to develop a strictly stereoselective route to **1**. Most of the stereoselective methods involve selective alkyne addition reactions. Some involve formation of the C-C bond between Me and the alkene group, requiring an alkyne substituted with R.[2] Alternatively, selective addition reactions of propyne derivatives requiring formation of the C-C bond between R and the alkene group have also been developed as routes to **1**. Alkylation of (Z)-3-iodo-2-alken-1-ols with organocoppers,[3] developed for the preparation of the *E* isomers of **1** is, in principle, applicable to the synthesis of **1** as well, but little is currently known about it. More developed is a method involving carbocupration of propyne,[4] but its current scope is essentially limited to those cases where R is alkyl. We now report that the Pd-catalyzed reaction of (Z)-3-iodo-2-buten-1-ol (**2**) with organometals,[5] especially those containing Zn, provides a selective, high-yielding, and convergent route to **1**.



(1)

We initially treated **2** and its trityl (Ph_3C) derivative (**3**) with *n*-BuLi.[6] However, the desired *n*-butylation product was obtained only in a very low (<5%) yield along with 2-butyn-1-ol and other unidentified products. The use of $LiCu(Bu\text{-}n)_2$[7] and $Li_2CuCN(Bu\text{-}n)_2$[8] in place of *n*-BuLi did produce **1a** (R = Bu-*n*) from **2** in 42 and 60%, respectively. Similarly, the reaction of **3** with $Li_2CuCN(Bu\text{-}n)_2$ gave **4** in 49% yield. All of the desired products were ≥98% Z. However, distinctly more favorable results were obtained by the use of *n*-BuZnCl,[9] generated *in situ* by the treatment of *n*-BuLi with dry $ZnCl_2$, and a catalytic amount (1-5 mol %) of a Pd complex, such as $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ and *n*-BuLi (2 equiv)[10] in DMF. Thus, **2** and **3** were converted to **1a** and **4** in 77 and 98% yields, respectively, within 16 h at 25 °C. These products were also ≥98% Z. The use of polar aprotic solvents, such as DMF, is critically important, because the use of THF in place of DMF led to a <10% yield of **4** after 16 h at 25 °C. Cumbersome trityl protection-deprotection

can be readily circumvented by treating **2** with an ethylzinc halide generated *in situ* by the treatment of EtMgBr with dry $ZnCl_2$. In this manner, the sacrificial use of one equivalent of a more precious organozinc reagent can be avoided.



As the results presented in Table I indicate, the procedure is indeed very general. Thus, it can accommodate various alkyl, aryl, alkenyl, and alkynyl groups as R. On the other hand, the use of allylzinc bromide did not give the desired product in a significant yield (<5-10%). In all cases where the products were isolated and identified, the stereoselectivity of the reaction was >96-98% *Z*, the *E* isomers being undetectable by ^1H and ^{13}C NMR spectroscopy. That the applicability of the current method is not limited to the preparation of **1** is readily seen in the satisfactory conversion of (*Z*)-3-iodo-2-nonen-1-ol (**5**) into the benzyl and phenylethynyl substituted derivatives in 82 and 98% yields respectively. For comparison of various metals used in the Pd-catalyzed cross coupling[11] the reactions of (*E*)-1-hexenylmetals containing Al, B, Sn, Zn, and Zr with **2** were carried out using the procedures recommended in the literature. The decreasing order of the yields of **6** was: Zn[11] (81%), Sn[12] (68%), B[13] (52%), Al plus $ZnCl_2$[11] (49%), and Zr plus $ZnCl_2$[11] (21%). In the reaction of (*E*)-1-hexenyldiisobutylalane **7** was also formed in 37% yield. It is noteworthy that allyltributylstannane reacted with **2** in the presence of 2 mol % of $Pd(PPh_3)_4$ in refluxing benzene for 20 h to give **8** in 55% yield, whereas the use of the generally more favorable catalyst, i.e., $Cl_2Pd(MeCN)_2$,[12a] and DMF gave no more than traces of **8**. The use of 3-metallo derivatives of **2** was also investigated. Dilithiation of **2** followed by treatment with 2 equiv of $ZnCl_2$ did not provide a satisfactory reagent, and attempted lithiation with *t*-BuLi of *t*-$BuMe_2Si$-protected **2** led to known *O*-to-*C* silyl migration.[14] On the other hand, the thexyldimethylsilyl[15] derivative of **2** was cleanly lithiated (*t*-BuLi) and then zincated ($ZnCl_2$) at -110 °C. The resultant reagent smoothly reacted with (*E*)-1-iodo-1-hexene, allyl bromide, and the thexyldimethylsilyl derivative of **2** in the presence of 5 mol % of $Pd(PPh_3)_4$ in DMF at 25 to 50 °C to give **6** (84%), **8** (71%), and **9** (78%), respectively, in the yields shown in parentheses.

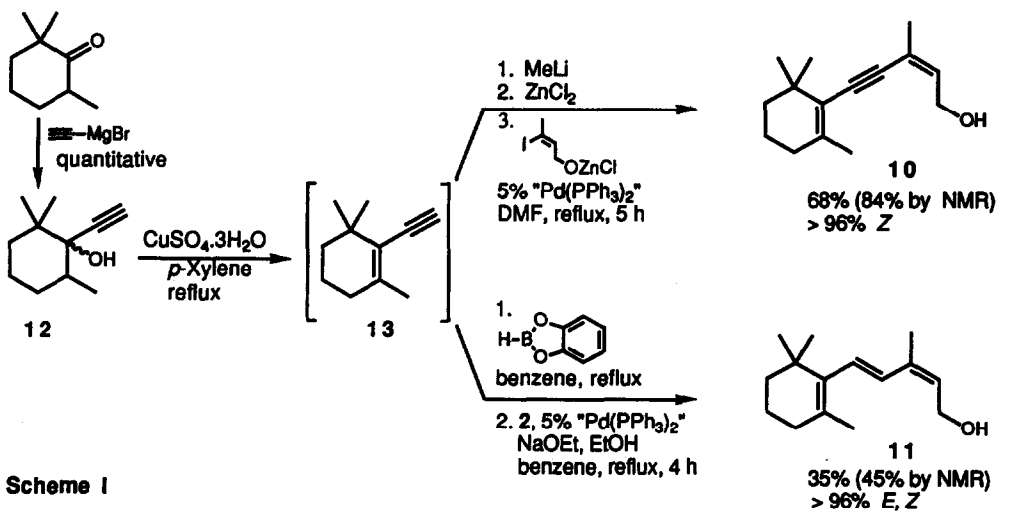
The preparation of **10**[16]and **11**[17] (Scheme I), which can serve as intermediates for the stereoselective synthesis of (9*Z*)-retinoids and carotenoids[17,18] via **12** and *in situ* generated **13**,[19] indicates the potential synthetic value of the current procedure. From a broader synthetic viewpoint *it has now been experimentally demonstrated that (Z)-3-methyl-2-alken-1-ols containing virtually the entire range of carbon groups can be synthesized in a highly stereoselective manner by the Pd-catalyzed cross coupling using 2*. Its application to the synthesis of various natural products is underway.

The following procedure is representative. 2-Lithioanisole, generated by treating 2-bromoanisole (1.2 mmol) with *t*-BuLi (2.4 mmol) in ether at -78 to 0 °C, was added to dry $ZnCl_2$ (1.2 mmol) in THF. To this was added the zinc derivative of **2**, generated by treating **2** (1.0 mmol) with an ethylzinc derivative which, in turn, was generated by treating

Table I. (*Z*)-3-Methyl-2-alkene-1-ols via Palladium-Catalzyed Cross Coupling of (*Z*)-3-Iodo-2-buten-1-ol with Organozincs in DMF

R of RZnCl[a]	Protecting Group of 2	Catalyst[b]	Yield[c] of 1, %
n-Bu	ZnCl	A	77 (60)
n-Bu	CPh_3	A	>98 (97)
n-Bu	$SiMe_2Bu$-*t*	B	90 (83)
n-Hex	ZnCl	A	80 (64)
i-Bu	ZnCl	B	54 (43)
$PhCH_2$	ZnCl	A	>98 (90)
$CH_2{=}CH(CH_2)_2$	ZnCl	B	84 (75)
$Ph(CH_2)_2$	ZnCl	B	72 (59)
$MeC{\equiv}C(CH_2)_2$	$SiMe_2Bu$-*t*	B	>98 (92)
(*E*)-*n*-BuCH=CH	ZnCl	B	81 (73)
p-Tol	ZnCl	A	93 (80)
o-$MeOC_6H_4$	ZnCl	B	97 (88)
p-ClC_6H_4	ZnCl	B	80 (78)
n-Hex$C{\equiv}C$	ZnCl	A	92 (67)
$PhC{\equiv}C$	ZnCl	A	>98 (90)
13	ZnCl	A	84 (68)

[a]RZnCl/2 = 1.2. [b]A = $Cl_2PdPPh_3)_2$ + 2*n*-BuLi. B = $Pd(PPh_3)_4$. The amount of the Pd catalyst was 5 mol %. [c]By ^1H NMR or GLC. The numbers in parentheses are isolated yields.



Scheme I

EtMgBr (1.0 mmol) with dry $ZnCl_2$ (1.0 mmol). After addition of $Pd(PPh_3)_4$ (0.05 mmol) and DMF (2 mL) the reaction mixture was stirred overnight at 25 °C, worked up in the usual manner, and chromatographed (silica gel, hexane/EtOAc = 70/30) to give (*Z*)-3-(*o*-anisyl)-2-buten-1-ol (0.16 g, 88%).

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REFERENCES AND NOTES

(1) (a) Postdoctoral Fellow on funds partially provided by NATO (TUBITAK), on leave from Ankara University, Turkey. (b) On leave from UBE Industries, Japan.

(2) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1853. (c) Sato, F.; Ishikawa, H.; Watanabe,H.; Miyake, T.; Sato, M. *J. Chem. Soc., Chem. Commun.*, **1981**, 718.

(3) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. (b) For a modified procedure, see Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(4) (a) For a review, see Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.

(5) (a) For the original use of organozincs in the Pd-catalyzed cross coupling, see Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821; King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) For a review, see Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) For methylation of (*Z*)-3-iodo-2-alken-1-ols, see Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem* **1986**, *51*, 4080.

(6) Linstrumelle, G. *Tetrahedron Lett.* **1974**, 3809.

(7) For a review, see Posner, G. H. *Org. React.* **1975**, *22*, 253.

(8) For a review, see Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(9) For the original use of alkylzincs in the Pd-catalyzed cross coupling see (a) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 1871. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. For a recent review, see Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(10) For generation of an active Pd(0) catalyst by this reaction, see Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Organomet. Chem.* **1987**, *334*, 181.

(11) (a) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N.; Luo, F. T. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (b) Negishi, E.; Owczarczyk, Z.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453. (c) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683.

(12) (a) For a procedure using $Cl_2Pd(MeCN)_2$ in the absence of a phosphine, see Bumagin, N. A.; Bumagina, I. G.; Kashin, A. N.; Beletskaya, I. P. *Zh. Obshch. Khim.* **1982**, *52*, 714. (b) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551. (c) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

(13) (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(14) Kim, K. D.; Magriotis, P. A. *Tetrahedron Lett.* **1990**, *31*, 6137.

(15) Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515.

(16) For a non-stereoselective preparation of **10**, see Inhoffen, H. H.; Erdmann, D. *Liebigs Ann. Chem.* **1956**, *598*, 51.

(17) For a non-stereoselective preparation of **11**, see Robeson, C. D.; Cawley, J. D.; Weisler, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111.

(18) For a review, see Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931.

(19) (a) Julia, M.; Descoins, C. *Bull. Soc. Chim., Fr.* **1962**, 1939. (b) Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Patcliffe, N. M.; Worthington, P. A. *J. Chem. Soc. Perkin Trans. I* **1983**, 1579.

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