Synthesis of the Multisubstituted Halogenated Olefins via Cross-Coupling of Dihaloalkenes with Alkylzinc Bromides

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The 1-fluoro-1-haloalkenes undergo Pd-catalyzed Negishi cross-couplings with primary alkylzinc bromides to give multisubstituted fluoroalkenes. The alkylation was trans-selective giving pure Z-haloalkenes in most cases. The highest yields were obtained with Pd2(dba)3 and PdCl2(dppb) catalysts but the best stereochemical outcome was obtained with less reactive Pd(PP3)4. The tertiary alkylzincs also produced desired fluoroalkenes in high yields. Coupling of 1-fluoro-1-haloalkenes undergo Pd-catalyzed Negishi reactions or (b) formation of a new C6–C6′ double bond in analogous of type B (X = H) followed by dehydrobromination (DBU) was found to be ineffective to yield vinyl 6′-bromides B (X = Br), we turned our attention to direct synthesis of halovinyl analogues B via selective coupling employing dihalovinyl precursors of type E.

The Pd-catalyzed cross-coupling reactions are powerful methods for the formation of carbon–carbon bonds under conditions that are compatible with a broad range of functional groups. However, despite the wide application of Csp2–Csp3 and Csp3–Csp3 couplings, couplings involving Csp3 centers are less explored2 with the exception of couplings between Csp2 as electrophiles and Csp3 as nucleophiles.6 Moreover, the monosub-cross-coupling of 1,1-dihaloalkenes with Csp2 or Csp3 nucleophiles are less common and monocouplings between 1,1-dihaloalkenes and Csp3 nucleophiles are scarce.7,8 Panek et al. utilized a double coupling strategy with


(α-iodo)vinyl silanes for the synthesis of trisubstituted alkenes to overcome difficulties in selective alkylation of vinyl dibromides.\(^7\) McCarthy\(^8a\) and Burton\(^8b\) and their co-workers developed coupling between 1-bromo(or chloro)-1-fluoroalkanes with vinyl/aryl organostannanes and boranes to prepare the conjugated 1-substituted-1-fluoroolefins.\(^9\)

We were prompted to undertake model studies on Pd-catalyzed cross-coupling between vinyl dihalides and alkyl organometallics because the synthesis of analogue B (X = halogen) via Pd-catalyzed monoalkylation between dihalo-homovinyl nucleoside (or carbohydrate) derivatives of type E and organozinc reagents was difficult.\(^2\),\(^10\) Moreover, there are only a few reports on selective monoalkylation of 1,1-dihaloalkanes.\(^5\),\(^6a\) Herein, we report a novel Negishi monoalkylation of 1-fluoro-1-haloalkenes, derived from the conjugated or unconjugated aldehydes and ketones, as well as 1,1-dichloroalkenes with alkylzinc bromides to provide access to the multisubstituted fluoro or chloro alkenes.

The 1-fluoro-1-haloalkenes 4–6 were chosen as precursors to study Pd-catalyzed Negishi\(^5\) coupling with alkylzincs. We expected formation of monoalkylated fluoroalkenes in view of the inertia of fluorides\(^3a\) toward couplings. The terminal dihaloalkanes 4–6 were prepared in high yields by the McCarthy’s procedure\(^11\) that involves (i) condensation of aldehydes 1a–c and ketone 1d with sulfonylestabilized fluorophosphonates to give (α-fluoro)vinyl sulfones 2, (ii) radical stannyldesulfonylation with Bu3SnH/AIBN to yield (α-fluoro)vinyl stannanes 3, and (iii) the halodestannylation\(^12\) with NIS, NBS, or Cl2 to give 1-fluoro-1-ido- (4), 1-fluoro-1-bromo- (5), or 1-fluoro-1-chloroalkenes (6), respectively (Scheme 1). It is noteworthy that dihaloalkenes of series c with a benzyloxy substituent at the allylic carbon are structural analogues of the dihalomonomovinyl nucleoside or ribofuranosyl precursors of type E, which also has an oxygen atom at the γ carbon from the halovinyl site.

Initially, we attempted couplings of the conjugated 1-fluorovinyl iodide 4a (E/Z, 95:5) with 2 equiv of primary alkylzinc bromide [BrZn(CH2)3CO2Et] in the presence of Pd(PPh3)4 in benzene (65 °C, 10 h), which gave fluoro alkenoate 7a as a single Z isomer (JF–Hirnais = 39.8 Hz) in 70% yield (Scheme 2; Table 1, entry 1). The coupling occurred with retention of configuration via trans-selective alkylation (vide infra) but the E/Z descriptors changed owing to the change in Cahn–Ingold–

\[\text{O} \quad \text{a} \quad \text{b} \quad \text{c} \quad \text{d} \quad \text{E} \quad \text{F} \quad \text{R} \quad \text{1} \quad \text{R}^1 \]

\[\text{Compds 1-6} \quad \text{R} \quad \text{R}^1 \]

\[\begin{align*}
\text{a} & \quad \text{Ph} & \quad \text{H} \\
\text{b} & \quad \text{PhCH2CH2} & \quad \text{H} \\
\text{c} & \quad \text{PhCH2OCH2} & \quad \text{H} \\
\text{d} & \quad \text{Ph} & \quad \text{CH3} \\
\end{align*}\]

\[\text{4} \quad \text{5} \quad \text{6} \quad \text{X} \quad \text{Cl} \quad \text{Br} \quad \text{Et} \]

\[\text{X} = 1 \quad \text{X} = \text{Br} \quad \text{X} = \text{Cl} \]

\[\text{7} \quad \text{R}^2 = \text{CH}_2\text{CO}_2\text{Et} \quad \text{8} \quad \text{R}^2 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Et} \quad \text{9} \quad \text{R}^2 = \text{CH}_2\text{OCH}_2\text{Et} \]

* Reagents and conditions: (a) PhSO4CHFPO(OEt)2/LHMDSD/TiH2/78 °C; (b) Bu3SnH/AIBN/benzene/Δ; (c) NIS/CH3Cl; (d) NBS/CH3Cl; (e) Cl3C/CH3Cl.

**SCHEME 1.** Stereoselective Synthesis of 1-fluoro-1-haloalkenes 4–6

**SCHEME 2.** Couplings of 1-fluoro-1-haloalkenes with Alkylzincs

We found that tris(dibenzylideneacetone)palladium [Pd2(dba)3] and 1,4-bis(diphenylphosphinobutane)palladium chloride [PdCl2(dppe)] gave smooth conversion of 4a into 9a in 2 h at 50 °C. The Pd(PPh3)4 effected only 11% conversion of 4a into 9a under analogous conditions and Pd(OAc)2 and PdCl2(dpff) were also less effective. Coupling of 4a with BrZn(CH2)3CO2Et in the presence of PdCl2(dpff) gave improved yield of 7a(Z) (93%, entry 2 vs entry 1) under milder conditions (50 °C, 2 h).

The unconjugated 1-fluorovinyl halides 4b (E/Z, 78:22) coupled with primary alkylzinc bromides in the presence of Pd(PPh3)4 to give 7b, 8b, and 9b in high yields (entries 9, 13, and 14). The conversion of 4b into 7b was achieved in higher yields under milder conditions with PdCl2(dpff) as catalyst (entry 12).

The vinyl iodide 4c (E/Z, 75:25) with benzylxymethyl substituent at carbon β (analogue of the nucleoside precursor of type E) reacted with BrZn(CH2)3CH==CH2 [Pd(PPh3)4] to give the internal fluoroalkane 8c(Z) in moderate yield (56%, entry 17) in addition to unchanged 4c with enriched Z to E ratio (56:44). The PdCl2(dpff) catalyst not only increased the yield but also led to the formation of 8c as a mixture of E/Z isomers.
(E/Z, 15:85) of 1-fluoro-1-iodoalkene 4b were prepared by separation of the corresponding (α-fluoro)vinyl stannanes 3b followed by the stereospecific iododemethylation. Treatment of 4b (E) with BrZn(CH$_2$)$_3$CO$_2$Et or BrZn(CH$_2$)$_3$CH(OCH$_2$)$_2$ [Pd(PPh$_3$)$_2$]/12 h/65 °C) resulted in smooth conversion (GC/MS, $^{19}$F NMR) to 7b(Z) or 9b(Z) with isolated yields of 88% and 95%, respectively (entries 10 and 15). On the other hand, analogous Negishi treatment of 4b (E/Z, 15:85) yielded 7b(Z) or 9b(Z) in 14% (96% conversion of E isomer; entries 11 and 16) while the corresponding 7b(E) or 9b(E) were not formed. Prolonged reaction time and harsher conditions resulted in decomposition of the 4b(Z) isomer (GC/MS, $^{19}$F NMR).

Generally, only in a few instances did we observe formation (above detection limit$^{13}$ of 1–2%, $^{19}$F NMR) of the corresponding E isomers via cis-couplings (entries 18, 19, and 21). For example, alkylation of 4c (iodide) and 5c (bromide) in the presence of PdCl$_2$(dpbb) produced 8c as an E/Z (20:80) mixture. These results are in agreement with trans-selective mono-coupling of 1,1-dihaloalkanes reported previously.$^{3c,5,6,14}$ Burton and co-workers showed that trans selectivity with 1-bromo-1-fluoroalkenes originates in the oxidative addition step since formation of the E-palladium complex is faster than the formation of the Z-palladium complex, which is hampered by steric hindrance of the vicinal cis-substituent.$^{14a}$ They applied this finding for the kinetic resolution of the E and Z coupling products.$^{8b,14}$

The major byproduct isolated from the coupling reactions resulted from the reductive homocoupling of dihalide components. For example, the self-coupling product of 4a, e.g., (Z,Z)-2,3-difluoro-1,4-diphenyl-1,3-butadiene 12 was also isolated (8%; 16% consumption of 4a).$^{4b}$ Pd(db)$_2$ catalysts (95% based on GC-MS).$^{3}$ (Z)-1-Fluoro-4-phenyl-1-butene, E isomer of 8b, and (Z,Z)-4,5-difluoro-1,8-diphenyl-3,5-octadiene were also detected in crude reaction mixture ($^{19}$F NMR), 98% based on GC-MS.$^{5}$ 56% based on $^{19}$F NMR.$^{2}$ E/Z, 20:80.$^{3}$ E/Z, 16:84 based on $^{19}$F NMR and GC-MS.

We also examined the Pd-catalyzed coupling of 1,1-dihaloalkenes with branched alkylzincs. Thus, PdCl$_2$(dpbb) was found to be effective for monoalkylation of 4a (E/Z, 95:5 with i-BuZnBr (10a) to provide 11a (80%; 3 h; 50 °C; Scheme 4). The Pd(db)$_2$ and Pd(PPh$_3$)$_2$ catalysts were less effective leading to the formation of a significant amount of self-coupling byproduct 12 [e.g., 20%, 40% consumption of 4a for Pd(PPh$_3$)$_2$]. Interestingly, attempted couplings of 4a with secondary 2- or 3-pentyne bromides (10b or 10c) gave various amounts of desired products 11b or 11c (in the range of 5–50%) along with the isomerization byproduct 11d (35–70%) and self-coupled diene 12 as well as reduced (Z)-β-fluorostyrene. Since purifications of desired products 11b and 11c from other byproducts (especially from 11d) turned out also to be difficult.

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SCHEME 5. Couplings with 1,1-Dibromo- and 1,1-Dichloroalkenes

![Diagram](image-url)  

Reagents and conditions: (a) BrZn(CH2)3CO2Et/PdCl2(dppf)/THF/65 °C (oil bath).

no further effort was undertaken to improve these reactions. Formation of byproducts derived from isomerization of the branched alkyl group during Negishi reaction is known. 4,15

We also investigated differentiation of the two halogens in 1,1-dibromo- or 1,1-dichloroalkenes for selective monoalkylation with alkylzincs. We found that \( \beta,\beta \)-dichlorostyrene 13 reacted [PdCl2(dppf)/THF/65 °C/14 h] with BrZn(CH2)3CO2Et to give a desired trisubstituted chloroalkene 15 (Z, 65%) in addition to the monosubstituted/doubly reduced product 18 (22%; Scheme 5). Analogous couplings in the presence of PdCl2(dpbb) produced 15 (53%) and 18 (15%) in addition to dialkylated product 17 (27%). Similar couplings with more reactive \( \beta,\beta \)-dibromostyrene 14 produced mainly dialkylated 17 (57–69%) in addition to 18 (24–28%).

In summary, we have developed Pd-catalyzed Negishi cross-coupling of 1-fluoro-1-(iodo, bromo, or chloro)alkenes with alkylzincs, thus providing stereoselective access to the internal fluoralkenes. The primary alkylzincs also produced desired fluoralkenes in high yields. The \( \beta,\beta \)-dichlorostyrene gave selective coupling to produce multisubstituted chloroalkenes. Application of 1,1-dihaloalkenes for selective double alkylolation strategy, which can be used for the synthesis of tetrasubstituted alkene as well as synthesis of carbohydrate and nucleoside analogues of type B, will be published elsewhere.

Experimental Section

Experimental procedures [A (synthesis of vinyl sulphones 2 via Wittig reaction), B (preparation of vinylstannane 3 via stannyldisulfonylation), C (synthesis of dihaloalkenes 4–6 via halodestannylation of 3), D (couplings of 1-fluoro-1-haloalkenes 4–6 with alkylzincs), and E (couplings of 1,1-dichloro- 13 and 1,1-dibromoalkenes 14 with alkylzincs)] are described in the Supporting Information.

Ethyl 5-Fluoro-6-phenyl-5(Z)-hexenolate (7a): Procedure D. 4-Ethoxy-4-oxobutylzinc bromide (0.5 M/THF; 0.60 mL, 0.30 mmol) was added via syringe to a stirring solution of 4a (EtZ, 95%; 50 mg, 0.20 mmol) in dried benzene (5 mL) containing Pd-(PPh3)4 (7 mg, 0.006 mmol) under N2. The resulting mixture was heated at 65 °C for 5 h. Additional Pd(PPh3)4 (4.5 mg, 0.004 mmol) and 4-ethoxy-4-oxobutylzinc bromide (0.20 mL, 0.10 mmol) were then added and heating was continued for an extra 5 h. Volatiles were evaporated and the residue was partitioned (NaHCO3/H2O/EtOAc). The organic layer was washed (brine), dried (Na2SO4), evaporated, and chromatographed (hexane 15% EtOAc/hexane) of 7a (33 mg, 70%; 74% based on the conversion of \( \mathcal{E} \) isomer only): 1H NMR \( \delta \) 1.26 (t, \( J = 7.1 \) Hz, 3H), 1.95 (quint, \( J = 7.3 \) Hz, 2H), 2.39–2.48 (m, 4H), 4.15 (q, \( J = 7.1 \) Hz, 2H), 5.50 (d, \( J = 3.9 \) Hz, 1H), 7.15 (t, \( J = 7.2 \) Hz, 1H), 7.30 (t, \( J = 7.4 \) Hz, 2H), 7.45 (d, \( J = 7.4 \) Hz, 2H); 13C NMR \( \delta \) 14.6, 22.1, 32.7 (d, \( J_{C-F} = 26.9 \) Hz), 33.6, 60.8, 106.9 (d, \( J_{C-F} = 8.5 \) Hz), 127.2, 128.7, 128.9, 134.0, 160.2 (d, \( J_{C-F} = 266.7 \) Hz), 173.5; 19F NMR \( \delta \) –102.20 (dt, \( J = 39.8, 19.7 \) Hz); MS m/z 237 (100%, MH+). Anal. Calcd for C14H17FO2 (236.12): C, 71.16; H, 7.25. Found: C, 70.80; H, 7.16. Analogous treatment (50 °C, 2 h total) of 4a (0.20 mmol) with 4-ethoxy-4-oxobutylzinc bromide (0.37 mmol) and PdCl2(dpbb) (6.0 mg, 0.01 mmol) gave 71 (93%).

3,3-Dimethyl-2-fluoro-1-phenyl-1-butene (11a). Procedure D. 4a (EtZ, 95.5; 40 mg, 0.16 mmol) with PdCl2(dpbb) (5% molar) and tert-butylzinc bromide (0.5 M; 0.6 mL, 0.32 mmol) as described in procedure D [3 h, 50 °C] gave 11a (23 mg, 80%; 95% based on GC-MS and 13C NMR); 1H NMR \( \delta \) 1.15 (s, 9H), 5.40 (d, \( J = 40.7 \) Hz, 1H), 7.17–7.41 (m, 5H); 13C NMR \( \delta \) –109.47 (d, \( J = 40.7 \) Hz); GC-MS m/z 178 [80%, M]+; \( t_{R} = 10.78 \) min). HRMS calcd for C14H17FO (M + H)+ 219.1237, found 219.1246.

(Z)-Ethyl 5-Chloro-6-phenyl-5-hexenolate (15): Procedure E. 4-Ethoxy-4-oxobutylzinc bromide (0.5 M; 1.45 mL, 0.72 mmol) was added via syringe to a stirring solution of 13 (50 mg, 0.29 mmol) in dried THF (3 mL) containing PdCl2(dpbb) (24 mg, 0.029 mmol) under N2. The resulting mixture was heated at 65 °C overnight. Volatiles were evaporated and the residue was partitioned (NaHCO3/H2O/EtOAc). The organic layer was washed (brine, dried (Na2SO4), evaporated, and chromatographed (hexane 10% EtOAc/hexane) to give 15 (47 mg, 65%) and 18 (14 mg, 22%). 1H NMR \( \delta \) 1.19 (t, \( J = 7.1 \) Hz, 3H), 1.94 (quint, \( J = 7.1 \) Hz, 2H), 2.31 (t, \( J = 7.4 \) Hz, 2H), 2.47 (t, \( J = 7.1 \) Hz, 2H), 4.08 (q, \( J = 7.1 \) Hz, 2H), 6.40 (s, 1H), 7.26–7.52 (m, 5H); 13C NMR \( \delta \) 14.2, 22.8, 32.9, 40.28, 60.3, 125.2, 127.5, 128.2, 129.0, 133.6, 135.0, 173.2; GC-MS m/z 252 (30%, M]+; \( t_{R} = 20.00 \) min). HRMS calcd for C15H15ClO2 (M + H)+ 253.0995, found 253.0989.

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Supporting Information Available: Experimental procedures, characterization data, and copies of 1H NMR spectra. This material is available free of charge via the Internet at [http://pubs.acs.org](http://pubs.acs.org).