

Coupling between Vinyl or Aryl Iodides and Vinyl Zinc Bromides (either Bearing an Alkoxy Moiety or Trisubstituted) under Pd(0) Catalysis

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Abstract: A *tert*-butoxy group in allylic or homoallylic position on vinyl zinc bromides does not hinder their coupling with *p*-iodoanisole under Pd(0) catalysis, as does a methoxy group. Furthermore, use of a polar solvent and of a stoichiometric amount of CuBr greatly enhances the reactivity of a trisubstituted vinylic zinc reagent towards vinyl or aryl iodides under Pd(0) catalysis.

Coupling reactions of vinyl zinc halides with aromatic or vinylic halides are usually performed in tetrahydrofuran, with a catalytic amount of palladium - phosphine complex. These conditions afford satisfactory results with unsubstituted or disubstituted vinyl zinc reagents¹. To our knowledge, such reactions have not been reported when the vinyl zinc derivative either bears an oxygen moiety or when it is trisubstituted. We describe herein the results of our first investigations in both cases.

When β or β,β' - disubstituted vinyl zinc bromides, bearing a *primary* allylic or homoallylic oxygen atom *cis* to the metal, were submitted to arylation² under the usual conditions (THF, Pd(PPh₃)₄), we observed either excellent couplings, or a complete failure according to the nature of the ether moiety (see Table 1). Thus, an allylic or homoallylic *tert*-butyl ether is tolerated (entry 2,5 and 7) but not a methyl ether (entry 1 and 4), which probably coordinates more efficiently to the zinc atom. The influence of a bulky *thexyldimethylsilyl* ether is even more dramatic since the reaction occurs when it is located in homoallylic but not in allylic position (entry 3 and 6). Furthermore, a *secondary* allylic or homoallylic *tert*-butyl ether *cis* to the metal (entry 8 and 9) also allows a good coupling³.

When we employed the standard conditions stated above, with compound **1**⁴, very low yields (< 10%) of vinylation or arylation were obtained (eq. 1).

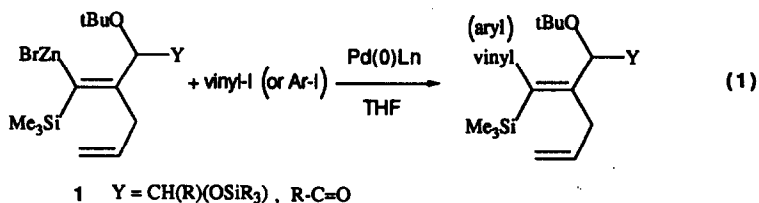
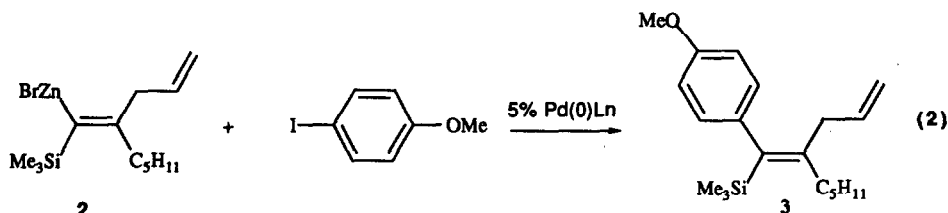


Table 1 : Arylation of (Z) Vinyl Zinc Bromides Bearing an Alkoxy Substituent in Allylic or Homoallylic Position by *p*-Iodoanisole^a

Entry	substrate ^b	R	Yield % ^c
1		Me	0
2		<i>t</i> -Bu	80 (77)
3		SiMe ₂ thex	0
4		Me	0
5		<i>t</i> -Bu	82 (78)
6		SiMe ₂ thex	70 (62)
7			74 (68)
8			(60)
9			(60)

^a Conditions : THF, Pd(PPh₃)₄, 20°C, 0.5 to 1h. ^b prepared from the corresponding iodoalkene by metallation with *t*-BuLi in -80°C and transmetallation with ZnBr₂ in THF at 0°C. ^c G.C. Yields, isolated yields in parentheses.

This failure should result from the steric hindrance brought by the trisubstitution pattern, since the presence of a *tert*-butoxy group in allylic position is of no consequence here, according to the preceding study. To overcome this difficulty, we first studied the coupling of the simple trisubstituted vinyl zinc halide **2**⁵ with *p*-iodoanisole, in the presence of tetrakis(triphenyl)phosphine palladium (eq. 2)



When run in THF in the presence of 5% Pd(PPh₃)₄ at 65°C for 24h, this reaction gives a 20-25% yield in **3**. A more basic solvent like dimethyl acetamide⁶ (DMA) added to THF in a 3/7 ratio, has a dramatic influence, the reaction being over within 1 hr at 65°C (yield 76%). A second improvement was brought by the presence of copper bromide, either catalytic (0.1 equiv., 24h, 20°C, yield 71%) or stoichiometric (1 equiv., 1h, 20°C, yield 73%). Such beneficial influence of Cu(I) salts in the palladium catalyzed arylation or vinylation of vinylstannanes has been reported by Marino⁷ and Liebeskind⁸ who used catalytic amounts of CuI. In the present case, the reaction can now be performed at room temperature.

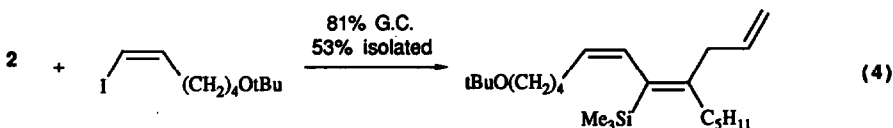
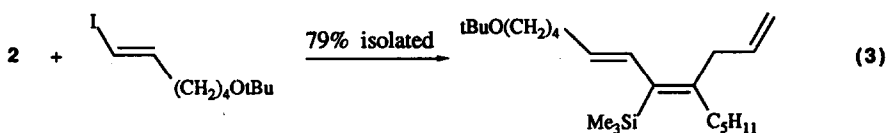
Finally, the yield could be slightly improved by using a ligand deficient catalyst such as Pd(PPh₃)₂, prepared *in situ* by reduction of PdCl₂(PPh₃)₂ with 2 equiv. of diisobutylalane and used at room temperature (Table 2).

Table 2. Influence of the Nature of the Catalyst on Reaction (2)^a

catalyst	temperature (°C)	time (h)	G.C. yield %
Pd (PPh ₃) ₄	65	1	76
" "	20	1	73 ^b
PdCl ₂ (PPh ₃) ₂ + 10% DIBAH	65	1	52
" "	20	0.5	83 ^b

^a solvent : THF/DMA (7/3). ^b in the presence of 1 equiv. of CuBr. When a mixture containing CuBr is warmed (65°C), side reactions occur.

Thus, coupling according to equation 2 is best performed (83%) when a THF/DMA mixture (7/3) is used with 5% of *in situ* prepared Pd(PPh₃)₂ and a stoichiometric amount of copper bromide at room temperature for 0.5h^{9,10}. Under these conditions, an *E* or *Z* vinylic iodide reacts in the same way (eq. 3 and 4).



However, in the case of the vinyl zinc reagents bearing a methoxy group (Table 1, entry 1, 3 and 4), the addition of DMA and copper salts did not improve the result.

In summary, the scope of the palladium catalyzed vinylation or arylation of trisubstituted vinyl zinc bromides, bearing no methoxy group in allylic or homoallylic position, can be enlarged appreciably by use of copper bromide in THF/DMA. An allylic or homoallylic *tert*-butoxy substituent, contrary to a methoxy one, does not impede the condensation.

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REFERENCES AND NOTES

1. Negishi, E.I. *Acc. Chem. Research*, 1982, 340, and references cited herein.
2. *p*-Iodoanisole was chosen as a representative, since it is well known that, if such Pd(0) catalyzed arylation works with an electron-donating group substituted iodobenzene, it will work even more easily with iodobenzene or with an electron-withdrawing group substituted iodobenzene.

3. All synthesized compounds described in this paper exhibited spectral properties (^1H NMR, ^{13}C NMR, IR) in accordance with the assigned structures.
4. Compounds **1** were prepared *in situ* in 4 steps from 1-trimethylsilyl-3-*tert*-butoxy-prop-1-yne in THF by metallation with *n*-BuLi (-80°C, 25 min), addition of allyl zinc bromide (-80°C), warm up to 20°C, heating 30 min at 65°C, addition of an electrophile (ex. RCHO/TMSCl) at -80°C, then warm up to 20°C. For such Metalla-Claisen reaction, see : Normant, J.F. ; Quirion, J.Ch. ; Alexakis, A. ; Masuda, Y. *Tetrahedron Lett.* **1989**, *30*, 3955.
5. Preparation of **2** according to Molander, G.A. *J. Org. Chem.*, **1983**, *48*, 5409.
6. Amides have been used as solvents in Pd(0) catalyzed reactions of stannanes and zinc reagents, see for example : a) Beletskaya, I.P. *J. Organomet. Chem.* **1983**, *250*, 551. b) Scott, W.J. ; Stille, J.K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. c) Tamaru, Y. ; Ochiai, H. ; Sanda, F. ; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5529.
7. Marino, J.P. ; Long, J.K. *J. Am. Chem. Soc.* **1988**, *110*, 7916.
8. a) Liebeskind, L.S. ; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293. b) Liebeskind, L.S. ; Fengl, R.W. *J. Org. Chem.*, **1990**, *55*, 5359.
9. The vinylation or arylation of compounds **1** were successful under these conditions. (Paper submitted to publication).
10. Typical procedure : compound **2** was prepared from the iodo derivative (1.0 mmol in 5 mL dry THF) by metallation with *t*-BuLi in pentane (2.2 mmol) at -80°C, then warm up to -10°C, followed by addition of ZnBr₂ (1.2 mL of a 1M solution in dry THF) at -80°C. After warm up to 15°C, a mixture of *p*-iodoanisole (or *E* or *Z* vinylic iodide) (1.0 mmol) and Pd(0)L_n (0.05 mmol) in DMA (5.5 mL) was added, eventually followed by the addition of CuBr (1.0 mmol). The reaction generally turned dark (within a few minutes). It was controlled by GC, and, when achieved, treated with aqueous NH₄Cl/NH₃, extracted with ether. The organic phase was stirred for 2h with Na₂S crystals (to remove zinc salts), filtered on cellite. The organic phase was washed twice with brine, dried over MgSO₄, concentrated and purified by flash chromatography on silica gel, eluted with cyclohexane / ethyl acetate mixtures.

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