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Trisubstituted alkenes from alkynes and aryl iodides by boron-to-zinc transmetallation and palladium(0) catalyzed cross coupling

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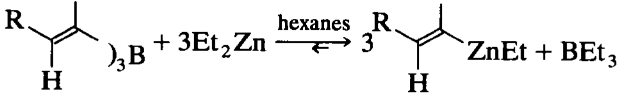
Abstract

Alkenylethylzincs, obtained from the corresponding trialkenylboranes by transmetallation with diethylzinc, couple with aryl iodides in the presence of $Pd(PPh_3)_4$, 0.19–0.28 mol%, to produce trisubstituted alkenes in good isolated yields. Both the transmetallation and subsequent coupling occur with complete retention of stereochemistry.

Alkenes of defined stereochemistry are important in synthetic methodology, natural product synthesis, in the perfume and cosmetic industry, and in medicine, to name but a few applications [1]. The stereoselective construction of alkenes is, therefore, of great importance and has justly been the object of many fine studies. One of the more general routes to stereodefined alkenes is the cross coupling reaction and its various modifications [2]. Particularly good partners for the cross coupling of vinyl/aromatic halides with organometallic reagents are alkenylzincs [3]. However, stereodefined alkenylzincs are usually themselves obtained by a multistep methodology [4], limiting their more extensive use in synthesis. Hydrometallation of alkynes is a good method of modifying double bonds stereoselectively [5]. One of the most versatile hydrometallation protocols is without a doubt hydroboration of alkynes [6]. Thus hydroboration of alkynes under suitable conditions generates alkenylboranes of defined stereochemistry and in high chemical yields. Unfortunately, alkenylboranes do not readily undergo cross coupling with vinyl/aromatic halides. Suzuki and co-workers [7] have discovered that base is required for the reaction to proceed satisfactorily, and under their best conditions 3–5 mol% palladium catalyst is required. In addition a relatively long time in refluxing THF is generally part of the protocol. On the other hand, alkenylzincs are known to couple with vinyl/aromatic halides under milder conditions [3]. Recently, we have shown that alkenylboranes are readily transmetallated with dialkylzincs, in particularly diethylzinc, to give essentially pure alkenylzincs [8]. Depending on the ratio of boron-to-zinc, either alkenylethylzincs or dialkenylzincs are the predominant zinc species. Thus in a 1:3 stoichiometry of boron to zinc, alkenylethylzincs are preferentially formed (eqn. (1)). The reaction time for transmetallation is short, 5–10 min in hexanes at 25°C, and the alkenyl groups are transferred quantitatively to zinc. We subsequently demonstrated that these alkenylzincs react readily with aldehydes to generate allylic alcohols under conditions where alkenylboranes do not react [8].



(1)

We now report that alkenylethylzincs, generated by transmetallation from the corresponding alkenylboranes, readily couple with a variety of aryl iodides in

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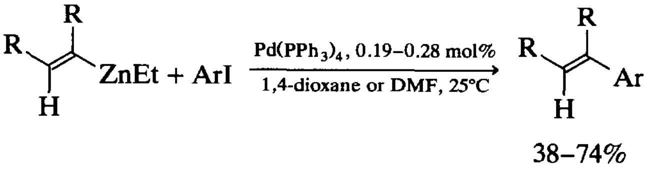
the catalytic presence of palladium(0) to provide trisubstituted alkenes in good isolated yields (eqn. (2)).



(2)

In the present case we found that a stoichiometry of 1:3 alkenylborane to diethylzinc affords the best yields of coupling product. This ratio of alkenylborane to diethylzinc in hexanes is expected to yield predominantly alkenylethylzincs, since it has been demonstrated that in the case of mixed dialkylzincs, R^1R^2Zn, prepared by reacting $(R^1)_2Zn$ and $(R^2)_2Zn$, the equilibrium greatly favors the mixed dialkylzinc, especially when one of the R groups attached to zinc is an alkenyl group [9]. Initially we studied the coupling reaction of iodobenzene and (ethyl)((*E*)-4-octenyl)zinc under a variety of conditions. Catalyst and solvent are crucial to the success of the present methodology. Hydrocarbon solvents, such as hexanes, or weakly coordinating solvents, such as ethyl ether, in which transfer of the alkenyl groups from boron to zinc was shown to be fast, were ineffective. More strongly coordinating solvents markedly increased the yield of the coupling product. Thus either 1,4-dioxane or dimethylformamide were highly compatible with the reaction conditions. On the other hand, TMEDA proved incompatible, probably due to irreversible complexation with the zinc species [10]. Nickel catalysts were not suitable under the present conditions, and their use resulted in low yields or no reaction. The results are summarized in Table 1. The alkenylethylzincs reported here are thermally stable in solution at room temperature for a number of hours. Stability of the alkenylzincs is greatly enhanced by adding donating solvents such as 1,4-dioxane, or DMF [11*]. Dialkyl(alkenyl)boranes undergo transmetallation from boron to zinc as well. Thus, Oppolzer and Radinov, using our procedure have very recently demonstrated that dicyclohexyl(alkenyl)boranes are effective reagents in the transmetallation step. Only the alkenyl group transfers to zinc under their conditions [12*]. Their modification greatly expands the scope of the procedure.

TABLE 1. The effect of solvent and catalyst on the reaction of (ethyl)((*E*)-4-octenyl)zinc with iodobenzene [a]

Reaction	Solvent [b]	Catalyst, mol% [c]	Yield, % (GC) [d]
1	Hexanes	Pd(PPh$_3$)$_4$, 0.30	14.6
2	Dichloromethane	Pd(PPh$_3$)$_4$, 0.20	10.8
3	Ethyl ether	Pd(PPh$_3$)$_4$, 0.20	24.0
4	THF	Pd(PPh$_3$)$_4$, 0.17	58.0
5	1,4-Dioxane (1 equiv.)	Pd(PPh$_3$)$_4$, 0.20	35.3
6	1,4-Dioxane (4 equiv.)	Pd(PPh$_3$)$_4$, 0.37	72.1
7	Dimethoxyethane (4 equiv.)	Pd(PPh$_3$)$_4$, 0.53	62.0
8	TMEDA (1 equiv.)	Pd(PPh$_3$)$_4$, 0.20	0
9	DMF (4 equiv.)	Pd(PPh$_3$)$_4$, 0.20	70.0
10	1,4-Dioxane (4 equiv.)	Ni(dpe)$_2$Cl$_2$, 1.90	0
11	THF	Ni(dpe)$_2$Cl$_2$, 1.20	19.2
12	1,4-Dioxane (4 equiv.)	Ni(acac)$_2$, 2.20	0

[a] Organoborane to organozinc ratio of 1:3. [b] See Experimental. [c] Based on alkenyl groups on boron. [d] In the presence of an internal standard.

Under a standard set of conditions (1,4-dioxane or DMF, Pd(PPh$_3$)$_4$) *in situ* generated alkenylethylzincs were allowed to react with several representative aryl iodides (Table 2). Addition of an aryl iodide to a solution of catalyst and *in situ* generated alkenylethylzinc gives rise to a somewhat exothermic reaction. The reaction is complete within 15–20 min (GC). Workup is simple and consists of filtration under an inert atmosphere and removal of volatiles under reduced pressure, followed by column chromatography. The products are isolated in good yields and are stereoisomerically pure as judged by GC, ^{1}H NMR and ^{13}C NMR. As can be seen from Table 2, the reaction is tolerant of various functional groups and is compatible with ethers, esters, and other halides. A particularly important advantage of the present methodology is that only a small amount of palladium catalyst is required (0.19–0.28 mol% based on alkenyl groups, or 0.063–0.093 mol% based on boron). This system is, therefore, at least one order of magnitude more reactive than comparable systems developed by Suzuki and co-workers [7b]. In addition all alkenyl residues on zinc are utilized in the coupling, making for efficient use of the reagent. No competitive cross-coupling involving the ethyl group was observed. The major side-product is derived from homo-coupling of two alkenyl units. Non-symmetrical alkenylboranes undergo the reaction. Thus the zinc reagent derived from 1-trimethylsilylhexyne gives good yield of the cross-coupled product. Finally, since a variety of functionalized and non-functionalized alkenylboranes are available by hydroboration of alkynes [13], the corresponding alkenylethylzincs are equally accessible. In this context, we are investigating additional boron-to-zinc transmetallations and reactions involving the latter species will be reported in due time.

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* Reference number with an asterisk indicates a note in the list of references.

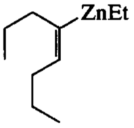
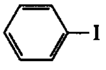
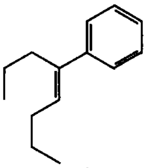
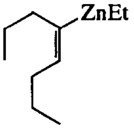
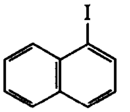
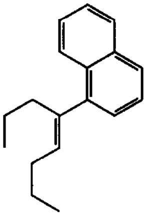
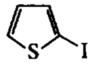
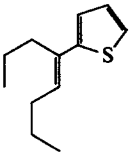
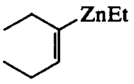
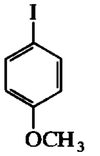
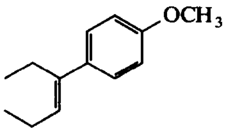
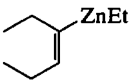
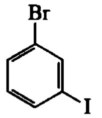
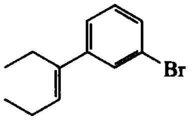
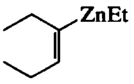
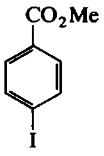
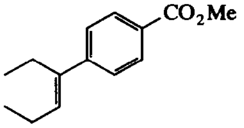
1. Experimental details

Glassware, syringes and needles were oven dried at 120°C, assembled while hot and dried under a flow of argon. Reactions were done under a positive pressure of argon. ^{1}H NMR spectra were obtained at 400 MHz relative to TMS. ^{13}C NMR spectra were obtained at 101 MHz relative to TMS. All solvents were dried and distilled prior to use—hexanes from sodium, 1,4-dioxane from $LiAlH_4$, DMF by azeotropic distillation from benzene. The alkynes were purchased from Farchan and the aryl iodides were purchased from Aldrich. The alkynes were distilled from CaH_2 and stored in ampules under argon. The aryl iodides were used without further purification. Reactions were monitored on a HP 5790A GC fitted with a HP 3393A integrator. Analysis was done on a SE-30 (0.25 mm ID) capillary column. IR spectra were obtained on a Nicolet 60SX FTIR. NMR spectra were run on a Varian VXR-400 instrument. Mass spectra were obtained on a HP 5988A GC/MS fitted with a 25 m methylsilicone capillary column.

1.1. The preparation of (E)-4-phenyl-4-octene

In this typical procedure a 100 ml round bottom flask fitted with a side-arm, teflon-lined stirring bar and gas-regulating valve, was oven-dried for 3–4 h at 120°C, assembled while hot and cooled under a stream of argon. 10 mmol of a 1 M hexanes solution of tris-4-octenylborane was transferred by syringe to the reaction flask and the hexanes were removed under vacuum. Then 10.2 ml 1,4-dioxane (4 equiv) and 30

TABLE 2. Cross coupling of alkenylethylzincs with aryl iodides in the presence of $Pd(PPh_3)_4$ [a]

Reaction	Alkenylzinc [b]	Aryl iodide	Mol% catalyst	Product [c]	Yield, % isolated (GC) [d]
1			0.28		57 (88)
2			0.28		50 (75)
3			0.19		38 (56)
4			0.23		72 (82)
5			0.23		50 (87)
6 [e]			0.24		74 (77)

[a] For typical reaction conditions, see Experimental. [b] Derived from the corresponding borane, see text. [c] All structures are consistent with ^{1}H NMR, ^{13}C NMR, MS and IR. [d] GC crude yield. [e] Reaction run in DMF.

mmol of a 2 M hexanes solution of Et_2Zn were added. The solution was then allowed to equilibrate at 25°C for 10 min after which 98 mg (0.28 mol%) $Pd(PPh_3)_4$ was added while maintaining a positive pressure of argon. Finally, iodobenzene, 3.36 ml (30 mmol) was added dropwise. The reaction is exothermic, with liberation of heat starting while the addition of iodobenzene is still is progress. 5–10 min after the addition, a copious precipitate is observed. After 15–20 min the reaction mixture was diluted with hexanes and filtered under an inert atmosphere. The precipitate was washed with hexanes several times. The combined extracts were then concentrated under reduced pressure during which time a white solid precipitated. The concentrate was triturated with hexanes, and washed successively with HCl_{aq} (most of the white solid dissolved during the acid washing), H_2O, $NaOH_{aq}$, H_2O and finally again with HCl_{aq}. The organic phase was dried over granular Na_2SO_4 and all volatiles removed under reduced pressure. Pure compound was obtained by flash chromatography (Silica gel, 200–425 mesh; hexanes). Yield: 3.19 g (17.0 mmol, 57%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.6, 140.1, 129.2, 128.1, 126.4, 31.75, 30.70, 23.12, 21.86, 14.01 (though only ten peaks were observed, the structure is consistent with other spectral data, *vide infra*); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.346–7.180 (5H, m), 5.656 (1H, t, $J = 7.29$ Hz), 2.492–2.454 (2H, m), 2.200–2.145(2H, m), 1.526–1.422 (2H, m), 1.409–1.315 (2H, m), 0.961 (3H, t, $J = 7.36$ Hz), 0.878 (3H, t, $J = 7.35$ Hz); GCMS (*m/e*): 188 (M^+), 145, 117, 91, 77, 65; FTIR (neat): 3058, 3022, 1599, 1493, 1445, 1378, 894, 756, 697. Anal. Found: C, 88.94; H, 10.89. $C_{14}H_{20}$ (188.314) calcd.: C, 89.29; H, 10.71%.

1.2. (E)-4-(1-naphthyl)-4-octene

The reaction was run as above, except that 1-iodonaphthalene (4.40 ml, 30 mmol) was used. Yield: 3.57 g (15.0 mmol, 50%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.0, 139.5, 133.7, 131.9, 131.2, 128.2, 126.6, 126.1, 125.6, 125.44, 125.41, 125.2, 34.69, 30.33, 23.10, 21.78, 14.16, 14.03; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.996 (1H, dd, $J = 5.94$ and 3.29 Hz), 7.822 (1H, dd, $J = 6.27$ and 3.26 Hz), 7.722 (1H, d, $J = 8.06$ Hz), 7.448–7.415 (2H, m), 7.387 (1H, d, $J = 7.98$ Hz), 7.243–7.212 (1H, m), 5.466 (1H, t, $J = 7.32$ Hz), 2.512–2.473 (2H, m), 2.300–2.245 (2H, m), 1.558–1.466 (2H, m), 1.349–1.256 (2H, m), 1.009 (3H, t, $J = 7.32$ Hz), 0.861 (3H, t, $J = 7.33$ Hz); GCMS (*m/e*): 238 (M^+), 209, 195, 179, 178, 167, 165, 153, 152, 141, 128, 115; FTIR (neat): 3059, 1584, 1507, 1460, 1385, 1336, 1248, 1180, 1075, 1015, 862, 777, 736.

1.3. (E)-4-(2-thienyl)-4-octene

The reaction was run as above except that 2-iodothiophene (3.31 ml, 30 mmol) was used. Yield: 2.21 g (11.4 mmol, 38%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.5, 133.6, 128.1, 127.2, 122.7, 121.9, 32.38, 30.49, 22.93, 22.30, 14.15, 13.99; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.076 (1H, dd, $J = 1.79$ and 4.44 Hz), 6.957–6.936 (2H, m), 5.892 (1H, t, $J = 7.32$ Hz), 2.461–2.423 (2H, m), 2.183–2.128 (2H, m), 1.540–1.435 (4H, m), 0.955 (3H, t, $J = 7.35$ Hz), 0.944 (3H, t, $J = 7.37$ Hz); GCMS (*m/e*): 194 (M^+), 165, 151, 124, 123, 97, 91, 79, 77, 65, 45; FTIR (neat): 3021, 1461, 1378, 1227, 1049, 890, 816, 691.

1.4. (E)-3-(4-methoxyphenyl)-3-hexene

The reaction was run as above except that 4-iodoanisole (7.02 g, 30 mmol, dissolved in 6.5 ml of 1,4-dioxane) was used. No precipitate formed during the reaction. The filtration step was omitted. Pure product was obtained by flash chromatography using ether/hexanes, 2%. Yield: 4.10 g (21.6 mmol, 72%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.3, 140.3, 135.6, 128.6, 127.2, 113.5, 55.28, 22.86, 21.70, 14.61, 13.74; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.289 (2H, dd, $J = 6.74$ and 2.10 Hz), 6.846 (2H, dd, $J = 6.71$ and 2.12 Hz), 5.564 (1H, t, $J = 7.29$ Hz), 3.804 (3H, s), 2.478 (2H, q, $J = 7.54$ Hz), 2.225–2.151 (2H, m), 1.049 (3H, t, $J = 7.53$ Hz), 0.973 (3H, t, $J = 7.53$ Hz); GCMS (*m/e*): 190 (M^+), 161, 146, 115, 91, 77, 65; FTIR (neat): 3035, 1575, 1509, 1463, 1376, 1250, 1181, 1113, 1038, 885, 827, 756.

1.5. (E)-3-(3-bromophenyl)-3-hexene

The reaction was run as above except that 1-bromo-3-iodobenzene (3.82 ml, 30 mmol) was used. Yield: 3.59 g (15.0 mmol, 50%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.4, 139.9, 131.3, 129.7, 129.43, 129.36, 124.9, 122.4, 22.80, 21.77, 14.42, 13.65; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.491–7.482 (1H, m), 7.347–7.327 (1H, m), 7.272–7.255 (1H, m), 7.177–7.138 (1H, m), 5.631 (1H, t, $J = 7.18$ Hz), 2.470 (2H, q, $J = 7.57$ Hz), 2.236–2.161 (2H, m), 1.056 (3H, t, $J = 7.53$ Hz), 0.967 (3H, t, $J = 7.51$ Hz); GCMS (*m/e*): 240/238 (M^+), 211/209, 159, 130, 117, 91; FTIR (neat): 3062, 3014, 1558, 1470, 1375, 1279, 1070, 996, 861, 749, 693. Anal. Found: C, 60.10; H, 6.23; Br, 33.12. $C_{12}H_{15}Br$ (239.156) calcd.: C, 60.27; H, 6.32; Br, 33.41%.

1.6. (E)-3-(4-methoxycarbonylphenyl)-3-hexene

The reaction was run as above except that 4-iodobenzoic acid methyl ester (4.60 g in 33 ml of DMF, 17.6 mmol) was used. Instead of 1,4-dioxane, DMF (5.46 ml, 4 equiv) was used after the initial equilibration. No precipitate formed and the filtration step was omitted. Pure product was obtained by flash chromatography using ether/hexanes, 2%. Yield: 2.84 g (13.0 mmol, 74%); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.1, 147.7, 140.3, 132.1, 129.6, 128.0, 126.1, 52.00, 22.61, 21.84, 14.34, 13.65; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.980–7.959 (2H, m), 7.426–7.405 (2H, m), 5.750 (1H, t, $J = 7.33$ Hz), 3.909 (3H, s), 2.526 (2H, q, $J = 7.47$ Hz), 2.268–2.193 (2H, m), 1.074 (3H, t, $J = 7.53$ Hz), 0.982 (3H, t, $J = 7.55$ Hz); GC/MS (m/e): 218 (M^+), 189, 159, 129, 115, 91, 59, 51; FTIR (neat): 1724, 1606, 1564, 1435, 1275, 1184, 1017, 967, 774.

Acknowledgments

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